THE GLOBAL METHAMPHETAMINE PROBLEM: APPROACHES TO ELUCIDATE THE NEUROBIOLOGY, EPIDEMIOLOGY AND THERAPEUTIC EFFECTIVENESS

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EDITORIAL
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Editorial: The Global Methamphetamine Problem: Approaches to Elucidate the Neurobiology, Epidemiology, and Therapeutic Effectiveness

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Editorial on the Research Topic

The Global Methamphetamine Problem: Approaches to Elucidate the Neurobiology, Epidemiology, and Therapeutic Effectiveness

Methamphetamine-use disorder (MUD) is a global problem and is of great public health concern. The rapid increase in methamphetamine (MA) use in Europe, particularly in young adults has led to a significant medical shortfall in many regions. MUD is a particularly difficult addiction to treat, in part, because of the psychiatric comorbidities and the effects of MA on the neurobiological mechanisms that affect higher-order cognitive functions relevant for adaptive behavior and successful completion of treatment programs. Moreover, little is known about the risk factors and susceptibility of MUD or the trajectories in neurocognitive and neurobiological deficits and treatment response. This special issue on the global methamphetamine problem, therefore, focuses on MA use as a multi-faceted construct that needs to be evaluated in the context of risk factors, neurobiology, therapeutic approaches, and comorbidities that likely interact with treatment outcomes.

We start with the cognitive dysfunctions associated with MUD, as these deficits have lasting impact on daily life behavior and treatment outcomes. The systematic review presented by May et al. highlights the abnormalities in emotion regulation, goal-directed decision making, and responses to negative reinforcement in MUD. This review provides a comprehensive evaluation of MA-associated cognitive deficits, which have been considered in the following papers examining abstinence and treatment. For example, in Bernhardt et al. patients with MUD show improvements in sustained attention but no change in impulsive choices after 3 months of abstinence. Similarly, Bensmann et al. report that some tests of executive function are impaired, while others normalized after abstinence. These differences in executive function have significant implications for treatment. The study presented by Lake et al. presents evidence that individual variability in the aversion to losses and in the predilection for large and immediate rewards is a

factor in successful contingency management treatment outcomes. In line with these results, naltrexone-induced changes in large-scale brain networks that are important for many of the deficits in executive function seen in MUD is associated with MA abstinence and addiction severity (Kohno et al.). Together, these studies show the importance of interventions to consider cognitive control and decision-making deficits as a factor in order to enhance the effectiveness of different treatment approaches.

Cognitive deficits and maladaptive decision-making associated with MUD also has implications on public health at large, which is highlighted in a paper by Schecke et al. that reports that MA use in sexual settings is related to higher rates of HIV. In addition to the public health concern, an increase in mental health disorders are associated with MA use in sexual settings, which underscores the importance of identifying psychiatric comorbidities when treating MUD. For example, comorbid substance use disorders influence the trajectory of MUD recovery, where the presence of a dual diagnosis is associated with greater occurrence of relapse, death, or incarceration (Tan et al.). Similarly, incarceration rates in MUD interacted with levels of psychopathy and corticostriatal brain connectivity (Hoffmann et al.). As this brain network is important for executive function and cognitive control, these results are in line with the study presented by Arunogiri et al. that show impairments of emotion recognition and impulsive choice in MUD and the additional presence of psychotic symptoms potentiating these effects.

Treatments that limit MA use through improvements in decision-making skills or modification of neural networks are imperative, as a study that evaluates the first German-language therapy manual for specific short-term treatment of MUD (Petzold et al.) shows that shorter periods of MA use is a primary predictor for positive treatment responses. An innovative study protocol to limit MA use has also been proposed, which will examine the efficacy of retrieval-extinction training combined with virtual reality to reduce cue-evoked responses in MUD (Liu et al.). Another important consideration in reducing MA use is genetic risk factors. A preclinical study showing that Homer2 expression regulates the rewarding/reinforcing properties of MA highlights the need to identify genetic susceptibility for MUD to develop tailored models for prevention and treatment (Brown et al.).

Overall, the selection of these studies highlights the complex dynamics of MUD and the need for interdisciplinary research. Extending the results from these published articles would be of great value in identifying the interactions between psychosocial, genetic, neural and behavioral markers that are associated with stimulant use and has the potential to advance therapeutic strategies for addiction.

AUTHOR CONTRIBUTIONS

MK, CB, and MP wrote the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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History of Alcohol and Opioid Use Impacts on the Long-Term Recovery Trajectories of Methamphetamine-Dependent Patients

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Methamphetamine (MA) has become one of the most widely used illicit substances in China and the rest of the world as well. Relapse, incarceration or death was observed after compulsory rehabilitation. However, the knowledge of recovery patterns among MA-dependent patients, early or late occurrence of these negative consequences, is limited. The aims were to explore the long-term recovery patterns and associated factors among MA-dependent patients in Shanghai, China. MA-dependent patients discharged from Shanghai compulsory rehabilitation facilities in 2009–2012 were recruited in a baseline survey. The baseline data of 232 patients were then linked with their long-term follow-up data from official records. Group-based trajectory modeling was applied to identify distinctive trajectories of the occurrence of negative consequences (incarceration, or readmission to compulsory rehabilitation, or death). Patients with monthly status data were found recovering with three distinctive trajectories: rare, late, and early occurrence groups. Multinomial logistic regression showed that having alcohol use history was associated with an increased likelihood of being in the late occurrence group relative to the rare occurrence group. Having opioid use history was associated with an increased likelihood of being in the early occurrence group relative to the rare occurrence group. In addition, being female was associated with decreased likelihood of being in the late occurrence group relative to the rare occurrence group.

Keywords: long-term follow-up, recovery pattern, negative consequences, trajectory, methamphetamine

INTRODUCTION

While ranking second in the share of the global burden of disease attributable to drug use disorders after opioids, amphetamine-type stimulants (ATS) are the most frequently used class of illicit drugs in China, and people using opioids also gradually switched to ATS (1, 2). Methamphetamine (MA) is the primary drug used among ATS. MA dependence has a relapse rate of 30%–90%, and a study in 2014 showed that 61% of the MA users relapsed within 1 year following treatment discharge (3–5). MA use is also linked to crime, such as drug dealing, property crime, fraud or violent crime, especially acquisitive crime (6–9).

Relapse is associated with more than a single factor. Previous studies found that both biological and sociocultural characteristics of patients could influence relapse (10, 11). It was revealed that some demographic factors such as age, gender and education level related to relapse among ATS users (12, 13). Meanwhile, patients' mental comorbidities, having psychotic symptoms and polydrug use, were risk factors or protective factors (13–15). Crime is also related to a combination of drug use and sociocultural characteristics (12). It was found that frequent drug and alcohol use were risk factors for incarceration among Thai MA users (16). Furthermore, there was a picture of mutual influence between relapse and crime. Among Japanese patients with MA use disorder, history of incarceration was associated with treatment retention (13).

In China, there is a compulsory treatment program, according to the Chinese narcotic control law, for patients who fail to remain abstinent from drug use in the community. The compulsory rehabilitation program is an enforced residential drug treatment. Thus, participants in this study maintained abstinence from entrance to discharge. It is conducted by a judicial office, and the patient who has an addiction to illicit drugs may be sent to obtain a compulsory treatment, which is usually for 2 years. This compulsory treatment program aimed for comprehensive recovery of physical health (daily physical exercise), from drug dependence and of social functioning, which includes medication or physical rehabilitation, psychotherapy and vocational skills training and anti-relapse education. In this program, they received no medications related to drug dependence. When the compulsory treatment program is completed, there are social worker networks to prevent relapse and crime and promote social functioning recovery (17). Patients who are discharged from the compulsory treatment program are assigned to participate in the community-based drug rehabilitation program that serves at their place of residence. After the compulsory treatment program, patients will participate in the community-based drug rehabilitation program, and social workers could provide psychological counseling, vocational training and social welfare consultation, which is funded by the government (18). Therefore, to assess the comprehensive recovery of patients after the treatment using the Chinese model, we define negative consequences (NC) (including incarceration, readmission to compulsory rehabilitation and death) to assess rehabilitation, which was used in our previous study among heroin patients (19).

In community-based rehabilitation, patients have different recovery trajectories. Some patients have NC, while others abstinence. The time points of NC occurrence were different, which range from a few months to years in our observation. However, a few research has indicated how the trajectory develops and what factors affect rehabilitation trajectories. Recently, there was a nationwide systematic multicenter survey of the characteristics of drug use behaviors in club drug users and associated high-risk sexual behavior in China, which showed that the pursuit of euphoria was the main reason for drug use. High-risk sexual behaviors were common in these users. The factors of polydrug use, long use history and severe acute intoxication after drug use were associated with risky sexual behaviors. With this survey, this study has required part of the baseline data to explore the recovery trajectories (20). We investigated recovery patterns of MA-dependent patients and associated risk factors, based on an electronic monthly summary record system of persons using illicit drugs in Shanghai, China. This follow-up database, which was established by Shanghai Municipal Narcotics Control Committee, provided us a unique opportunity to describe the recovery patterns among MA-dependent patients. We used group-based trajectory modeling (GBTM) to identify distinctive trajectories of the presence of NC after patients were discharged from compulsory rehabilitation programs.

METHODS

Design

This study was a cohort study. The baseline data were collected from the project "Research on mathematical model for AIDS epidemic trend assessment and prediction in China" (20). After the baseline assessment, our participants were passively followed up: participants' long-term outcomes were ascertained from the electronic monthly summary record system, which was managed by social workers. Unique ID numbers were used to link baseline data to follow-up data.

This study was approved by the institutional Review Boards in Shanghai Mental Health Center. Written informed consent was obtained from all participants. All procedures were in accordance with the approved guidelines.

Participants

At baseline, we used convenience sampling to recruit 429 MA-dependent patients from two compulsory rehabilitation centers in Shanghai from September 2009 to May 2010 and from August 2012 to February 2013. Patients who met the inclusion criteria should: a) have MA dependence according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* diagnostic criteria; b) be at the age of 18 and above; c) have used MA in 30 days (by urinalysis) before the mandatory drug rehabilitation; and d) have the ability of informed consent. The exclusion criteria were: a) serious physical or neurological illness that required pharmacological treatment; b) other Axis I disorder of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* criteria, such as bipolar disorder, schizophrenia, depression and substance dependence (other than nicotine and MA) within the past 5 years; and c) neurological diseases, such as stroke, seizure, migraine, and head trauma. The process is displayed in **Figure 1**.

Measurements

At baseline, a commonly used Chinese version of the Addiction Severity Index (ASI) was used to assess patients' sociodemographic characteristics and drug use history, including age, sex, employment, marriage, alcohol/drug usage and so on (21, 22).

The follow-up data of participants after compulsory rehabilitation programs were derived from the electronic monthly summary record system from 2009 to 2017. Shanghai Municipal Narcotics Control Committee established this database in March 2007. Social workers who are employed by the Shanghai government

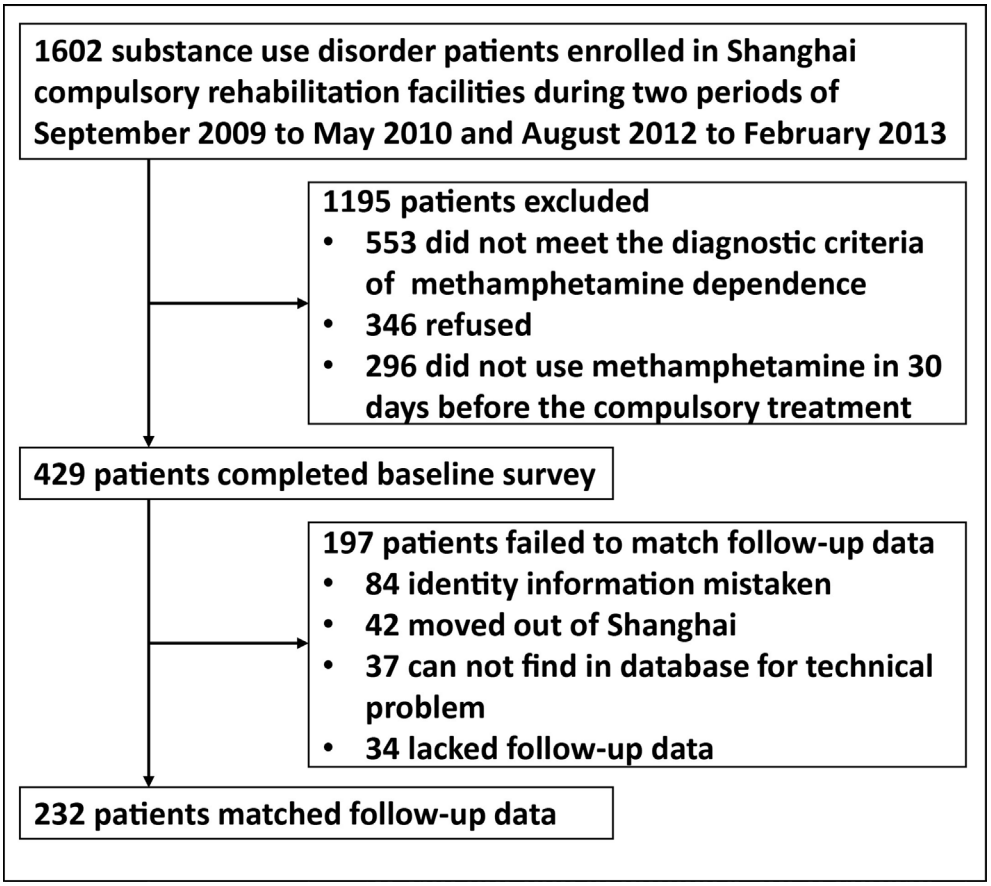

FIGURE 1 | Flowchart of enrollment and follow-up of subjects in the study.

are responsible for managing this administrative database, while helping the patients with drug dependence recover in the community. The following categories of drug-related information were recorded each month in chronological order, including incarceration, readmission to compulsory rehabilitation programs, death, methadone maintenance treatment participation, etc. These events were recorded as binary variables (happened or not).

For the present study, recovery outcomes were classified into four monthly outcomes: incarceration, readmission to compulsory rehabilitation programs, death, and the rest (not encoded as any of other cases). Our outcome variable of interest, negative consequences, is defined as having incarceration, readmission to compulsory rehabilitation programs or death. According to the Anti-drug Law in China (17), patients who were discharged from compulsory rehabilitation programs should participate in a long-term community-based rehabilitation program. During the community-based rehabilitation program, using illicit drugs could lead to readmission into compulsory rehabilitation programs. Readmission was only triggered by seriously violating the community-based recovery agreement or reusing drugs, which means those readmission cases relapsed. According to clinical observation, we hypothesized the recovery patterns of patients, which can be divided to the following: 1) NC happened in a relatively short time after compulsory rehabilitation programs (early occurrence group); 2) NC happened long after compulsory rehabilitation programs (late occurrence group); and 3) NC rarely happened (rare occurrence group).

Statistical Analyses

Group-based trajectory modeling (GBTM) was used to analyze the patient's recovery trajectories. GBTM is a specialized application of finite mixture modeling. In this study, GBTM identifies clusters of individuals with similar recovery trajectory and explores heterogeneity across groups. The monthly repeated measures of NC were estimated by a polynomial relationship as below:

$$\text{Status}_{ijt} = \beta_{0j} + \beta_{1j} \times Month_{it} + \beta_{2j} \times Month_{it2} + \varepsilon_{it}$$

Where *i*, *j*, and *t* indicate subjects, latent group, and time, respectively, and ε is a disturbance normally distributed with a zero mean and a constant residual variance.

The shape of trajectory for each group determined β_0, β_1 and β_2, which represent the intercept, linear and quadratic parameters, respectively. (23, 24). We used 'traj' plugin in Stata release 12 for analysis (25–27). Corresponding to the binary variables of the recovery data, the Logistic Model was used. A series of models were fitted with an increasing number of

trajectory groups. The goodness of fit model was evaluated with the Bayesian Information Criterion (BIC) (28). The best fitting model was chosen with a reasonably low absolute value of BIC and sufficient number of subjects (10% of total sample or more) in each group (29).

For the subgroups with separated trajectories, multinomial logistic regression was used to explore the relationship between one's recovery pattern and baseline factors.

RESULTS

Attrition and Characteristics of Patients

Among 429 participants, 232 patients' follow-up data were found in the official database and were linked to their baseline data. The rest of the participants' follow-up data were not found due to mistaken identity, those who moved out of Shanghai or technical problems (see **Figure 1**). Among all 429 patients, 68.2% were male; 46.9% were unemployed or had spent time in prison in the 3 years prior to the baseline interview; over half (60.3%) were not currently married; they had, on average, a 3.1 ± 2.6-year history of MA use, and in 30 days before compulsory rehabilitation, they had 15.0 ± 12.0 times of drug use on average (see **Supplementary Table 1**).

Status During 30 Months of Follow-Up and Recovery Patterns

As participants were discharged at different time, our follow-up data ranged from 30 to 86 months. Thus, we truncated the first 30 months after compulsory rehabilitation programs for analysis. The monthly prevalence of each NC and incidence rates of all NC after compulsory rehabilitation are graphically displayed in **Figure 2**. Incidence rates were calculated by person-time methods, dividing the number of NC by the number of NC and in community monthly. Two peaks of NC were observed. Thus, we confirmed our hypothesis that the recovery patterns of patients can be divided as early occurrence group, late occurrence group and rare occurrence group.

A series of group-based trajectory models, from a two- to five-trajectory pattern, were fitted to identify the optimal model. The BIC values (BIC = −1,538.40) in the two-trajectory model, three (BIC =−1,236.76), four (BIC = −1,145.07) and five (BIC = −1,046.75) were used for model evaluation. To evaluate class separation, the relative entropy of the posterior probability distribution was calculated and had a value of 0.8, indicating the acceptable separation between classes (30). When the relatively low absolute value of BIC and the sufficient number of subjects in each group and clinical interpretability were considered, the three-trajectory model was selected as potential optimal models.

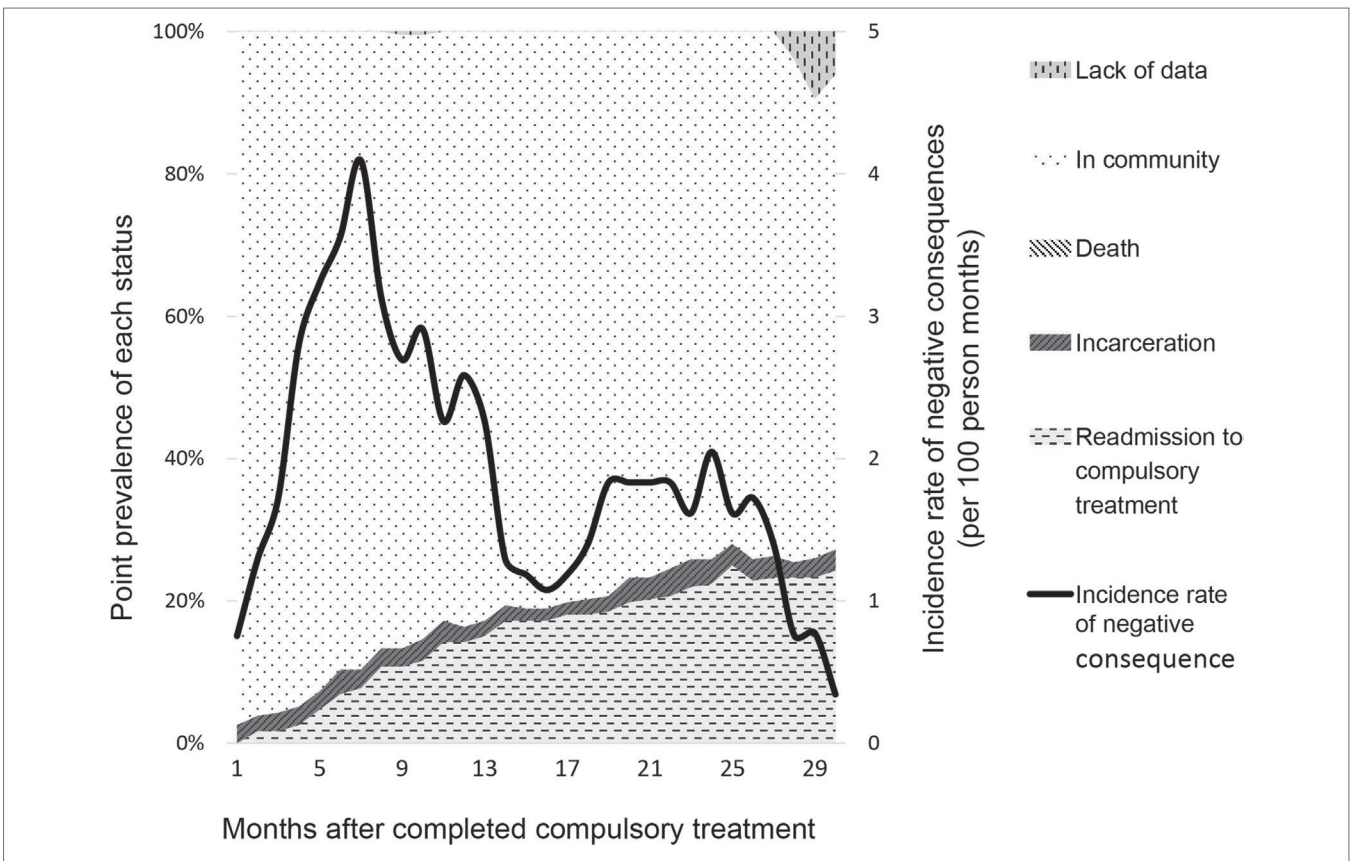

FIGURE 2 | Recovery status of methamphetamine patients after completed the compulsory rehabilitation program in Shanghai, China.The line displayed the incidence rate (per 100 person months) and the area in the figure showed the monthly prevalence of each negative consequence (incarceration, readmission to compulsory treatment and death). There was no death case that happened during this period.

The trajectories and baseline characteristics are displayed in **Figure 3** and **Table 1**, respectively.

Associated Factors of Negative Consequences

When distinct trajectories were identified by GBTM, multinomial logistic regression was used to explore the relationship between one's recovery pattern and baseline characteristics. Regression results are presented in **Table 2**. Having alcohol use history (use more than 15 days per month) was associated with the increased likelihood (OR = 2.74, $p = 0.027$) of being in the late occurrence group relative to the rare occurrence group. Having opioid use history was associated with increased likelihood (OR = 2.35, $p = 0.053$) of being in the early occurrence group relative to the rare occurrence group, although the estimation association was marginally significant. In addition, being female was associated with the decreased likelihood (OR = 0.37, $p = 0.051$) of being in the late occurrence group relative to the rare occurrence group, and the association was also marginally significant.

DISCUSSION

To our knowledge, this is the first study examining recovery patterns among MA-dependent patients after compulsory rehabilitation programs in China. Our findings extended our knowledge of long-term recovery trajectories of MA-dependent patients and associated factors. By using GBTM, we identified three groups among MA-dependent patients: early occurrence group, late occurrence group, and rare occurrence group. Alcohol use history, opioid use history and being female might be associated with patients' recovery trajectories.

We found that baseline alcohol use history was associated with increased likelihood of being in the late occurrence group relative to the rare occurrence group, and baseline opioid use history was associated with increased likelihood of being in the early occurrence group relative to the rare occurrence group. These findings were consistent with previous studies showing that drug use disorders were closely associated with alcohol use (31). In addition, heavy alcohol consumption increased the risk of violent behaviors, and alcohol use accounted for 12–18% of the violence risk related to MA use (32). Violent behaviors might result in incarceration, which is another aspect of NC. Moreover, brain image research of functional links in valuation networks demonstrated that heroin abstinence could influence functional connectivity and resulted in impulsive behaviors (33). A recent animal study showed that the sensitivity to opioids, which involved the mu-opioid receptor (MOP-r) regulated systems, has a negative genetic correlation with MA consumption in mice (34). This indicated that opioid sensitivity and MA intake were genetically associated, and opioid-mediated pathways influence MA use. Previous studies found that in long-term opiate abusers, the function of the MOP-r is altered in response to its ligands (35–37). It is also observed that MA use was a problem in patients in methadone maintenance treatment (38, 39). Furthermore, in patients with severe alcoholism, a neuroadaptation to an alcohol-induced release of endogenous ligands appeared to reduce MOP-r (40). The change of MOP-r might be related to the higher risk of relapse, the main part of

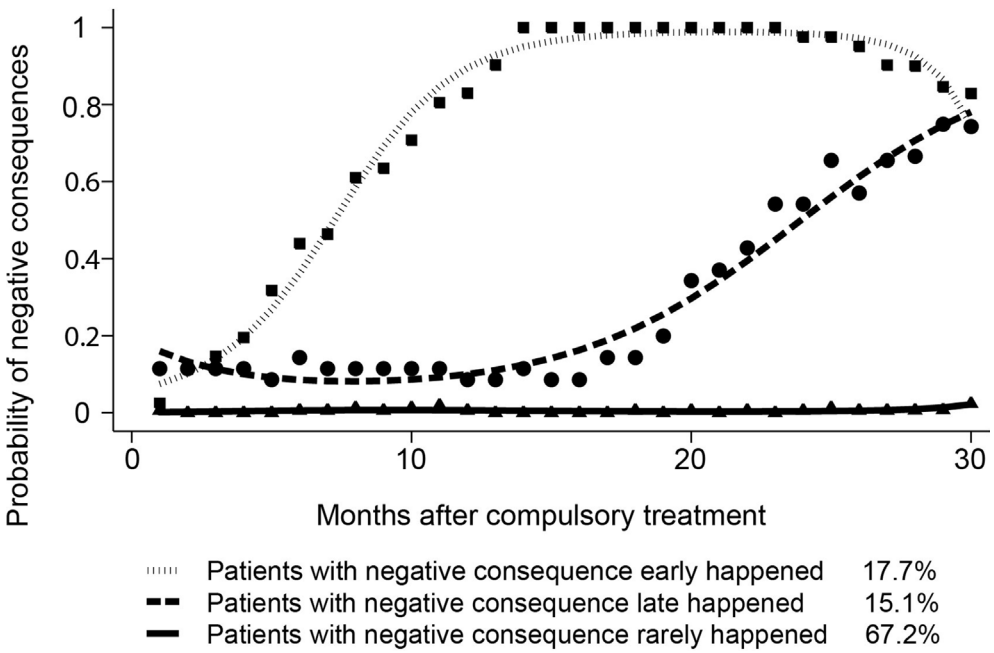

FIGURE 3 | Trajectories as defined by group-based trajectory modeling (GBTM) analysis of recovery status over time.Three-trajectory group-based trajectory modeling was used to fit the recovery data of methamphetamine patients and predict possibility of negative consequences. Negative consequences included incarceration, readmission to compulsory treatment and death.

TABLE 1 | The social demographic and drug use characteristics of the participants with follow-up.

	Total ***n*** **= 232, (100%)**	**Rare occurrence group** ***n*** **= 156, (67.2%)**	**Late occurrence group** ***n*** **= 35, (15.1%)**	**Early occurrence group** ***N*** **= 41, (17.7%)**
Demographic characteristics				
Age, years (mean, std)	35.62, (8.24)	36.21, (8.55)	34.66, (6.71)	34.24, (8.19)
Gender				
Male (*n*, %)	146/227, (64.3%)	92/152, (60.5%)	28/35, (80%)	26/40, (65%)
Female (*n*, %)	81/227, (35.7%)	60/152, (39.5%)	7/35, (20%)	14/40, (35%)
Ethnicity				
Han (*n*, %)	225/231, (97.4%)	150/155, (96.8%)	35/35, (100%)	40/41, (97.6%)
Others (*n*, %)	6/231, (2.6%)	5/155, (3.2%)	0/35, (0%)	1/41, (2.4%)
Employment				
Employed (*n*, %)	117/230, (50.9%)	81/156, (51.9%)	18/34, (52.9%)	18/40, (45%)
Unemployed (*n*, %)	113/230, (49.1%)	75/156, (48.1%)	16/34, (47.1%)	22/40, (55%)
Currently married				
Yes (*n*, %)	88/229, (38.4%)	62/154, (40.3%)	13/34, (38.2%)	13/41, (31.7%)
No (*n*, %)	141/229, (61.6%)	92/154, (59.7%)	21/34, (61.8%)	28/41, (68.3%)
Accommodation				
Live with parents or children (*n*, %)	98/229, (42.8%)	67/153, (43.8%)	18/35, (51.4%)	13/41, (31.7%)
Live alone or with others (*n*, %)	131/229, (57.2%)	86/153, (56.2%)	17/35, (48.6%)	28/41, (68.3%)
Education				
Less than high school (*n*, %)	152/229, (66.4%)	107/153, (69.9%)	19/35, (54.3%)	26/41, (63.4%)
High school (*n*, %)	65/229, (28.4%)	38/153, (24.8%)	15/35, (42.9%)	12/41, (29.3%)
More than high school (*n*, %)	12/229, (5.2%)	8/153, (5.2%)	1/35, (2.9%)	3/41, (7.3%)
Education experience, years (mean, std)	9.48, (2.14)	9.39, (2.08)	9.80, (2.06)	9.51, (2.41)
Drug use history				
Use history, years (mean, std)	2.91, (2.62)	2.85, (2.73)	3.00, (2.54)	3.05, (2.28)
Onset age, years (mean, std)	32.75, (8.75)	33.42, (9.09)	31.66, (7.77)	31.2, (8.15)
30 days frequency, times (mean, std)	13.85, (12.04)	13.31, (11.89)	15.45, (12.09)	14.4, (12.7)
Opioid use history				
Yes (*n*, %)	89/203, (43.8%)	53/133, (39.8%)	15/34, (44.1%)	21/36, (58.3%)
No (*n*, %)	114/203, (56.2%)	80/133, (60.2%)	19/34, (55.9%)	15/36, (41.7%)
Marijuana use history				
Yes (*n*, %)	55/232, (23.7%)	34/156, (21.8%)	9/35, (25.7%)	12/41, (29.3%)
No (*n*, %)	177/232, (76.3%)	122/156, (78.2%)	26/35, (74.3%)	29/41, (70.7%)
Use with partner				
Yes (*n*, %)	45/229, (19.7%)	33/153, (21.6%)	5/35, (14.3%)	7/41, (17.1%)
No (*n*, %)	184/229, (80.3%)	120/153, (78.4%)	30/35, (85.7%)	34/41, (82.9%)
Alcohol use[a]				
Yes (*n*, %)	74/203, (36.5%)	42/133, (31.6%)	16/34, (47.1%)	16/36, (44.4%)
No (*n*, %)	129/203, (63.5%)	91/133, (68.4%)	18/34, (52.9%)	20/36, (55.6%)

[a]*Regularly drink (more than 15 days per month) more than 1 year before compulsory rehabilitation.*

NC. It would be interesting to explore in future research whether what we found in the current study that alcohol and opioid use history predicted the occurrence of NC was related to the severity of MOP-r dysfunction. Our findings also suggested that being female was associated with decreased likelihood of being in the late occurrence group relative to the rare occurrence group. This was consistent with our previous study with heroin-dependent patients, which was found that female patients were less likely to experience negative outcomes than male patients (19).

In our results, when opioid and alcohol use affected the occurrence of NC, social and family factors did not seem to have a critical impact on it. This suggests that neurobiological changes caused by poly-substance use may have a greater impact on long-term rehabilitation. Therefore, the experience of pharmacotherapy in alcohol and opioid dependence could enlighten long-term NC prevention in MA dependence (41, 42), and it might be necessary to address the problem of poly-substance use that shares the similar neurobiological change.

TABLE 2 | Multinomial logistic regression analysis of the three recovery trajectory groups.

	Odds ratio of late occurrence vs. rarely (95% confidence interval)	Odds ratio of early occurrence vs. rarely (95% confidence interval)
Demographic characteristics		
Females (vs. Males)	0.35 (0.12,1.00)	0.72 (0.30,1.74)
Employed (vs. Unemployed)	1.40 (0.58,3.38)	0.81 (0.35,1.86)
Current married (vs. Current unmarried)	0.55 (0.22,1.38)	0.65 (0.27,1.55)
Accommodation[a]	1.48 (0.62,3.53)	0.89 (0.38,2.10)
Drug use history		
Use daily (vs. lower frequency)	0.77 (0.29,2.03)	0.89 (0.36,2.22)
Use year (vs. < 1 year)		
1 year	0.54 (0.13,2.32)	0.28 (0.06,1.26)
2–5 year	0.70 (0.20,2.52)	0.72 (0.23,2.32)
>5 years	1.91 (0.39,9.42)	0.98 (0.20,4.72)
Opioid use history (vs. not)	1.41 (0.59,3.37)	2.31 (0.99,5.40)
Marijuana use history (vs. not)	1.09 (0.38,3.08)	1.46 (0.56,3.81)
Alcohol use[b]	2.74 (1.12,6.73)*	2.30 (0.94,5.64)

[a]*Live with parents or children vs. live alone or with others.*
[b]*Regularly drink more than 1 year vs. occasionally or never drink.*
*$p < 0.05$.

Our study had several limitations. First, although NC might be better than considering relapse or crime separately in assessing recovery trajectory, readmission in NC could cause underestimation of relapse because we could not directly measure patients' relapse. Thus, our outcome of readmission might not be an ideal proxy for relapse, as patients may relapse but were not found by social workers or readmitted to a compulsory rehabilitation center. In addition, we did not have data on patients' mental health, healthcare obtained, and other characteristics that changed with time, which might also impact on patients' recovery trajectory. Furthermore, our results might not be generalized to MA-dependent patients in other areas of China, considering regional variations across China, or those who were not admitted to compulsory rehabilitation programs.

In conclusion, MA-dependent patients presented various recovery patterns after being discharged from compulsory rehabilitation programs in Shanghai, China. When caring for MA-dependent patients, healthcare providers should take patients' alcohol use problem into consideration to prevent the occurrence of NC. Future prevention and early intervention of NC should also consider more about patients with the history of poly-substance use.

DATA AVAILABILITY STATEMENT

The datasets for this study will not be made publicly available because the authors do not have permission to share data.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of name of guidelines, name of committee with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the name of committee.

AUTHOR CONTRIBUTIONS

MZ and HJ designed this study, and all the authors participated in this process. NZ, YZ and ZC collected the data, and HT and DL analyzed the data and drafted the manuscript. All the authors edited the paper.

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SUPPLEMENTARY MATERIAL

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Effects of Naltrexone on Large-Scale Network Interactions in Methamphetamine Use Disorder

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Naltrexone attenuates craving, and the subjective effects of methamphetamine and extended-release naltrexone (XR-NTX) reduces functional connectivity between regions of the striatum and limbic cortex. Naltrexone modulates neural activity at dopaminergic synapses; however, it is unclear whether naltrexone has an effect on large-scale brain networks. Functional networks interact to coordinate behavior, and as substance-use disorders are associated with an imbalance between reward and cognitive control networks, treatment approaches that target interactive brain systems underlying addiction may be a useful adjunct for behavioral therapies. The objective of this study was to examine the effect of XR-NTX on large-scale brain networks and to determine whether changes in network relationships attenuate drug use, craving, and addiction severity. Thirty-nine participants in or seeking treatment for methamphetamine-use disorder were enrolled in a clinical trial of XR-NTX between May 2013 and March 2015 (Clinicaltrials.gov NCT01822132). Functional magnetic resonance imaging (fMRI) and questionnaires were conducted before and after double-blinded randomization to a 4-week injection of XR-NTX or placebo. In the XR-NTX group, methamphetamine use was reduced along with a decrease in the coupling between executive control (ECN) and default mode (DMN) networks. As decoupling of ECN and DMN networks was associated with change in the severity of dependence, the results suggest that XR-NTX may modulate and enhance ECN attentional resources and suppress DMN self-referential and emotional processing. This study identifies the effect of naltrexone on changes in the intrinsic functional coupling of large-scale brain networks and provides a more systematic understanding of how large-scale networks interact to promote behavioral change in methamphetamine-use disorder.

Keywords: naltrexone, resting-state functional magnetic resonance imaging, methamphetamine, striatum, functional connectivity

INTRODUCTION

Although methamphetamine (MA) is a highly addictive psychostimulant causing severe physical, neurological, and emotional disruptions (1), there are no FDA-approved medications for MA-use disorder (2). Psychosocial interventions, such as cognitive behavioral therapy, are the mainstay of treatment and are used to strengthen cognitive control over behaviors that promote drug use (2). The efficacy of behavioral interventions for MA use may be undermined by abnormalities in brain structure and function that are associated with impairments in executive functioning (3, 4) and linked to clinical features of addiction such as craving (5). Pharmacological interventions that alter neural network connectivity in individuals with MA-use disorders may have the potential to improve treatment outcomes.

Naltrexone, a competitive mu-opioid receptor antagonist, attenuates craving and subjective effects of MA in humans (6, 7). Although a 12-week study showed no differences between extended-release naltrexone (XR-NTX) and placebo on overall MA-use behavior (8), the effects of naltrexone on dopaminergic synapses to strengthen cognitive control could be a useful adjunct to behavioral therapy. Naltrexone, through downstream effects mediated by mu-opioid receptor antagonism, inhibits dopamine signaling in limbic regions. Consistent with naltrexone's pharmacologic actions, we recently demonstrate that XR-NTX decreased connectivity between the nucleus accumbens, amygdala, hippocampus, and midbrain (9) using seed-based resting-state functional connectivity. Studies in healthy controls have demonstrated that changes in dopamine signaling affects the overall topography of resting-state networks that extend beyond dopamine terminal regions (10, 11). This study, therefore, examined the impact of XR-NTX on large-scale network interactions that may support behavioral approaches by strengthening cognitive control to abstain from MA use.

Advances in understanding the functional organization of brain systems suggest that a collection of interconnected brain areas work together to form functional networks that interact to coordinate behavior. Core networks include the Default Mode Network (DMN), which is comprised of the posterior cingulate cortex, temporal and medial prefrontal cortices and is associated with self-monitoring function and internal attention; the Executive Control Network (ECN), which includes the dorsolateral prefrontal cortex and posterior parietal cortices and is important for cognitive control; and the Salience Network (SN), which is comprised of the insula, anterior cingulate cortex, amygdala, ventral striatum, dorsomedial thalamus, hypothalamus, and substantia nigra/ventral tegmental area and is responsible for processing motivational stimuli and reward saliency (12). The goal of this study was to determine whether XR-NTX could alter the coupling between the ECN, DMN, and SN and to assess whether individual differences were associated with reductions in MA use and craving. We anticipated that XR-NTX would increase SN-DMN coupling, and this increase would be associated with reductions in MA craving. Prior work has also demonstrated that individuals with MA use disorder have greater coupling between the ECN and DMN than control participants (13). Effective treatments for MA-use disorders may ameliorate abnormalities in network correlations; therefore, we hypothesize that XR-NTX would decrease coupling between the ECN and DMN.

MATERIALS AND METHODS

Participants

Thirty-nine participants were enrolled in a randomized, double-blind, placebo-controlled clinical trial of XR-NTX (Vivitrol, Alkermes). Participants were recruited from community-based treatment programs and primary care clinics in Portland, Oregon, USA, between May 2013 and March 2015 and were included in a previous study examining seed-based resting-state connectivity (9). Inclusion criteria were a DSM-IV diagnosis for methamphetamine dependence, no other substance dependence except tobacco and/or nicotine dependence, no history of psychiatric disorder except depression and/or post-traumatic stress disorder, aspartate transaminase (AST) and alanine transaminase (ALT) < 5 times the upper limit of normal, between the ages of 18 and 55 years, right-handed, English speaking, and free of drugs and alcohol >72 h and no more than 6 months prior to study assessments. Exclusion criteria included opioid use in the last 30 days or opioid dependence in the past 5 years, asensitivity to naltrexone, PLG (polylactide-co-glycolide), carboxymethylcellulose, or any other diluent components, a potential need for opioid analgesics during study period, pregnancy, magnetic resonance imaging (MRI) contraindications, or serious medical illness in the past 30 days.

Study Design

The study was approved by the Oregon Health and Science University and Veterans Affairs Portland Health Care System Joint Institutional Review Board, and all participants provided written informed consent. At baseline, participants underwent resting-state functional MRI and completed survey assessments (Visit 1). Using a double-blind design, participants were randomized to XR-NTX (n = 19) or placebo (n = 20) groups based on the output from a computerized random number generator. To reduce issues with study drug adherence challenges associated with daily-dosed oral naltrexone, both the XR-NTX and placebo conditions involved a single 4-week injection, which was donated by the manufacturer. Survey and brain imaging assessments were repeated 4 weeks after baseline scans (Visit 2).

Neuropsychiatric Assessment

A Mini International Neuropsychiatric Interview (MINI) (14) was conducted to confirm substance dependence diagnoses and psychiatric disorders and the Addiction Severity Index-lite (ASI-lite) (15, 16) was used to assess past 30-day substance use. MA craving was measured with a visual analog scale (VAS) ranging from 0 (no craving) to 100 (most intense craving possible) (17). The Substance Dependence Severity Scale (SDSS), which is sensitive to change in clinical status, was administered to assess the severity of substance use (18).

MRI Imaging Acquisition

Imaging was performed on a 3 Tesla Siemens TIM Trio MRI scanner. A localizer scan was acquired in order to guide slice alignment during anatomical and functional scans. A T_2*-weighted image was acquired using an echo planar imaging scheme (EPI; 24 slices, 4-mm thick, gap width = 1 mm, TR/TE/α = 2,000 ms/38 ms/80°, matrix = 128 × 128, FOV = 240 × 240 mm, 170 volumes, in-plane pixel size of 1.9 mm^2), while subjects stared at a white cross on a black screen for 6 min. One high-resolution T_1-weighted magnetically prepared rapid acquisition gradient echo (MPRAGE; 76 slices, 1-mm thick, TR/TE/TI/α = 2,300 ms/3.4 ms/1,200 ms/12°, FOV = 224 × 256 mm) was acquired for co-registration with functional images and statistical overlay.

Resting-State Processing and Group-Level Analyses

Image analysis was performed using FSL 5.0.2.1 (www.fmrib.ox.ac.uk/fsl). Images were skull-stripped, spatially smoothed [5-mm full width at half maximum (FWHM) Gaussian kernel], and realigned to compensate for motion (19). Automatic Removal of Motion Artifacts (AROMA) was then used to reduce motion-induced signal variation using independent component analysis (ICA) with a classifier that uses two temporal and two spatial features to remove motion artifacts. To identify large-scale resting-state networks across all subjects, cleaned outputs from AROMA underwent ICA analysis with Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC). The number of components generated was not restricted, and 67 group-average independent components were identified. The spatial maps of these independent components were cross correlated with resting-state templates (20) to identify ECN, DMN, and SN networks (**Figure 1**). FSL's dual regression was used to regress the group spatial maps of the ECN (left and right), DMN, and SN networks for each subject to identify subject-specific spatial maps of each network. For each subject and scan, average time courses were extracted for ECN, DMN, and SN networks. Time courses from the ECN, DMN, and SN for each scan were imported into R (version 3.3.2) and used to generate between pairwise Pearson correlations between each network for each subject. Correlation coefficients were converted to z-scores *via* Fisher's transformation.

Statistical Analysis

Student's t-tests and Fisher's exact tests, where appropriate, were used to compare groups in baseline demographic and clinical variables (**Table 1**). Repeated measures ANOVAs were used to examine the effects of XR-NTX on craving and MA use. The main effect of treatment (XR-NTX or Placebo) and time (Visit 1 or Visit 2) and the interaction of treatment and time were examined on each measure separately. To assess changes in large-scale resting-state network correlations, two-way repeated measures ANOVAs on pairwise correlations between the ECN, DMN, and SN were tested for main effects of group (XR-NTX and Placebo), time (Scan 1 and Scan 2), and the interaction of group by time in SPSS 22. Bivariate correlations were conducted to explore the association between changes in network coupling associated with XR-NTX administration and changes in craving, frequency of MA use, and substance dependence severity between Visit 1 and Visit2.

Results

Participant Characteristics

A total of 220 individuals were screened for the study, and 104 were eligible for participation. The most common reasons for exclusion at pre-screening were polysubstance use, abstinence from MA for over 6 months, and MRI contraindications. Of the 104 eligible participants, 52 were randomized (50% of those who were eligible; 23.6% of those screened). Three eligible participants declined randomization. Of those randomized, 39 completed baseline and follow-up assessments that were available for analysis. Reasons for exclusion from analysis of those randomized included scheduling conflicts/no-shows and MRI confounds.

At baseline, groups were well-matched on demographic variables (**Table 1**). Participants did not differ by mean age

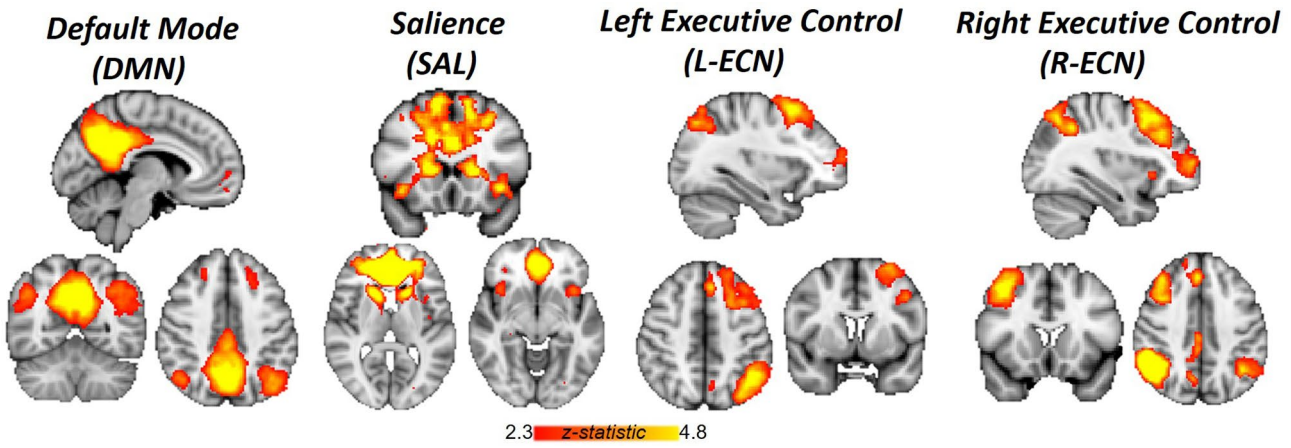

FIGURE 1 | Networks identified by independent component analysis. Spatial maps generated with group ICA and cross-correlated to resting-state template masks include Default Mode Network, Salience Network, and Left and Right Executive Control Network.

TABLE 1 | Participant Characteristics.

	Placebo (n = 20)	NTX (n = 19)	p-value
Age (years) [a]	36.47 ± 10.06	38.68 ± 9.30	0.49
Sex (M/F) [b]	15/5	15/4	0.77
Education	12.63 ± 0.83	12.78 ± 2.13	0.78
Craving			
Baseline	23.84 ± 27.27	32.83 ± 27.69	0.33
Follow-up	18.63 ± 25.16	20.06 ± 25.63	0.87
MA use: Days in the last 30			
Baseline	3.55 ± 6.42	5.05 ± 6.93	0.51
Follow-up	3.87 ± 7.09	1.56 ± 3.45	0.23
Substance Use Severity Scale			
Baseline	5.37 ± 3.76	8.17 ± 4.30	0.04
Follow-up	3.84 ± 4.25	3.42 ± 4.23	0.76
Smoking	17	14	0.34
Number of smokers [b]			
Positive HIV Status [b]	5	6	0.65

[a]*Data shown are means ± Standard Deviations.*
[b]*Data analyzed with Chi-squared test (X^2).*

(Placebo: 36.47 years; XR-NTX: 38.68 years, p = 0.49), sex (Placebo: 75% men; XR-NTX: 79% men, p = 0.772), mean years of education (Placebo: 12.63 years; XR-NTX: 12.78 years, p = 0.78), or smoking status (Placebo: 85%: XR-NTX: 74%, p = 0.34). There were no significant group differences in MA use in the 30 days prior to study enrollment (Placebo: 3.55 days; XR-NTX: 5.05 days, p = 0.444), craving for MA indexed by the VAS (Placebo: 23.84; XR-NTX: 32.83, p = 0.327), or HIV status (XR-NTX: 25%; Placebo group: 32%, p = 0.65) but significant differences in SDSS (Placebo: 5.37; XR-NTX: 8.17, p = 0.04). One HIV-positive subject in each group had no current or past history of taking stable antiretroviral therapy, but all other HIV-positive patients were taking stable antiretroviral therapy prior to and during the study.

Change in Methamphetamine Use, Substance Dependence Severity, and Craving

On average, the number of days in the past 30 days of self-reported MA use decreased from 5.05 to 1.56 in the XR-NTX group but increased in the Placebo group from 3.55 to 3.87 in the Placebo group. The repeated measures ANOVA resulted in a significant time by treatment interaction (p = 0.03), with the XR-NTX group showing greater reductions in MA use compared to the Placebo group. Mean craving scores decreased from 32.83 to 20.07 in the XR-NTX group and from 23.84 to 18.63 in the Placebo group. There were no significant time by treatment interactions on craving and (p = 0.52) or on SDSS (p = 0.13).

Changes in Coupling Between ECN, DMN, and SN

Correlations between networks for each subject and scan are depicted in **Figure 2** for illustrative purposes. In the repeated measures group analyses, a significant interaction of group and time was seen in the correlation between Left ECN and DMN connectivity (p = 0.002, corrected for multiple comparisons) (**Figure 3**), with no significant differences in correlation at Time 1 (p > 0.05) or at Time 2 (p > 0.05). The group by time interaction remained significant (p = 0.01) after controlling for the group difference in SDSS. There were no significant group by time interactions on the connectivity between SN and Left ECN (p = 0.086), SN and Right ECN (p = 0.280), DMN and SN (p = 0.704), DMN and Right ECN (p = 0.898), or Left ECN–Right ECN (p = 0.424).

Relationship between resting-state functional connectivity and clinical outcome measures

As a group by time interaction on Left ECN and DMN correlations was detected, we explored how changes in Left ECN–DMN coupling affect MA use, craving, and substance dependence severity. When examining the relationship between change in MA use and change in network coupling, we found a significant group interaction (**Figure 4**, p = 0.04); where the XR-NTX group showed a positive relationship between change in Left ECN–DMN network coupling and change in MA use, while the Placebo group showed a negative relationship. Similarly, the groups differed in the relationship between Left ECN–DMN network change and substance dependence severity (**Figure 4**, group by connectivity interaction: p = 0.014), where the XR-NTX group showed a positive relationship and the Placebo group showed a negative relationship. Results remained significant after controlling for duration of MA abstinence (p = 0.003), confirming that changes in ECN–DMN coupling was an effect of group and not reductions in MA use. There were no significant interactive effects of group and connectivity on craving (p > 0.05).

DISCUSSION

This study provides novel evidence indicating that XR-NTX modulates connectivity between large-scale brain networks in individuals with MA dependence. Specifically, XR-NTX reduced coupling between the Left ECN and DMN, which was related to a reduction in MA use and severity of substance dependence. These results are consistent with the role of the ECN in directing attention toward relevant stimuli, flexibly responding to shifting

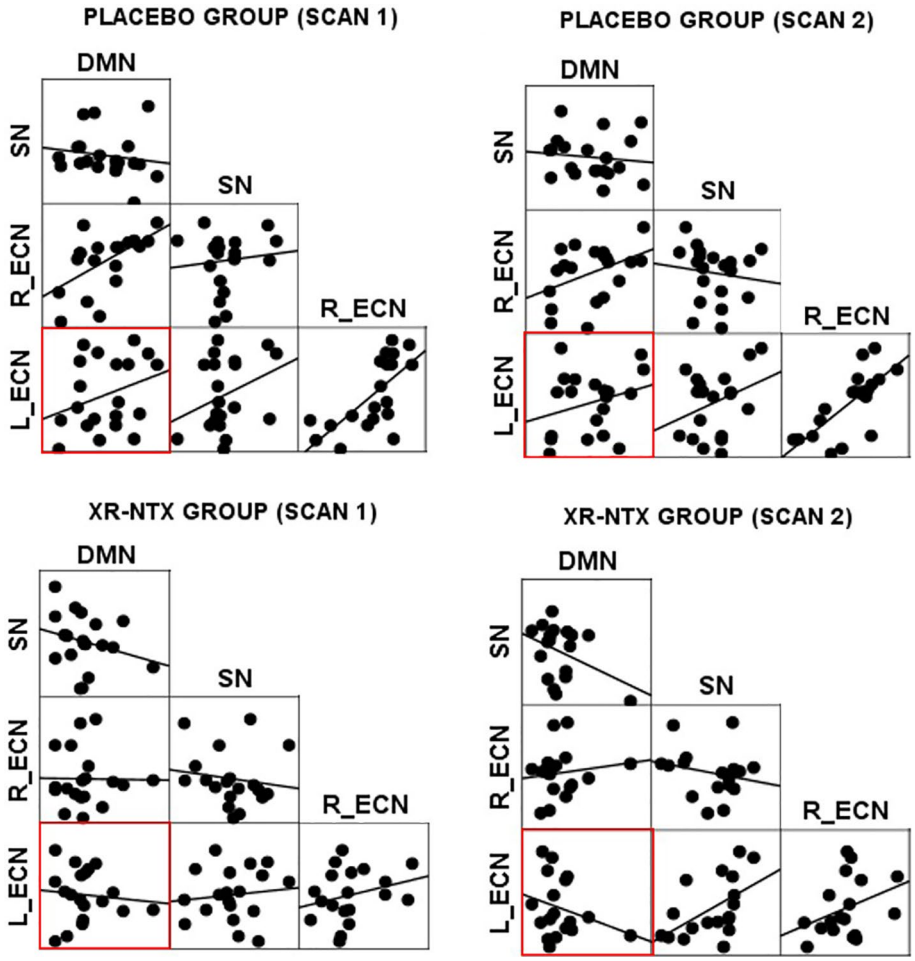

FIGURE 2 | Network correlations. Scatter plots depict the relationships between networks in each group for each scan.

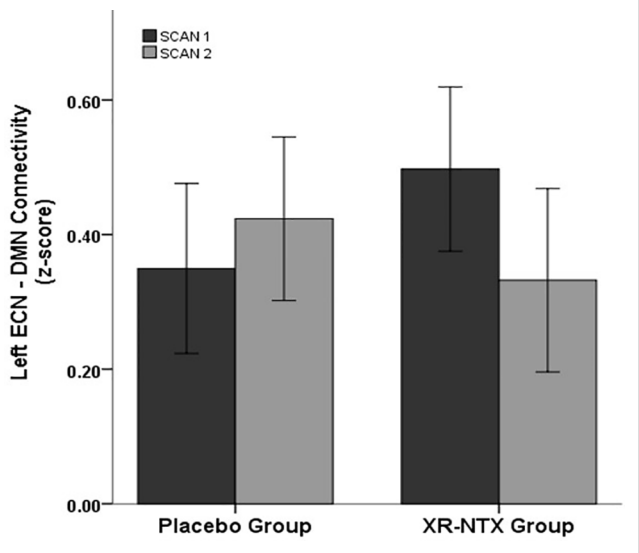

FIGURE 3 | Change in network correlations. Left ECN–DMN correlation. The XR-NTX group show significant reductions between Scan 1 and Scan 2 in Left ECN–DMN coupling compared to the placebo group ($p = 0.002$).

conditions and executing goal-directed behavior (12) and the DMN in processing internal states and episodic memory (21). Given that the activity of ECN and DMN are often anti-correlated and the decoupling from the DMN enables the ECN to allocate attentional resources and to flexibly switch attention in the face of changing cognitive demand, XR-NTX-induced decreases in network coupling may enhance network dynamics to strengthen cognitive resources to limit drug use. In a recent study, baseline DMN connectivity was a predictive factor for treatment outcome in obsessive–compulsive disorder, suggesting that brain connectivity patterns may reflect plasticity of networks that facilitate cognitive and behavioral change (22). As cognitive behavioral therapy requires cognitive flexibility to regulate craving and withdrawal, XR-NTX may be a useful adjunct to treatment to induce network changes that enable plasticity of executive control networks to function without constraint of self-referential DMN activity during abstinence.

Our findings provide support that medication-induced alterations in dopamine signaling impact resting-state connectivity between the ECN and DMN in individuals with a MA dependence. In particular, one study found that MA-dependent individuals with and without MA-induced

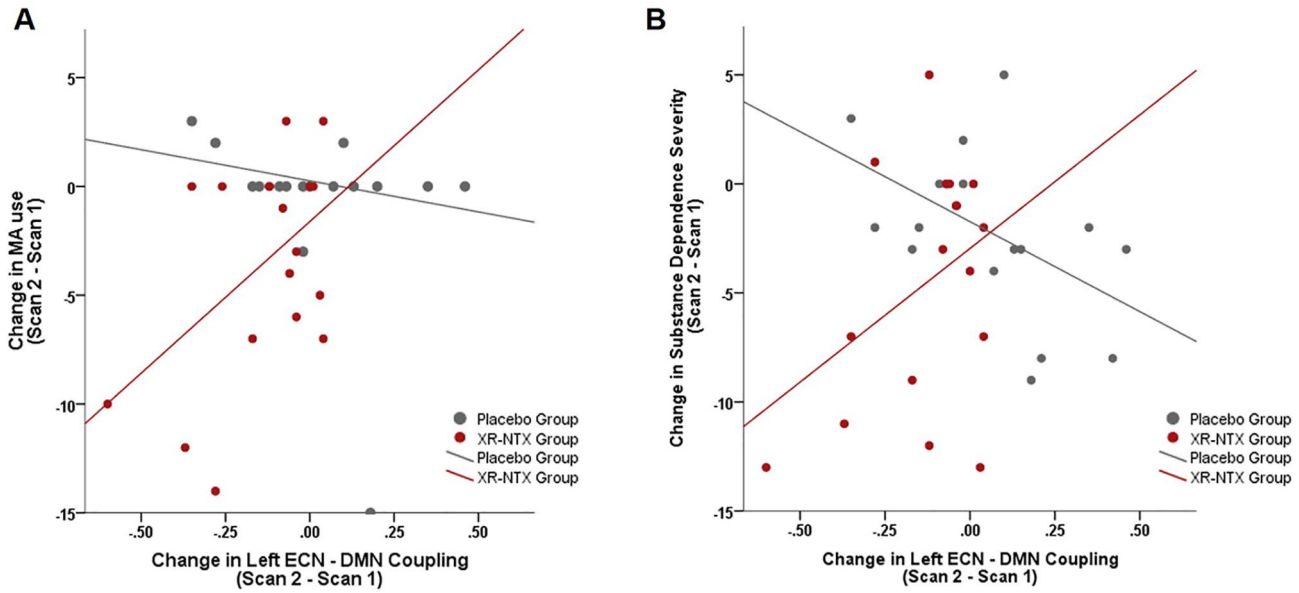

FIGURE 4 | Change in Left ECN–DMN correlations is associated with change in MA use and Substance Dependence Severity. **(A)** In the XR-NTX group, individuals with greater reductions in network correlations exhibit greater reductions in MA use between Scan 1 and Scan 2 with opposite effects in the Placebo Group ($p = 0.019$). **(B)** In the XR-NTX group, individuals with greater reductions in network correlations exhibit greater reductions in Substance Dependence Severity scores between Scan 1 and Scan 2 with opposite effects in the Placebo Group ($p = 0.014$).

psychosis had greater ECN–DMN connectivity than control participants (13). In the group of individuals with MA-induced psychosis, lower ECN-DMN connectivity was associated with longer exposure to antipsychotic medications such as the dopamine D2 receptor antagonist, haloperidol. In addition, this study showed that the duration of antipsychotic medication and ECN–DMN connectivity remained significant when controlling for duration of abstinence from MA, suggesting that changes in ECN–DMN connectivity are related to the medication as opposed to reductions in MA use, which is consistent with our findings. Since both antipsychotic medication and naltrexone impact multiple neurotransmitter systems, studies combining resting-state functional connectivity with positron emission tomography to assess neurotransmitter release or receptor density will be useful for uncovering the molecular underpinning of ECN–DMN interactions.

The association between XR-NTX-induced changes in ECN–DMN coupling, MA use, and substance dependence severity suggest that interventions that successfully alter ECN–DMN connectivity may be especially useful for treating MA-use disorders. In our sample, individuals with smaller changes in ECN–DMN correlations after XR-NTX used MA more frequently, suggesting that for these individuals, identifying other medications that have a greater impact on ECN–DMN coupling may improve treatment outcomes. For example, modafinil has been shown to increase negative coupling between the ECN and DMN and improve cognitive performance in individuals with alcohol-use disorder (23). Although some studies suggest that modafinil is not effective for decreasing MA use (24), these findings may be attributable to heterogeneous medication responses at the individual level.

Studies have shown a positive effect of naltrexone in reducing MA craving (6, 7); however, a recent study showed no differences in MA use after 12 weeks of placebo or XR-NTX (8). Mixed results could be attributed to the positive HIV status in the majority of subjects in the latter study, or it is possible that the effects of naltrexone on MA abstinence are time dependent. In the study where MA use did not differ after 12 weeks between the placebo and XR-NTX groups, the XR-NTX group did show a substantial increase in the proportion of participants abstaining from MA in weeks 3, 4, and 5 with no change in the placebo group. As our results show dynamic change in network interactions during this short window, it is possible that this network change may facilitate early MA abstinence. It is unclear whether groups in our study would have converged in MA use or network dynamics after 12 weeks of treatment, but perhaps early network changes coupled with other treatment approaches or cognitive behavioral therapy can help strengthen cognitive control to limit MA use.

Our findings should be interpreted with consideration of the following potential limitations. Although the difference between placebo and XR-NTX on changes in ECN–DMN coupling remained significant after controlling for frequency of MA use, more research is needed to determine whether changes in ECN–DMN coupling precede and causally impact MA use. Furthermore, our sample was relatively small, precluding our ability to examine whether there were sex by treatment interactions on large-scale network dynamics or clinical variables. In addition, future studies could take a data-driven approach to identify spatially constrained regions that drive alterations in large-scale network interactions. Last, although the placebo and XR-NTX groups were matched for cigarette

use, smoking has been linked to abnormalities in large-scale network dynamics (25). More research is needed to determine how XR-NTX impacts ECN–DMN coupling in individuals with MA-use disorders who do not smoke cigarettes; however, since the vast majority of individuals with MA-use disorder also smoke cigarettes (26), the design of our study may have greater generalizability.

CONCLUSION

This study provides new evidence of the effect of naltrexone on large-scale brain network dynamics. As the independence of the ECN from other network activity is thought to enable flexible resource allocation during high cognitive demand, the XR-NTX-induced reduction in network coupling between ECN and DMN may facilitate decreases in MA use. Network modifications can facilitate cognitive and behavioral control; however, substance-use disorders are accompanied by a number of psychosocial factors that need to be addressed to maintain recovery. Although XR-NTX-induced changes in network dynamics can support behavioral changes, it is likely that a combination of approaches that target neural function and cognitive behavioral changes may provide the most therapeutic benefit. This study provides new information on how network changes can affect MA dependence and use. Future studies are required to understand whether XR-NTX-induced brain changes coupled with behavioral therapy would enhance recovery. Conducting clinical trials with cross-over designs to examine the extent to which various medications can impact relevant biomarkers such as ECN–DMN coupling that facilitate behavioral therapy may be useful for tailored treatments that consider an individual's unique pharmacological response.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by OHSU IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PTK and WH designed and implemented the study. LD and HM managed and oversaw the study implementation. MK conducted the analysis and drafted the manuscript. MK and AM contributed to data interpretation. All authors took part in the revision of the manuscript and approved the article.

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Methamphetamine Users Show No Behavioral Deficits in Response Selection After Protracted Abstinence

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Introduction: Chronic recreational methamphetamine use causes dopaminergic neurotoxicity, which has been linked to impairments in executive functioning. Within this functional domain, response selection and the resolution of associated conflicts have repeatedly been demonstrated to be strongly modulated by dopamine. Yet, it has never been investigated whether chronic methamphetamine use leads to general impairments in response selection (i.e., irrespective of consumption-associated behavior) after substance use is discontinued.

Materials and Methods: We tested n = 24 abstinent methamphetamine users (on average 2.7 years of abstinence) and n = 24 individually matched controls in a cross-sectional design with a flanker task.

Results: Compared to healthy controls, former methamphetamine consumers had significantly slower reaction times, but did not show differences in the size of the flanker or Gratton effect, or post-error slowing. Complementary Bayesian analyses further substantiated this lack of effects despite prior consumption for an average of 7.2 years.

Discussion: The ability to select a correct response from a subset of conflicting alternatives, as well as the selective attention required for this seem to be largely preserved in case of prolonged abstinence. Likewise, the ability to take previous contextual information into account during response selection and to process errors seem to be largely preserved as well. Complementing previously published finding of worse inhibition/interference control in abstinent consumers, our results suggest that not all executive domains are (equally) impaired by methamphetamine, possibly because different cognitive processes require different levels of dopamine activity.

Keywords: dopamine, error processing, flanker effect, Gratton effect, methamphetamine abstinence, response selection

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INTRODUCTION

Amphetamines are the second most commonly used illicit drugs worldwide and out of all amphetamines, methamphetamine is considered to represent an especially large threat to global health (1). Low to moderate oral doses of methamphetamines actually improve cognitive functioning and lead to various mental and physical effects including a positive mood, euphoria, and reduced fatigue (2). In case of repeated consumption, consumers experience an attenuationof these pleasant (acute) effects due to a

development of tolerance, and rapidly become dependent (3–7). Repeated administration of large doses, as usually observed in substance use disorder, are associated with multiple deleterious medical consequences including psychosis, cardiovascular problems, nutritional deficiencies, sleep deprivation, and decreased cognitive functioning (e.g. 2, 8, 9–11).

These effects have been associated with acute increases in monoaminergic signaling and neurotoxic effects of the drug on the dopamine system (12–14). There is strong evidence that methamphetamine increases the release of monoamines *via* uptake transporters (2, 15), which leads to enhanced presynaptic release and heightened postsynaptic receptor binding (16, 17, 14). Prolonged use however results in the opposite, i.e., substantial reductions in presynaptic monoamine transporters and postsynaptic monoamine receptors, which effectively downregulate the dopaminergic system (18–20). Importantly, clinical markers of this pathology (like reduced DAT binding) have been shown to likely take more than a year to recover (21, 20), which suggests cognitive deficits that are associated with this dopaminergic dysfunction should also take at least a year, if not more, to recover.

In line with this, previous studies have suggested that dopamine-associated cognitive deficits may extend well into abstinence. In early stages of abstinence, deficits are comparable to those seen in currently abusing individuals across different domains of executive functioning. This includes cognitive flexibility, working memory and, perhaps to a greater extent, inhibitory control, as shown by deficits in the Wisconsin Card Sorting Test 22, 23), Digit Span Test (24, 25), and Stroop Task (26–28). These functions are pivotal for controlling substance intake (29) as well as for driving behavioral changes in the face of negative consequences (30). Yet still, it has remained rather unclear whether abstinent methamphetamine users also show behavioral differences in response selection that extend beyond consumption-associated behavior. This question is of great functional relevance, as the ability to select a correct response among several competing response alternatives and to resolve conflicts that arise between such options is a key prerequisite to goal-directed behavior (31). It has previously been demonstrated that the mental representation of behavioral goals/mental task sets depends on the input/output function of prefrontal cells, which is effectively modulated by dopamine (32) and plays an important functional role for response selection (33). As dopamine improves gain control mechanisms by amplifying the brain's ability to efficiently process input signals and reduce neuronal noise (34, 35), the dopamine deficiency reported in former methamphetamine users may render them unable to efficiently select responses and resolve response conflicts, or selectively attend to task-relevant information. Yet, research on potential response selection deficits in former methamphetamine users is still scarce. It has however been shown that methamphetamine seems to impair attentional processing (36, 26), and that cocaine users show functional deficits in error processing (37) which qualitatively resemble those of Parkinson's patients (38) and Huntington's patients (39). Furthermore, there is evidence that functional changes in dopaminergic signaling modulate response selection in different versions of the flanker tasks (40–42).

For this reason, we used a version of the Eriksen flanker task (43–45) to assess potential differences in response selection, attention, and error processing between former abstinent methamphetamine users and matched drug-naïve controls. The paradigm allows to investigate response conflicts and attention with the help of the flanker effect, as well as "carry-over" effects of previous contextual information with the help of the Gratton effect. While the flanker effect is characterized by better performance in trials with congruent flanker stimuli (as compared to incongruent trials, see 45), the Gratton effect is characterized by an interference effect of conflicts in the previous (n-1) trial on the current trial (n): Typically, the flanker congruency effect in the current trial (n) is smaller in case of an incongruent previous (n–1) trial (as compared to a congruent previous/n-1 trial) (46, 47). Additionally, the task allows to investigate error processing with the help of the post-error slowing (PES) measure, which has also been shown to be modulated by dopamine (48–52). Increases in dopamine signaling seem to improve response selection/decrease flanker effects (40, 41), while decreases in dopaminergic signaling likely impair response selection. In line with this, it has been suggested that patients with Parkinson's disease, who have a strong dopamine deficit, seem to show larger flanker effects under speed stress (53). Moreover, the Gratton effect was demonstrated to be modulated by dopamine, as shown by eye blinks as putative markers for dopamine (54). In line with this, it has been reported that patients with Parkinson's disease do not show the Gratton effect (55). We hence hypothesized that the supposedly dopamine-deficient abstinent methamphetamine users might not only show general control deficits but might also show larger flanker and Gratton effects, as compared to drug-naïve controls. Potential differences in post-error slowing were analyzed in an exploratory fashion.

Last but not least, it should be noted that several studies have shown that the downregulation of the dopamine system improves with protracted abstinence from methamphetamine (20, 56). While these studies have demonstrated remarkable improvement/normalization from <6 months to 12 to 17 months of abstinence, it has been reported that residual deficits could still be observed after 12 to 17 months of abstinence (20, 56). We hence decided to not limit our inclusion criteria to a certain abstinence duration. In this context, it should be noted that even after prolonged abstinence of more than 18 months on average, former methamphetamine consumers may still show deficits in inhibitory control (as reflected by a Stroop task) and in beneficial disengagement of working memory-associated control functions (assessed in a meta-control paradigm) (57).

In short, the main objective of the current study was to investigate whether former methamphetamine users show deficits in response selection, selective attention, or error processing during prolonged abstinence. For this purpose, we applied the Eriksen flanker task to a self-reporting sample of abstinent methamphetamine users and drug-naïve controls, who had been individually matched for sex, age, and education. We hypothesized to find larger flanker and Gratton effects in former methamphetamine users due to the dopaminergic toxicity of the drug.

METHODS

Sample

A group of n = 32 adult former/abstinent methamphetamine consumers (mean age 29.5; SD 5.04; range 20 to 38 years; 11 females) took part in this study. There were several inclusion criteria: All participants should have consumed methamphetamine at least three times a week for at least six consecutive months of their life and have experienced both craving and withdrawal symptoms during this time. Participants should consider themselves as former drug addicts and methamphetamine should be the main substance of addiction. All participants should be abstinent from methamphetamine, amphetamine, or other illicit drugs for at least two weeks prior to their first appointment, and should have started abstinence on their own or with the help of a medical care program (i.e. not for the purpose of this study). Participants should report no psychological or pharmacological treatment for coping with addiction or withdrawal at the time of data collection. However, past psychological treatment/counseling was not assessed. An experienced psychologist confirmed the ICD10 F15.2 diagnosis of methamphetamine dependence with current abstinence on the first study appointment. Moreover, participants had to be free from (diagnosed) psychiatric disorders or neurological diseases before they started consuming methamphetamine. Inclusion criteria concerning current mental health or additionally consumed substances during methamphetamine use were less strict, as long as methamphetamine was clearly the main substance of abuse and an experienced psychologist expected only minor or no task performance impairments due to psychiatric symptoms. While this certainly increased the variance within the sample, it also provides a more realistic picture of cognitive effects in former consumers.

We further recruited n = 32 healthy adults as a drug-naïve control group (mean age 29.3; SD 5.66; range 18 to 39 years; 11 females), which had been individually matched to an assigned former consumer with respect to sex, age (max ± 2.5 years) and education (a maximal difference of one educational or vocational degree was tolerated). Control participants reported to have no psychiatric, neurologic, or chronic diseases, no lifetime experience with any kind of illicit substance (e.g. methamphetamine, amphetamine, speed, MDMA, methylphenidate, cocaine etc.) and never have received a diagnosis of drug addiction or substance use disorder.

All participants had normal or corrected-to-normal vision. The study would only be conducted when abstinence from illicit drugs was confirmed by negative urine drug screenings using "nal von minden Drug-Screen" tests (nal von minden GmbH, Regensburg, Germany) for amphetamines, methamphetamine, morphine, and THC. Moreover, the participants had to present with a BAC of 0.00 ‰, as assessed with the help of the "Alcotest 3000" breath analyzer following the instructions of the manufacturer (Drägerwerk, Lübeck, Germany), and showed no obvious signs of withdrawal at all study appointments. Any participants who failed to present entirely sober upon any given study appointment would have been excluded from study participation.

After data collection, we had to exclude n = 8 former methamphetamine consumers for the following reasons: One participant reported a traumatic brain injury during childhood, one complained about impaired vision, two provided incoherent information about their addiction and consumption history and/or did not sufficiently meet the diagnostic criteria for (former) dependence, so that we could not assume previous addiction with sufficient certainty. Four more participants had to be excluded because they failed to perform the task above chance level and we could not determine the origin of these issues with certainty when analyzing the data (i.e., retrospectively determine whether these participants failed to understand the task instructions, or whether they failed to comply with them for various possible reasons). As methamphetamine users and controls had been matched individually, we also excluded all drug-naïve controls who had been matched to an excluded consumer. Each participant gave written informed consent and was reimbursed with 50€ for taking part in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics commission of the Medical Faculty of the TU Dresden.

First Study Appointment: Interview, Questionnaires, and Neuropsychological Tests

During the first of two study appointments, we assessed sociodemographic data, (illicit) substance consumption, potential comorbid psychiatric disorders, and executive functioning with the help of several questionnaires, structured interviews, and paper-pencil tests.

First, an experienced neuropsychologist assessed whether several psychiatric disorders such as depression or psychotic episodes were likely to be present in any of the participants with the help of the M.I.N.I. International Neuropsychiatric Interview (58). Afterwards, participants were asked to fill in Beck's depression inventory (BDI; 59) to assess potential depression symptoms which might interfere with cognitive performance. Subsequently, the subjects had to perform neuropsychological tests to assess overall cognitive functioning: A verbal version of the Stroop task (60) was conducted to measure inhibition and interference control. The trail-making test (TMT) (61) was used to measure cognitive flexibility and task set switching. To assess short-term memory and working memory in the verbal and spatial domain, the digit span test from the WAIS-IV test battery (62; 63) and the Corsi block span test (64; 65) were conducted. To collect sociodemographic and health-related data, participants had to fill in customized questionnaires. Furthermore, the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) (WHO ASSIST Working 66) was conducted with each participant to assess lifetime prevalence for common drugs of abuse and their use within the last three months preceding the appointment. To check for any inconsistencies or contradictions concerning addiction and abstinence, experienced psychologists discussed the individual addiction history with each of the self-reported abstinent addicts in the methamphetamine group.

Second Study Appointment: Experimental Paradigm

A standard flanker task was used (43, 44) to investigate response conflicts and carryover effects of previous contextual information (see **Figure 1**). Participants were seated at a 57 cm distance from a 17-inch CRT monitor and were asked to respond using a QWERTZ keyboard. We used Presentation software (Version 17.1 by Neurobehavioral Systems, Inc.) to present the stimuli and record behavioral responses. Before the start of the paradigm, subjects practiced the task until both the participant and the experimenter were confident that the task could be performed as instructed. Participants were asked to rest their index fingers on the response buttons (right and left Ctrl buttons) and react to the target as quickly and accurately as possible.

The target stimulus was a white arrowhead that was displayed in the center of the screen on a black background and either pointed to the left or the right. The target was flanked by two vertically aligned arrowheads, that either pointed in the same direction as the target (congruent) or in the opposite direction (incongruent). These flanker stimuli preceded the target by 200 ms so that the stimulus-onset asynchrony (SOA) was 200 ms. The target and flanker stimuli were then presented for 300 ms and switched off simultaneously. The response-stimulus interval between the first response and the onset of the following trial was jittered between 900 and 1,300 ms. To further increase task difficulty and given that time pressure might be required to see behavioral effects of dopamine deficiency (53), time pressure was administered by asking the participants to respond within 450 ms. In trials where the reaction time exceeded this deadline, an auditory warning stimulus (1000 Hz, 60 dB SPL) was given after this time interval. The subjects had to perform four blocks of 120 trials each. Of these 480 trials, 67% were congruent, and 33% were incongruent trials.

Statistics

Separate mixed effects ANOVAs were performed to analyze the behavioral data. All analyses used current trial (congruent vs. incongruent) as within-subject factor and consumption group (meth vs. control) as between-subject factor. Accuracy and hit RT analyses also used previous (n-1) trial (congruent vs. incongruent) as within-subject factor. PES did not use previous trial, as we did not have enough incorrect responses to reliably analyze this factor in that measure. To investigate the effects of abstinence duration, we additionally ran separate analyses in the meth consumption group only (i.e., when excluding all controls) using the between-subject factor abstinence subgroup (short vs. long abstinence). The degrees of freedom were adjusted using Greenhouse-Geisser correction, and results were Bonferroni-corrected, whenever necessary.

Potential group differences in scores of neuropsychological tests and questionnaires were analyzed with the help of independent samples *t*-tests whenever the scores were normally distributed, as assessed with KS tests. If this criterion was not met, Mann-Whitney *U* tests were used instead. Please note that we did not apply Bonferroni corrections because these tests were only exploratory and not used to answer the main research question of this study.

For all descriptive statistics, the mean and the standard error of the mean (SEM) are given as a measure of variability.

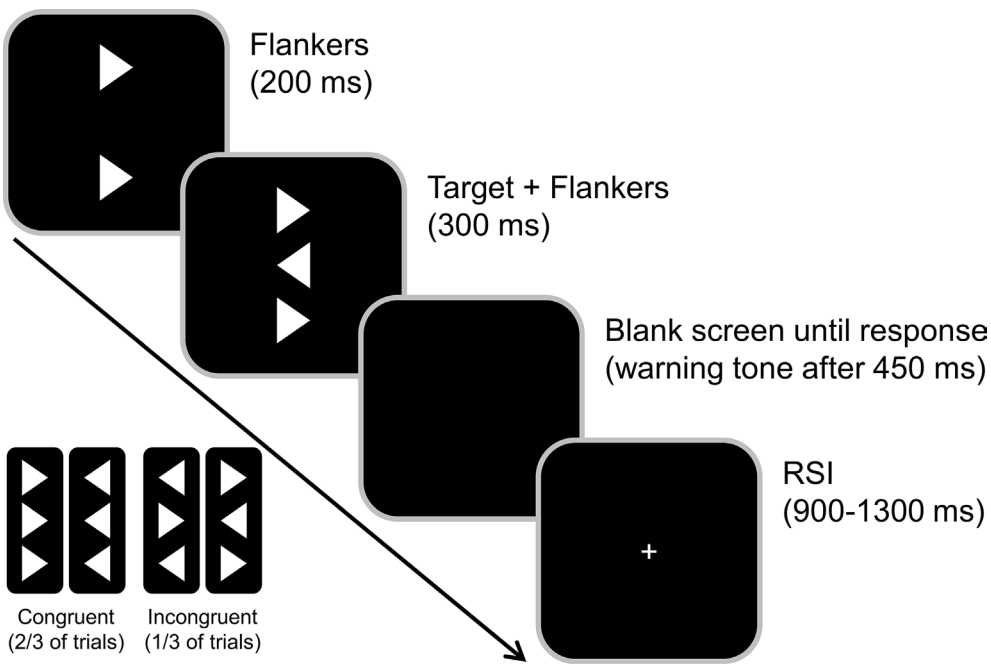

FIGURE 1 | Illustration of the flanker task. The congruent and incongruent flanker arrowhead appeared 200 ms before the target onset (middle arrowhead). Participants were asked to indicate the target direction by pressing the Ctrl button on the respective side of a standard keyboard. The response-stimulus interval (RSI) randomly varied between 900 and 1300 ms.

RESULTS

Sample Description of Former Methamphetamine Consumers

The n = 24 included abstinent methamphetamine consumers started consuming methamphetamine at the mean age of 18.4 years (± 3.9; range 13 to 30) and consumed it for 86.2 months (± 47.8; range 12 to 216), i.e. approximately seven years on average. Out of those 86.2 months, they recreationally used methamphetamine (as defined by irregular use, a subjective lack of withdrawal, craving, or negative social or occupational consequences, as well as the absence of drug-related crimes) for an average of 25.1 months (± 18.3; range 0 to 60) and reported having been subjectively addicted (as defined by regular use, the subjective presence of withdrawal and/or craving and negative social or occupational consequences) for an average of 59.0 months (± 36.1; range, 6 to 144). It should, however, be noted that all of this information was assessed retrospectively and may therefore not always accurately depict past events. The mean abstinence duration was 31.9 months (± 30.7; range 1.5 to 120). We also performed a median split of the methamphetamine group, thus forming a short and long abstinence subgroup to investigate the effects of abstinence duration. As each subgroup, however, only contained only n = 12 subjects and does therefore not have enough statistical power to allow for strong conclusions (67), we only provide these results in the **Supplementary Material**. Of note, this study's sample has previously been used to investigate meta-control and disengagement of control whenever automaticity would be most beneficial for behavioral performance in a working memory-modulated context (57). In that previous study, the data obtained from the assessed questionnaires and neuropsychological paper-pencil tests has already been published (57). But while there is a great overlap between the two samples, they still differed with respect to which subjects were excluded from the sample based on task performance. As a consequence, the results obtained in this sample are similar, but not identical to the previously published data. Hence, all of the information assessed in these tests can also be found in the **Supplemental Material**.

Behavioral Results

The behavioral data of the flanker task is illustrated in **Figure 2**. The analysis of accuracy (percentage of hits) revealed a main effect of previous trial [$F(1,46) = 146.70$, $p < .001$, =761]: Participants responded less accurately when the previous trial was incongruent (61.22% ± 2.58) than when the previous trial was congruent (75.87% ± 1.53). Moreover, there was a significant main effect of current trial [$F(1,46) = 159.65$, $p < .001$, $\eta_p^2 = 776$], with a higher accuracy in congruent (78.37% ± 1.43) than in incongruent current trials (58.71% ± 2.72). Additionally, there was an interaction of previous trial and current trial [$F(1,46) = 215.34$, $p < .001$, $\eta_p^2 = 824$]. Post-hoc t-tests revealed that the flanker effect (i.e. congruent minus incongruent current trial) was significantly smaller when the previous trial had been incongruent (1.94% ± 1.38), as compared to when the previous trial had been congruent (37.38% ± 2.40) [$t(47) = -14.53$; $p < .001$]. All other main effects and interactions, including those of consumption group, were not significant (all $F \leq 1.971$; $p \geq .167$).

With respect to response times (RTs), the repeated measures ANOVA revealed a main effect of consumption group [$F(1,46) = 5.11$, $p = .028$, $\eta_p^2 = 100$], indicating that RTs were longer in the meth group (369 ms ± 5) than in the control group (351 ms ± 5). Given the recent debate about the need for larger sample sizes in psychology (67), we additionally ran post-hoc power analyses using G-power software (http://www.gpower.hhu.de/) (68). These analyses informed us that the sample yielded a power of 77% (at α = 5% when entering the obtained effect size [f = 0.33] and item inter-correlation [r = 0.606]). There was also a main effect of previous trial [$F(1,46) = 43.33$, $p < .001$, $\eta_p^2 = 485$], showing faster RTs when the previous trial was congruent (354 ms ± 4), than when the previous trial was incongruent (366 ms ± 4). In addition, there was a main effect of current trial [$F(1,46) = 387.75$, $p < .001$, $\eta_p^2 = 894$], revealing faster RTs when the current trial was congruent (316 ms ± 4) than when the current trial was incongruent (403 ms ± 4). Furthermore, an interaction of previous trial and current trial was obtained [$F(1,46) = 118.88$, $p < .001$, $\eta_p^2 = 721$]. Post-hoc t-tests showed a significantly larger flanker effect (i.e. incongruent minus congruent current trial) in case of a congruent previous trial (115 ms ± 4) than in case of an incongruent previous trial (58 ms ± 5) [$t(47) = -11.01$; $p < .001$]. All other main effects and interactions of the RT analyses, including consumption group, were not significant (all $F \leq 4.021$; $p \geq .051$).

For the PES, there was a main effect of current trial [$F(1,46) = 6.56$, $p < .014$, $\eta_p^2 = 125$], with a higher PES in congruent (26.6 ms ± 3.2) than in incongruent trials (13.6 ms ± 5.2). All other main effects and interactions, including those of consumption group, were not significant (all $F \leq 1.57$; $p \geq .216$).

Non-significant results obtained with regular null hypothesis statistical testing are hard to interpret and should therefore be treated with caution. To substantiate the assumption that the consumption groups did indeed not differ in the assessed task measures, we conducted additional Bayesian analyses as suggested by Wagenmakers (69) using the template by Masson (70). These analyses require a transformation of sum-of-squares values generated by the standard analysis of variance. This approach generates a graded level of evidence indicating which model (e.g., effect absent versus effect present) is more strongly supported by the data. This analysis yields the value of $pBIC(H_0|D)$, which is the probability of the null hypothesis being true, given the obtained data. Values below .5 are in favor of the alternative hypothesis (i.e., indicate that the alternative hypothesis is more likely to be true than the null hypothesis). Values between .5 and .75 are interpreted as weak evidence, values between .75 and 95 are interpreted as positive evidence, values between .95 and .99 are interpreted as strong evidence, and values above .99 are interpreted as very strong evidence in favor of the null hypothesis (71). The results obtained in our Bayesian analysis of consumption group effects are summarized in **Table 1**.

Most of these results provide greater evidence, and most often even positive evidence for the null hypothesis (i.e. no differences between consumption groups) and thus the rejection of the alternative hypotheses (i.e., differences between consumption

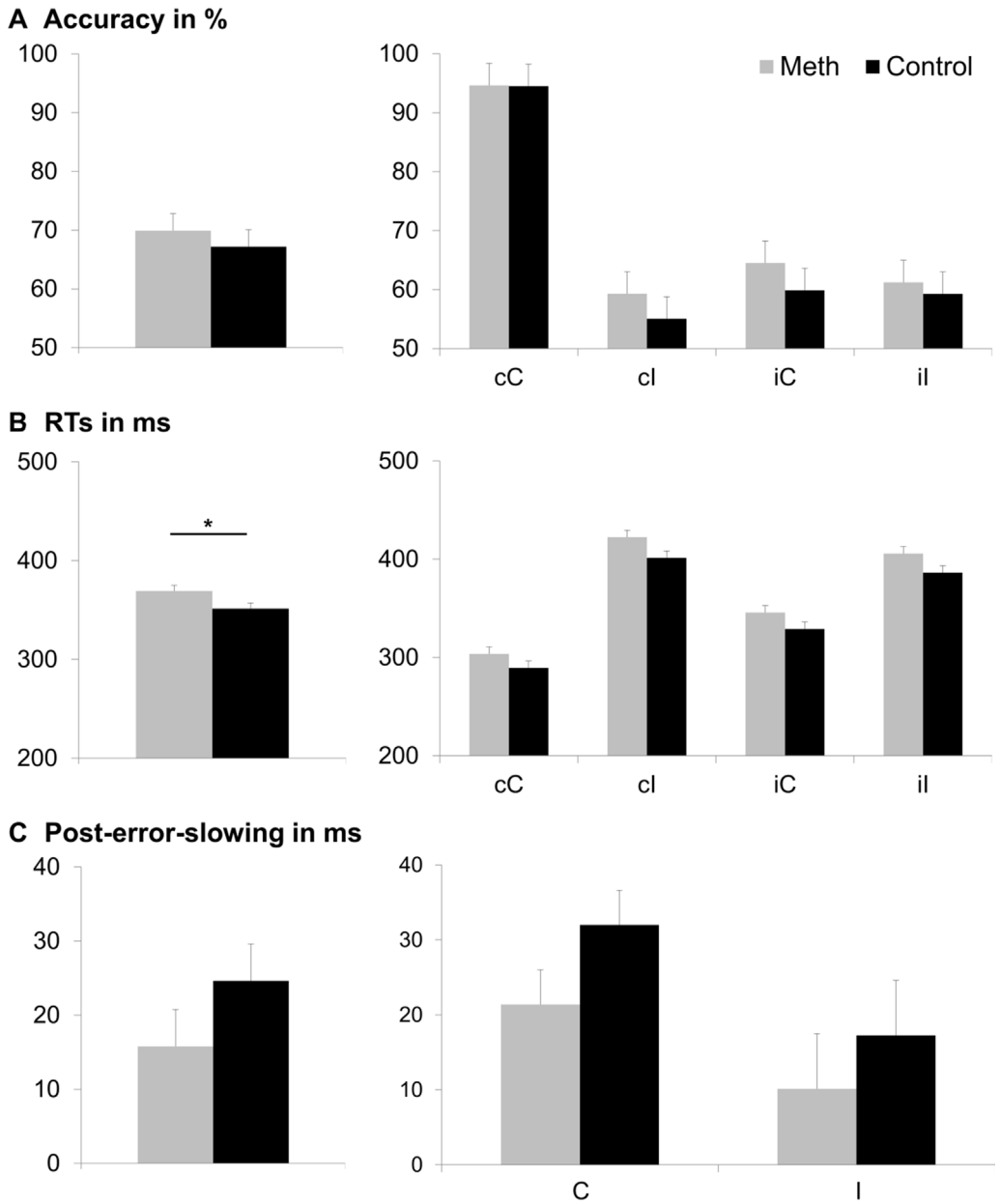

FIGURE 2 | Behavioral results. Part **(A)** displays accuracy (percentage of correct responses), part **(B)** displays hit reaction times (RTs in ms), and part **(C)** displays post-error-slowing (PES in ms). The main effects of consumption group (Meth vs. Control) are displayed in the left column. The group difference was only significant for hit RTs ($p \leq .05$; denoted with an asterisk), but not for accuracy or PES. For accuracy and hit RTs, each combination of previous trial (first letter: c = congruent; i = incongruent) and current trial (second letter: C = congruent; I = incongruent) is depicted separately in the middle and right columns. For PES, we only assessed the effect of the current trial (C = congruent; I = incongruent). Consumption group (Meth vs. Control), did not significantly interact with any of these factors. Error bars show the standard error of the mean (SEM) as a measure of variability.

groups) for all non-significant main and almost all non-significant interaction effects of the consumption group factor.

DISCUSSION

Chronic recreational methamphetamine use has repeatedly been suggested to cause impairments in executive functioning *via* dopaminergic neurotoxicity, which may (to a certain degree) prevail even over longer periods of abstinence (2, 15). Since dopamine plays a very important role in response selection (72), it may be assumed that these processes show deficits in methamphetamine users even after the initiation of abstinence. We used a version of the Eriksen flanker task (43–45) to assess potential differences in response selection between abstinent former methamphetamine users and drug-naïve controls, who

TABLE 1 | Bayesian analyses for all effects involving the consumption group factor.

	Accuracy in %	***RTs in ms***	***PES in ms***
Main effect consumption group	$pBIC(H_0\|D)$ = .846	$pBIC(H_0\|D)$ = .355(*)	$pBIC(H_0\|D)$ = .756
Current trial x consumption group	$pBIC(H_0\|D)$ = .917	$pBIC(H_0\|D)$ = .885	$pBIC(H_0\|D)$ = .867
Previous trial x consumption group	$pBIC(H_0\|D)$ = .897	$pBIC(H_0\|D)$ = .922	
Previous trial x current trial x consumption group	$pBIC(H_0\|D)$ = .369	$pBIC(H_0\|D)$ = .907	

**The main effect of consumption group was significant in the ANOVA.*

$pBIC(H_0|D)$ is the probability of the null hypothesis being true, given the obtained data. Please note that no data on the effects of previous trial are reported for post-error slowing (PES), as we did not have enough incorrect responses to reliably analyze this factor.

had been individually matched for sex, age, and education. We had hypothesized that compared to drug-naïve controls, abstinent methamphetamine users might show larger flanker and Gratton effects. This could possibly be due to the supposed dopamine deficiency.

In the current study, we were able to reproduce the flanker effect as well as the Gratton effect (40, 41, 43, 45). Moreover, abstinent methamphetamine users had significantly slower reaction times than healthy controls, indicating a general decrease in performance, as compared to drug-naïve controls. Add-on Bayesian analyses of this effect provided weak evidence for the alternative hypothesis being true, given the data ($pBIC(H_1|D$ = .645). However, we did not find any other significant behavioral differences between abstinent methamphetamine users and controls, or any significant interaction of the consumption group factor with any of the experimental manipulations/conditions. Further substantiating this lack of effects, post-hoc Bayesian add-on analyses confirmed that there was stronger (and most often, positive) evidence of the null hypothesis (H_0), thus indicating that there is likely no behavioral performance difference between abstinent methamphetamine users and controls in the domain of response selection. The only exception from this was the interaction between Gratton effect, flanker effect, and consumption group, where Bayesian analysis was slightly more in favor of the alternative hypothesis, but did not provide strong support for the alternative, either ($pBIC(H_1|D$ = .631). Also, this interaction did not reach significance.

These results obtained in the current study are hence not in line with previous studies demonstrating significantly reduced executive functioning in former methamphetamine users (e.g. 73): Using the Wisconsin Card Sorting Test (22, 23), Digit Span Test (24, 25), and Stroop Task (26–28), several studies suggested executive control deficits in methamphetamine users who have been abstinent for more than one month. Specifically, these studies demonstrated detrimental effects of methamphetamine on cognitive flexibility, working memory and, perhaps to a greater extent, inhibitory control. Yet still, our findings are not entirely at odds with these findings, as we were able to reproduce the repeatedly reported worsening of inhibitory control in the Stroop Task. Specifically, we found abstinent methamphetamine users to take significantly longer than controls to complete the conflict condition (Please find additional information on these findings in Stock, (74) and in the supplement) (compare 75–78). It should however be noted that this aspect of our findings had already been previously published elsewhere (57).

Nonetheless, our findings on response selection support a growing body of literature suggesting that former methamphetamine (ab)use does not necessarily influence all cognitive domains in the same way, or to the same extent. Deficits found in inhibitory control and cognitive flexibility can therefore not necessarily be generalized to response selection and error processing. One possible explanation is related to the underlying dopaminergic mechanisms: Dopamine seems to modulate executive functions in the fashion of an inverted U-shaped curve (79, 80). There seems to be an optimal level of dopamine, where input signal processing and neural noise reduction are most efficient. As a consequence, both too low and too high concentrations of dopamine may lead to a decline in gain control (34, 35, 81) and finally in behavioral performance (e.g. 79, 80). In this context, it could be demonstrated that the dopamine level which is optimal for performance, depends on baseline task performance as well as the difficulty of a given task (82–84). As a consequence, the amount of gain control required for a task might also differ. This makes it reasonable to assume that the optimal dopamine level depends on the cognitive domain tested in a given task. In other words, the optimal level of dopamine needed for optimal Flanker task performance might be lower than for the Stroop Task. If this was the case, it could explain why the behavioral performance of abstinent methamphetamine consumers differed from drug-naïve controls in the Stroop task, but not in the Flanker task. While the Flanker Task and Stroop Task are both regarded as measure of response inhibition, they are nonetheless functionally different: The Stroop Task assesses interference control *via* two interfering stimulus dimensions (font color and written word) of the same target stimulus, which simultaneously compete for cognitive resources and thereby induce a conflict (31). The flanker task, however, requires to shield task-relevant information provided by a target stimulus from distracting bottom-up influences provided by separate distractor stimuli, which induces a switch between mental representations driving response selection and thus a stimulus-stimulus conflict (31). It hence seems conceivable that even though former methamphetamine likely present with decreased interference control (as assessed by the stoop task), the ability to guide attention, select a correct response from a subset of alternatives in conflicting situations, and to take previous contextual information into account seem to be relatively preserved.

Yet still, it should not be ignored that the dopaminergic downregulation reported for methamphetamine users seems to partly improve with increasing duration of abstinence. Several studies have demonstrated that the reinstatement of comparatively

normal dopamine signaling may take from < 6 months of abstinence to 12 to 17 months of abstinence (20, 56). We therefore conducted add-on analyses of abstinence duration in the methamphetamine consumer's group only. Because the sample size of n = 12 subjects per group is very small and does likely not allow for valid conclusions due to lack of power, the results should be treated with ample caution and are therefore only presented in the **Supplementary Material**. Due to the relatively large span of abstinence duration in our sample and the rather long abstinence duration of more than two years, our study does not allow for conclusions about the immediate effect of very short abstinence duration (e.g., < 6 months), which may theoretically still be associated with noteworthy response selection deficits.

Lastly, our cross-sectional study design did not allow to examine executive functioning prior to the initiation of methamphetamine use. In contrast to this, a longitudinal design would have allowed for further conclusions on cause and effect. After all, it could also be possible that individuals with low cognitive resilience in form of decreased executive functioning are more likely to either start using drugs like methamphetamines, or maintain their consumption more steadily (18). Another limitation of this study is that even though we took measures to minimize the social desirability bias (please see methods section), applicants may still have answered questions about their substance consumption in a manner that they viewed as favorable with respect to their self-image or the social judgement of others. Moreover, we cannot exclude a selection bias: Prior research in individuals with a history of methamphetamine use has suggested that individuals with the greatest degree of dopamine transporter loss are most likely to not remain abstinent (85), which makes it possible that the subjects in our sample only experienced a comparatively mild degree of dopamine neurotoxicity. Given the heavy and prolonged consumption of approx. 5 years of daily substance abuse in our sample, we however deem it quite unlikely that the participants did not experience any dopamine toxicity at all. While we deem it plausible that methamphetamine-induced changes in control functions rely on modulations in dopaminergic/catecholaminergic signaling, our data does not allow to draw direct conclusions about dopaminergic changes in the investigated patients. Hence, further studies, including molecular imaging approaches, are needed to underpin such claims.

CONCLUSION

There is a general consensus that heavy methamphetamine use may cause a broad range of cognitive impairments *via* dopaminergic neurotoxicity, which partly persist during (early) abstinence. In a sample that had been abstinent for an average of 2.7 years, we found that abstinent former methamphetamine users showed no significant impairments in the ability to select a correct response from a subset of alternatives in conflicting situations as well as the ability to take previous contextual information into account, including error processing.

Taken together, our results suggest that former methamphetamine use does not appear to be associated with severe deficits in the ability to shield task-relevant information from distracting input in the self-reporting sample we investigated. In combination with the (previous) finding of worse inhibition/interference control in abstinent consumers, our findings suggest that not all cognitive domains are equally impaired by methamphetamine, possibly because different cognitive processes require different levels of dopamine activity.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the TU Dresden, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

A-KS, MR, and CB designed and planned the study. A-KS and MR collected the data. A-KS, MR, JE, WB, and AO analyzed and interpreted the data. All authors substantially contributed to the manuscript and approved its publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00823/full#supplementary-material

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Crystal Methamphetamine Use in Sexual Settings Among German Men Who Have Sex With Men

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Introduction: Men who have sex with men (MSM) are a vulnerable subgroup for problems with substance use, including crystal methamphetamine. Drug use in sexual settings, commonly referred to as "chemsex," has been an issue of growing concern in MSM communities. Recreational drugs commonly associated with chemsex include crystal methamphetamine, gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL), mephedrone, and ketamine. Drug use in sexual settings is correlated with sexual practices associated with the acquisition and transmission of sexually transmitted infections, including HIV and hepatitis C. Adverse mental health outcomes are often reported at higher rates among MSM who use methamphetamine.

Methods: This paper refers to a subset of participants from the *German Chemsex Survey*, an MSM-community recruited, self-completed online survey with a self-selected convenience sample. Participants who used crystal methamphetamine for sex (n = 130) were compared to participants who did not use drugs for sex (n = 177). The survey comprised 420 different items considering recreational substance use, substance use in sexual settings, harm reduction strategies, mental health, sexual transmitted infections, and mental health care service utilization.

Results: A total of 1,583 men started the survey; 1,050 participants provided information on substance use. Twenty-seven percent of participants used crystal methamphetamine in the last 12 months, and of those, 89% used methamphetamine in a sexual setting and 50% reported injecting methamphetamine. Regarding mental health, participants who reported methamphetamine use in sexual settings were more likely to report symptoms of depression, somatization, anxiety, and posttraumatic stress disorder (PTSD) than the German male general population. Participants who reported methamphetamine use for sex were more likely to report symptoms of major depression, being HIV positive, and taking HIV pre-exposure prophylaxis (PrEP) than participants who did not report methamphetamine use. Most participants used harm reduction practices to reduce the risks associated with using methamphetamine in sexual settings.

Conclusion: Crystal methamphetamine is used in the context of sexual activities by German MSM. Poorer mental health status than in the male general population was

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observed. MSM who used methamphetamine in this study seemed to be aware of potential health risks associated with their substance use and utilized harm reduction strategies and biomedical HIV prevention strategies like PrEP.

Keywords: methamphetamine, men who have sex with men, mental health, harm reduction, HIV, chemsex

INTRODUCTION

Men who have sex with men (MSM) are a vulnerable subgroup for problems with substance use, including crystal methamphetamine (1, 2). Methamphetamine use in MSM populations is a growing issue of concern globally. Numerous studies from the United States (3), diverse countries in Asia (4), the United Kingdom (5–7), Ireland (8), Australia (9, 10), and the European Union (11) have consistently reported a heightened prevalence of methamphetamine use among MSM compared to heterosexual men.

Drug use in sexual settings, now commonly referred to as "chemsex," has been an issue of growing concern in MSM communities in recent years (5). Recreational drugs commonly associated with chemsex include crystal methamphetamine, gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL), mephedrone, and ketamine, and are typically used with the intention to enhance, intensify, and prolong sexual experiences (2). Drug use in sexual settings can have benefits for MSM, such as fostering social and sexual connections with other men and the exploration of sexual desires (12). However, drug use in sexual settings is also associated with the acquisition and transmission of sexually transmitted infections (STIs), including HIV (13). It has been consistently shown that MSM who use drugs for sex are more likely to be HIV positive (14, 15) and have higher rates of STIs and hepatitis C (HCV) (16, 17) than those who do not engage in these practices. HIV-positive MSM are more likely to initiate methamphetamine use after seroconversion, for some men as a coping strategy (18). Current methamphetamine use also negatively affects adherence to the antiretroviral therapy (ART) in HIV-positive MSM (19).

Research indicates that injecting methamphetamine in sexual settings ("slamming") is also common in some networks of MSM (20, 5). Injecting drugs potentiates health risks such as blood-borne infections like HCV and HIV, injecting-related injuries and infections, overdose, and more severe substance dependence (21). Studies show that HCV infections are increasing among MSM, in particular among HIV-positive MSM who have never injected drugs (22–24). Drug use in sexual settings is also associated with engagement in group sex, having multiple sex partners (25, 26), transactional sex, sharing sex toys, sex practices with risks for injuries (27), and condomless anal intercourse (28) which also increases STI risks.

Adverse mental health outcomes are also reported at higher rates among MSM with longer-term methamphetamine use. In an US sample of ethnic minority MSM who use methamphetamine, a higher prevalence of major depressive disorder, social phobia, obsessive–compulsive disorder, antisocial personality disorder, and posttraumatic stress disorder (PTSD) and a higher risk for suicide attempts was reported, compared to the male US general population. In addition, mental health disorders were more commonly reported among men with more severe methamphetamine use disorders (29, 30). Lopez-Patton et al. found significantly higher rates for major depression and childhood trauma among methamphetamine-using MSM (31). In an online cohort study in Australia, while methamphetamine use overall was not negatively associated with mental health, men who were methamphetamine dependent were more likely to report depression and anxiety than men who used methamphetamine but were not dependent (32).

Crystal methamphetamine use is uncommon in most parts of Germany, with exceptions to regions near the Czech border (33). In a representative survey of the general population in Germany, the 12-month prevalence of methamphetamine use was only 0.2% among men (34). To date, there has been limited research about methamphetamine use among MSM in Germany. A recent study on motivations for psychostimulant use among German adults found that MSM most commonly reported using methamphetamine in sexual settings (35). However, little is known about German MSM who use crystal methamphetamine in sexual settings, nor their mental health (e.g., depression, anxiety, and posttraumatic stress), HIV prevention strategies such as pre-exposure prophylaxis (PrEP), or drug-related harm reduction practices. This paper aims to address these research gaps using findings from a recent national online survey. In addition, the paper examines the utilization of mental health, alcohol, and drug treatment and related support services among German MSM.

METHODS

Sample

The analysis refers to a subset of participants from the *German Chemsex Survey*, an MSM-community recruited, self-completed online survey with a self-selected convenience sample. Eligible participants were at least 18 years of age, identified as male, and as gay, bisexual, or MSM. The present study is focused on two groups: men who reported crystal methamphetamine use in sexual settings in the previous 12 months, and men who reported no illicit drug use in sexual settings in the previous 12 months.

The survey was promoted *via* Lesbian, Gay, Bisexual, Transexual, Intersexual and Queer (LGBTIQ)-community websites, social media postings, HIV non-profit organizations, free-of-charge advertisements on "planetromeo" (MSM-dating website/smartphone application), and HIV/sexual health care service providers. The survey was online for 12 weeks between September and December 2018 and used the open-source survey software "LimeSurvey." All data collected were anonymous. Participants could skip questions they did not want to answer and could withdraw from the survey

at any time during completion. At the end of the survey, links to nationwide accessible psychosocial support services were presented to offer support for participants who felt uncomfortable as a consequence of being confronted with questions on substance use and mental health issues. Ethical approval for the study was received from the Ethics Committee of the Medical Department of the University of Duisburg-Essen (UDE-18-8209-BO).

Measures

The survey consisted of 420 items including demographic characteristics, recreational substance use, substance use in sexual settings, mental health, sexual behavior, STIs, psychosocial/health outcomes of methamphetamine use, harm reduction practices, and use of mental health care and drug treatment services. Mental health was assessed using the German version of the Patient Health Questionnaire (PHQ-D) with subscales for depressive symptoms (PHQ-9), generalized anxiety symptoms (GAD-7), and somatization symptoms (PHQ-15) (36). The PHQ-9 scale assesses severity of depressive symptoms with a maximum score of 27. The PHQ-15 score gives information about symptoms of somatization with a maximum value of 30. GAD-7 measures symptoms of anxiety with a maximum of 21. A score of 10 or above on each of the three scales signifies an at least moderate major depressive episode, moderate levels of somatization, and moderate levels of clinical anxiety. For trauma and PTSD, the life events checklist for *DSM-5* (37) as well as the four-item PTSD primary care screener (38) were conducted.

Statistical Analysis

Given that participants were able to stop and save their data at any point of the survey and the survey software was not programmed in a "forced choice" format, sample size varies for different items. Data analysis was conducted using IBM SPSS Statistics 25.0. For group comparisons of participants who reported methamphetamine in sexual settings (methamphetamine group) with participants who did not report drug use in sexual settings (no drug use for sex = NDUS group), Chi^2 tests were used for binary and categorical dependent variables and Mann–Whitney U tests for continuous dependent variables which were not normally distributed. Where statistical tests were performed, p-values of <0.05 were taken to be statistically significant.

RESULTS

Sample

A total of 1,583 men started the survey, and 1,050 participants provided information on substance use (66.3%). Of the 1,050 participants who provided data on substance use, 231 (22%) reported any methamphetamine use: 36.8% ever, 26.8% in the last 12 months, 17.3% in the last 30 days, and 19% in the last 7 days. Fifty percent of the methamphetamine group had injected methamphetamines in the last 12 months. Methamphetamine use in a sexual setting in the last 12 months was reported by 130 participants (12.4%). Ninety-three percent also used amyl nitrite ("poppers"), 90% alcohol, 76.2% medication for erectile dysfunction, and 70.8% GHB/GBL in sexual settings in the last 12 months. All other substances are listed in **Table 1**.

The present analysis includes men who reported methamphetamine use in sexual settings in the last 12 months (n = 130; 8.2% of the sample) and men who reported no illicit drug use in sexual settings in the last 12 months (n = 170; 10.7% of the sample). For demographics of both groups, see **Table 1**.

Mental Health Measures

The median PHQ-9 score was significantly higher in the methamphetamine group compared to the NDUS group. Eleven percent of participants in the methamphetamine group and 12.1% in the NDUS group had PHQ-9 scores above the cutoff for moderate depressive symptoms (see **Table 2**). There was no significant difference between the methamphetamine group and the NDUS group regarding GAD-7 scores. Five percent of participants in the methamphetamine group and 8.7% of participants in the NDUS group had a GAD-7 score of 10 or above, which indicates at least moderate levels of anxiety. There was no significant difference between the methamphetamine group and NDUS group regarding PHQ-15 scores. Thirteen percent of participants in the methamphetamine group and 10.6% in the NDUS group had a score of 10 or above, indicating at least moderate levels of clinically relevant somatization. In both groups together, 76.4% of participants had experienced at least one potentially traumatizing event according to the *DSM-5* life events scale, with a mean number of 1.86 potentially traumatizing events. There was no significant difference between the two groups in the number of traumatic events reported. In the methamphetamine group, 6.4% had a score of 3 or more on the PTSD primary care screener, indicating a possible diagnosis of PTSD. In the NDUS group, 12.9% were above the cutoff for PTSD, although the difference between the groups was not statistically significant (see **Table 2**).

Infectious Diseases

Regarding HCV, 3.2% of the methamphetamine group reported that they were HCV positive. None of the NDUS group was positive for HCV. Fifty-three percent of the methamphetamine group reported being HIV positive, 42.9% were HIV negative, and 4.4% did not know their current HIV status. Compared to the NDUS group, participants in the methamphetamine group were significantly more likely to report being HIV positive (7.3% vs. 52.7%). All HIV-positive participants were taking HIV ART and reported having an undetectable viral load. Among HIV-negative men, a higher proportion of men in the methamphetamine group (53.8%) were currently taking PrEP than in the NDUS group (7.2%). Any condomless anal intercourse in the last 12 months was reported by a significantly higher proportion of men in the methamphetamine group (93.0%) than in the NDUS group (49.6%).

Harm Reduction Practices

Participants who reported methamphetamine use for sex reported a range of drug- and sex-related harm reduction practices. The practices that men most commonly reported always doing were: drinking enough non-alcoholic beverages, making sure

TABLE 1 | Sample characteristics and substance use.

	Methamphetamine group		No drug use for sex (NDUS)		p-value
		M (SD)		M (SD)	t-test
Age		**34.5 (10.1)**		**37.6 (12.6)**	**.000**
	N	**%**	**N**	**%**	χ^2
Country of birth	88		145		.172
Germany		85.2		91.0	
Outside Germany		14.8		9.0	
Gender identity	130		173		.073
Male		100.0		97.1	
Trans man		0.0		2.9	
Sexual identity	129		168		.307
Gay/homosexual		93.8		89.9	
Bisexual		6.2		8.9	
Queer		0.0		1.2	
Level of education	81		134		.533
University or university of applied sciences entrance diploma		72.8		76.9	
General certificate of secondary education		16.0		14.2	
Certificate of secondary education		11.1		7.5	
No certificate		0		2.2	
Employment status	88		147		.013*
Full-time employed		65.9		62.6	
Part-time employed		5.7		8.2	
Unemployed		8.0		4.1	
Retired		8.0		3.4	
Student		3.4		17.0	
Other		9.1		4.8	
Monthly net income	87		148		.043*
Less than 1.000 Euros		17.2		24.9	
1.000–2.000 Euros		24.1		33.1	
2.000–3.000 Euros		25.3		23.6	
More than 3.000 Euros		33.2		18.3	
Substance use last 12 months **in a sexual setting**			Substance use last 12 months, **not in sexual settings**		
	n = 130	%	n = 170	%	
Amyl nitrite ("poppers")		93.8		0	
Medication for erectile dysfunction		76.2		0	
Gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL)		70.8		0	
Amphetamines		62.3		0	
Alcohol		62.3		78.3	
Ecstasy		56.9		1.2	
Ketamine		53.8		0.6	
Cannabis		51.5		11.8	
Cocaine		46.9		0	
Mephedrone		40.8		0	
Opioid analgesic		5.4		4.1	
Heroin		0.8		0	

*$p < .05$.

to get enough sleep after consumption, and having enough lube available at all times **Table 3**).

Health Care and Psychosocial Support Service Utilization

Thirteen percent of men in the methamphetamine group and 4.1% in the NDUS group were seeing a psychotherapist at the time of the survey, while 6.9% in the methamphetamine group and 1.8% in the NDUS group were seeing a psychiatrist. Two percent (2.3%) of men in the methamphetamine group and 1.8% in the NDUS group were attending an outpatient alcohol and other drug counseling service at the time of the survey. In the methamphetamine group, the most common forms of engagement with the health care system were with a general practitioner (52.8%) or an infectious diseases specialist (35.2%). Participants also had contact with other psychosocial support services, including counseling for people living with HIV (17.4% methamphetamine group and

TABLE 2 | Mental health, infectious diseases, and biomedical HIV prevention.

Measure	Methamphetamine users			No Drug Use For Sex (NDUS)					
	N	Mdn= median	IQR IQR= interquartile range	N	Mdn= median	IQR IQR= interquartile range	Mann–Whitney U	p-value	Effect size (r)
PHQ-9	117	5.00	5.00	150	3.00	4.25	6,824.0	.002**	0.2
GAD-7	112	3.00	4.00	149	2.00	5.00	7,398.0	.113	0.1
PHQ-15	116	4.00	5.00	151	3.00	4.00	7,595.0	.061	0.1
Traumatic Events Lifetime	110	2.00	2.00	142	1.00	2.00	6,852.0	.087	0.1
	N	%		N	%		Chi^2	p-value	Effect size (Cramer V)
PTSD screening positive	110	6.4		139	12.9		2.949	.086	0.1
PHQ-9 > 10	117	11.1		150	12.0		.051	.822	0.01
GAD-7 > 10	112	5.4		149	8.7		1.074	.300	0.064
PHQ-15 > 10	116	12.9		151	10.6		.345	.555	0.036
HIV positive	91	52.7		96	7.2		30.670	.000**	0.418
Hepatitis C infection	93	3.2		70	0		2.300	.129	0.119
Condomless anal intercourse	100	93		139	49.6		50.070	.000**	0.458
PrEP	43	53.8		83	7.2		29.126	.000**	0.481

*PHQ-9, Patient Health Questionnaire (PHQ-D) subscale for depressive symptoms; GAD-7, PHQ-D subscale for generalized anxiety symptoms; PHQ-15, (PHQ-D) subscale for somatization symptoms; PTSD, posttraumatic stress disorder; PrEP, pre-exposure prophylaxis. Mdn, median; IQR, interquartile range. **p < .01.*

TABLE 3 | Utilization of harm reduction strategies of methamphetamine-using participants.

Strategy	% always	% often	% sometimes	% never
Safer use				
Only using own needles and syringes (iv-users only)	79.6	20.4	–	–
Avoiding simultaneous use with tranquilizers	70.0	10.0	9.0	11.0
Using a new syringe and needle for every iv application (iv-users only)	75	19.2	5.8	–
Avoiding simultaneous use with alcohol	56.4	13.9	14.9	14.9
Bring own needles, syringes, and other utensils for consumption to parties (iv-users only)	64.2	13.2	11.3	11.3
Only using own tubule for nasal consumption	44.3	23.7	16.5	15.5
Inhaling methamphetamine instead of injecting it	34.0	15.5	22.7	27.8
Avoiding simultaneous use with other stimulants	30.4	20.6	19.6	29.4
Trying a small dose of a new stash to estimate the impact	28.0	21.0	12.0	39.0
Dispensing a dose over a longer stretch of time	25.8	27.8	28.9	17.5
Avoiding simultaneous use with medication for erectile dysfunction	21.0	9.0	20.0	50.0
Avoiding simultaneous use with poppers and medication for erectile dysfunction	14.6	10.4	27.1	47.9
Avoiding simultaneous use with poppers	12.1	12.1	22.2	53.5
Health-related behavior				
Drinking enough non-alcoholic beverages	63.1	23.3	11.7	1.9
Getting enough sleep after use	60.0	26.0	12.0	2.0
Avoiding consumption when feeling depressed or anxious	48.0	10.0	14.0	28.0
Using an alarm clock to remember HIV medication or PrEP	31.1	7.8	6.7	54.4
Eating sufficiently before consumptions	27.5	30.4	32.4	9.8
Eating regularly during consumption	9.9	22.8	35.6	31.7
Sexual behavior				
Having enough lube available at all times	62.2	22.4	11.2	4.1
Having no anal intercourse for half an hour after "booty bumping" (= substance application *via* intestinal mucosa)	28.1	15.7	20.2	36.0
Having condoms available at all times	13.4	8.2	17.5	60.8
Not having sex with more than one partner	3.1	7.2	22.7	67.0
Frequency				
Not consuming more than 2 days in a row	60.2	21.4	10.2	8.2
Only using on long weekends or special occasions	52.0	20.0	16.0	12.0
Not consuming more than once a month	36.4	27.3	25.3	11.1
Setting limits for quantity of consumption	36.0	24.0	26.0	14.0

iv, intravenous.

2.9% NDUS group) and LGBTIQ-specific counseling services (9.2% of participants in methamphetamine group and 0.6% in the NDUS group).

DISCUSSION

In this study, German MSM who used crystal methamphetamine commonly did so in the context of sexual activities. Poorer mental health status was observed among MSM who used methamphetamine than in the general male population. Men who used crystal methamphetamine for sex seemed to be aware of potential health risks associated with their substance use and utilized harm reduction strategies and biomedical HIV prevention strategies like PrEP and HIV treatment as prevention (TasP).

These results support previous research in a German sample of people who use psychostimulant that methamphetamine use for sex is an important motive of MSM (35). Polydrug use was commonly reported in this subset of methamphetamine-using German MSM. Nearly all participants used amyl nitrite in the previous 12 months, and more than two-thirds used erectile dysfunction medications. Amyl nitrite is commonly used as a muscle relaxant to facilitate receptive anal intercourse, and erectile dysfunction medications are often reported by MSM who used methamphetamine for sex as psychostimulant use is often associated with difficulties gaining and maintaining an erection (39). About half of the sample reported consumption of other substances that are commonly associated with chemsex (e.g., GHB/GBL, mephedrone, ketamine) (2).

Eleven percent in the methamphetamine group had a score on the PHQ-9 scale indicating at least moderate depressive symptoms. This is comparable to a sample of MSM in the UK (40), but considerably lower than in an Australian study among MSM. Here, nearly one-third of gay and bisexual men reported moderate depressive symptoms on the PHQ-9 scale (32). Regarding most mental health measures, there were no significant differences between men who used methamphetamine for sex and men who reported no drug use for sex. However, both groups of MSM reported consistently higher levels of depression, somatization (41), generalized anxiety (42), number of traumatic life events (43), and PTSD (44) compared to representative data among the general population of men in Germany. Crystal methamphetamine use does not seem to be the most contributing factor, given that both groups of MSM showed lower mental well-being.

In summary, the results underline that both groups of MSM, irrespective of substance use, were more likely to experience poor mental health than the male general population. According to the minority stress model (45), a minority status, like a non-heterosexual sexual orientation, has an impact on psychological well-being and can increase likelihood of experiencing problems with mental health and substance use.

Besides this, poorer mental health status among men who used methamphetamine in our study may be traced back to the fact that half of the sample was HIV positive. Since ART, HIV is a chronic condition similar to other chronic conditions [e.g., diabetes (46)], and living with HIV and other chronic conditions is associated with an increased likelihood of experiencing depression (47). Experiences of HIV-related stigma may also be a contributing factor to the higher rates of depression reported, which can negatively impact mental health and well-being (48).

The heightened proportion of men who live with HIV in the methamphetamine group is consistent with previous research (14, 15). All HIV-positive men in the sample were taking ART and self-reported an undetectable viral load. Successful treatment of HIV is an important contribution to prevent HIV transmission (TasP). Large-scale, prospective studies have shown no HIV transmission in serodiscordant couples when the viral load of the HIV-positive partner was suppressed sufficiently by ART (49). The latest addition to biomedical HIV prevention strategies is PrEP. PrEP refers to the use of HIV-antiretrovirals in HIV-negative people at high risk for HIV to prevent infection (50). In Germany, PrEP is only available on prescription and has been available at an affordable price since 2017. As a result of an initiative of a pharmacist in Cologne and negotiations with a pharmaceutical company to distribute a generic version of PrEP, it was available nationally for 50 Euros (about 55 USD) per month. Since September 2019, PrEP has been covered by health insurance free of charge for people at high risk of becoming infected with HIV. HIV-negative men who use methamphetamine seem to reflect that they may be at risk for HIV infection due to their substance use in sexual settings and therefore decide for PrEP. Under the influence of methamphetamines, other prevention strategies, like condom use, may be compromised (51). Nonetheless, PrEP and TasP do not prevent the acquisition of other STIs.

Half of the methamphetamine user sample injected drugs in sexual settings, which carries a risk for the transmission of blood-borne viruses like HCV, as well as HIV. Although the prevalence of HCV was 10 times higher than in the German general population (52), it was significantly lower than in other groups of people who inject drugs in Germany, which has been estimated at between 42% and 75% (53). The routine utilization of harm reduction strategies can help prevent HCV among people who inject drugs (54). In the German Chemsex Survey sample, men who use methamphetamine seem to be aware and well informed about various harm reduction strategies. Most participants used at least some harm reduction practices to prevent negative health outcomes related to methamphetamine use. Injecting substances carries the highest risk for negative health consequences. Among those who injected methamphetamine in sexual settings, harm reduction practices appeared to be well established. More than two-thirds of men who injected methamphetamine stated that they always used their own needle and syringe and used a new needle and syringe every time they injected. There has been very little research published on the harm reduction practices of MSM. In a Canadian study, harm reduction strategies with focus on safety when injecting drugs were most common (55). Other strategies refer to restrictions of frequency or maintaining a healthy lifestyle, such as eating regularly, getting enough sleep, and staying hydrated (55). Avoidance of polydrug use is another important harm reduction practice, given the increased risk of overdose and other negative consequence of combining drugs in the same session. Half of the sample stated that they never refrain from simultaneous use of methamphetamine and amyl nitrite or erectile dysfunction medications. One-third

reported never avoiding using other stimulants at the same time as methamphetamine. Combined use of erectile dysfunction medications and alcohol, other recreational drugs, and especially amyl nitrite, increases risks for potentially fatal cardiovascular events and other serious drug interactions (56). Given that polydrug use was common in this sample and in other studies of MSM (57), there is some potential for improvement of applying this harm reduction strategy.

About one in five men of the sample currently consults a psychotherapist or psychiatrist. This is a good fit to the proportion of men who report mental health problems in the sample, so mental health care service utilization seems to be high. Only few men seek support from alcohol or drug treatment facilities. Perhaps, they do not need such treatment since they do not have any substance-related problems or disorders. Other reasons could be that there are only very few target group–specific services for MSM who use drugs for sex or that they fear rejection or stigmatization by service staff because of their sexual orientation. Future work could have a further look at what type of counseling or treatment services MSM who use drugs for sex need and where those services should be located. An integration of sexual health, LGBTIQ counseling, and drug treatment services would be helpful to exchange expertise and improve care for support-seeking MSM who use drugs for sex.

Limitations

About one in five participants reported lifetime methamphetamine use, which is a considerably higher prevalence than in the German male general population. The German Chemsex Survey was not designed to determine prevalence rates for methamphetamine use among MSM, but to recruit a sample of MSM who report substance use, and was advertised accordingly. The results should thus be interpreted with this in mind, and may not be generalizable to all MSM in Germany. The inclusion of a self-selected convenience sample may contribute to bias, with overestimation of substance use in sexual settings and mental health problems. In addition, the sample had a high socioeconomic and educational status, clearly above the average in the German male general population. Moreover, the sample was not diverse as very few trans men or men born outside of Germany participated. The survey was only available in German, so men with insufficient German language skills would have been discouraged from participating. The high number of HIV-positive participants may be due to the recruitment sources as the survey was promoted *via* community-based organizations that provide services for people living with HIV. Another obvious limitation is the high rate of attrition, most likely due to the large number of items. Despite these limitations, the study provides some relevant findings on MSM who use substances in sexual settings, regarding mental health, biomedical HIV prevention, and harm reduction strategies.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Department of the University of Duisburg-Essen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HS: study conceptualization, data analysis, article writing. TL: article writing, language editing. AB: data analysis and literature search. DS: study conceptualization, editing article. TK: consulting data analysis. NS: editing article. DD: study conceptualization, editing article.

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Emotion Recognition and Impulsive Choice in Relation to Methamphetamine Use and Psychosis Symptoms

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Introduction: The cognitive profiles of people with methamphetamine use disorder are characterized by impulsivity and impairment in social cognition. However, previous studies have not fully accounted for the presence and impact of co-occurring mental health problems on these domains. For instance, psychotic symptoms are commonly experienced by people who use methamphetamine and may influence cognitive performance. We aimed to examine decision making and emotion recognition in individuals with methamphetamine use, compared to healthy controls, to map the nature and degree of impairments in relation to the presence of psychotic symptoms.

Method: In this naturalistic study, we assessed reward-based decision-making and facial emotion recognition across three groups, methamphetamine-using individuals with (MAP, n = 29) and without psychotic symptoms (MNP, n = 70), and healthy controls (HC, n = 32).

Results: In comparison to healthy controls, methamphetamine-using individuals presented with poorer performance on tasks of decision-making and emotion recognition. Emotion recognition was impaired across all methamphetamine-using individuals, with significantly poorer recognition of anger and sadness in those with psychotic symptoms.

Conclusion: We found specific impairments in emotion recognition in relation to psychotic symptoms in people who use methamphetamine regularly. This builds on previous evidence on cognitive profiles in methamphetamine use disorder, highlighting the need to assess co-morbid mental health and psychotic symptoms. Our finding that methamphetamine-using individuals with psychotic symptoms present with particular difficulties recognizing anger has implications for frontline clinicians.

Keywords: methamphetamine, psychosis, social cognition, cognition, comorbidity

INTRODUCTION

A significant public health consequence of growing global methamphetamine use is the burden of associated mental health problems (1, 2), particularly methamphetamine-related psychosis (MAP), on acute health and psychiatric inpatient services (3, 4). Observed in between 20 and 60% of individuals who use the drug regularly (5), MAP is characterized by a transient paranoia, with or without hallucinations, which is very similar in appearance to acute paranoid schizophrenia (6). MA use has been associated with psychotic symptoms in both experimental studies and during acute intoxication with illicit use (5–7), with persistent forms resembling chronic primary psychotic disorder (5, 8, 9).

Although there is a growing body of evidence characterizing the MAP syndrome, there is currently little evidence about its cognitive underpinnings (10). Cognitive markers are a promising avenue of investigation across psychotic syndromes, and present an objective, reliable means of characterizing clinical phenotype. In terms of MA use, cognition has been studied in relation to persistent versus transient MAP (8, 11). A study examining persistent MAP identified impairments in verbal learning and memory, and executive function and decision making that were comparable to those found in a chronic schizophrenia comparison group, with poorer performance compared to both healthy controls or people who used methamphetamine regularly and did not have psychosis (8). Two studies assessing cognition in transient MAP also found impairments in executive function and memory compared to healthy controls, with MAP participants and individuals with schizophrenia presenting with (similar) deficit profiles (12, 13). Notably, impairments in similar cognitive domains, particularly verbal memory, have also been demonstrated in studies investigating first episode psychosis (14), contributing to a growing body of evidence pointing to commonalities in the process of psychosis in MAP and primary psychotic disorders (5). Impairments in social cognition have also been identified across a range of primary psychotic disorders (15). Deficits in facial emotion recognition (FER), a specific domain of social cognition, have been consistently found in both ultra-high risk (for psychosis) and first episode psychosis populations (16), suggesting these impairments may be pre-existing, and independent of the stage of psychotic illness.

On the other hand, studies of cognition in MA use disorder highlight the possibility that cognitive deficits arise from prolonged drug use and related neuro-adaptation (17). A recent meta-analysis of studies of cognition in MA identified impairments in social cognition and impulsive and reward-related processes, including emotional decision-making (e.g., a preference for immediate small rewards over larger delayed rewards) (17). However, none of the studies to date have examined the impact of psychosis co-morbidity, even though sub-threshold psychotic symptoms are extremely common in people who use MA regularly. Consequently, it remains unclear whether cognitive deficits in people who use MA relate only to drug use itself, or to co-occurring psychotic symptoms.

We investigated the relationship between psychotic symptoms and cognitive impairments (including FER) in methamphetamine-using adults and healthy controls. We hypothesized that methamphetamine-using participants with past-month clinically significant psychotic symptoms (MAP) would present with cognitive impairments relative to both methamphetamine using participants without psychotic symptoms (MNP) and health controls (HC).

METHOD

Study Design, Participants and Setting

This cross-sectional study compared cognition across three groups (MAP, MNP and HC). Methamphetamine-using participants were recruited from both public and private residential alcohol and other drug treatment facilities and the community in metropolitan Melbourne, Australia between March 2015 and February 2017 (n = 99).

Inclusion criteria were (i) being aged 18 or over, (ii) at least weekly methamphetamine use in the past month, (iii) not being currently dependent on drugs (other than methamphetamine, nicotine, alcohol or cannabis), (iv) no previous diagnoses of primary psychotic disorders including schizophrenia or bipolar disorder (screened using the Structured Clinical Interview for DSM-IV TR (SCID) (18), and (v) no lifetime history of loss of consciousness for more than 30 minutes, HIV, epilepsy or any central neurological illness. Participants with previous non-psychotic psychiatric disorders were included. Age and gender matched healthy control participants (HC, n = 32), mainly students, were recruited from the same area. Participants completed informed consent and were reimbursed AU$30. Ethics approval was obtained from the Monash University Human Research Ethics Committee (CF15/40-2015000222).

MEASURES

Psychotic Symptoms

Past-month clinically-significant psychotic symptoms were defined as a score of 4 or greater on any of the Brief Psychiatric Rating Scale (BPRS) (19) positive psychotic symptom items of suspiciousness, hallucinations or unusual thought content. This method has been previously used to examine the prevalence and correlates of psychotic symptoms in studies of MA and MAP, with high inter-rater reliability reported in original studies (IRR = 0.67–0.88) (20–22). Methamphetamine-using participants were divided into those with clinically-significant past month psychotic symptoms (MAP, n = 29) and without psychotic symptoms (MNP, n = 70).

Methamphetamine Use

Days of methamphetamine use in the past month was assessed using the Timeline Followback (23), as previous research has found has found a strong dose-response effect between days of use and psychotic symptoms (20). The TLFB is a validated measure of psychoactive substance use and shows 88% sensitivity, 96% specificity, and a 95% hit-rate and 0.77 test–retest agreement, for the use of amphetamines in the past 30 days (24). Severity of

dependence on methamphetamine was assessed with the Severity of Dependence Scale (SDS), with scores ranging from 0 (low) to 15 (high) (25), with high validity and reliability in substance-dependent populations (26). Age of first methamphetamine use was based on self-report.

Cognitive Battery

The neuropsychological test battery targeted cognitive domains associated with psychostimulant use (17) and deficits in emotion recognition associated with methamphetamine use and primary psychotic disorders (27, 28). The tasks were administered in a set order and nested within the structured interview.

Impulsivity and Reward-Based Decision-Making

Iowa Gambling Task (IGT): a computerized task evaluating reward and punishment-based decision-making (29). The task instructs participants to try and win as much money as possible by making 100 selections of cards from four decks (A, B, C, D). Two of the decks (A and B) result in high immediate gains but in the long term will take more money than they give and can be considered 'disadvantageous'. In contrast, two decks (C and D) have low immediate gains but will yield more money than is taken and can be considered 'advantageous'. The outcome variable was the net score, calculated by subtracting the number of disadvantageous choices (decks A + B) from the number of advantageous choices (decks C + D) for each block of 20 trials.

Impulsive Choice in Decision-Making

Delay Discounting Task (DDT): a measure of impulsivity in decision-making, specifically the inability to delay gratification. The task involves examining the outcome of 27 choices between smaller immediate rewards versus larger delayed rewards, based on the Kirby Monetary Choice Questionnaire (30), with the main outcome variable calculated as the k score based on methods detailed by Kirby and colleagues (30), with higher k scores indicating higher levels of impulsivity.

Facial Emotion Recognition

The Ekman Faces Test (EFT) was used to assess FER (31). The EFT is a computerized test that presents 60 faces portraying six basic emotions (fear, anger, sadness, disgust, happiness and surprise). Dependent variables were the number of correct identifications for each emotion (ranging from 0 to 10) and total number of correct identifications (ranging from 0 to 60).

Statistical Analysis

In order to investigate the primary hypothesis, we compared cognitive performance across all groups, using a non-parametric omnibus test (Kruskall Wallis test), and subsequent between-group differences with a post-hoc Dunn test. Confounding sociodemographic variables that were significantly different between the three groups (MAP, MNP, HC groups) were investigated using chi-squares, one-way ANOVAs for parametric variables, and Kruskal Wallis test for non-parametric variables. Drug use variables were compared between the two MA-using groups (MAP and MNP) using chi-squares and t-tests for parametric variables, and Mann–Whitney U tests for non-parametric variables.

We also examined differences in accuracy of identification of discrete emotions within the FER task (E.G., Anger, fear) based on the number of correct identifications per emotion. We compared accuracy of discrete emotion recognition between groups using a generalized linear model (GLM) to estimate the association between an individual's group membership (MAP, MNP, HC) and correct identification of discrete emotions. In this analysis, the outcome variable was the number of trials (Out of 10) where the participant correctly identified the emotion. The outcome variable and group (MAP, MNP, HC) was the predictor variable, with HC nominated as the reference group. The model was based on a binomial distribution and a logit link function. A sandwich (robust) estimator was used to calculate the standard errors in the model, to correct for any potential lack of independence between the 10 attempts for an individual.

All tests were two-tailed with statistical significance set at $p < 0.05$. Statistical analyses were performed using Stata 15 (Statacorp LP, College Station, TX, USA).

RESULTS

The MAP (N = 29) and MNP (N = 70) groups did not differ from the healthy control group (N = 32) on any socio-demographic measures, including years of education (see **Table 1**). The two methamphetamine-using groups (MNP N = 70, MAP N = 29) did not differ on any indices of methamphetamine use (see **Table 1**). Methamphetamine use frequency was high across both the MNP group (Mean 21.7 days of use in past 28), and the MAP group (Mean 23.5 days of use in past 28), with both groups having a high severity of dependence score (MNP mean SDS 10.1, MAP mean SDS 11.2).

In terms of cognitive performance across all three groups, there was no significant difference between verbal memory and recall (delayed recall score) between the HC (Mean 8.72 ± 1.78), MNP (Mean 8.59 ± 2.50) and MAP (8.48 ± 2.31) groups ($p = 0.946$). There were significant differences between groups for performance on emotion recognition, the Iowa Gambling Task and the Delay Discounting Task (**Table 2**). Post-hoc tests comparing each group revealed the HC group had significantly better performance on the Iowa Gambling Task compared to both MA using groups, with no difference between the MAP and MNP groups. For the Delay Discounting Task, post-hoc testing found significantly higher levels of impulsivity (k score) in the MNP group compared to the HC group, with no significant difference between the HC and MAP groups. Finally, for emotion recognition, the MAP group were significantly poorer at accurately identifying emotions in comparison to the MNP group and the HC group; there was no significant difference in

TABLE 1 | Participant characteristics.

	HC* (n = 32)	Methamphetamine-using participants		Test statistic[1]	p-value
		MNP* (n = 70)	MAP* (n = 29)		
Male, n (%)	22 (69)	49 (69)	25 (86)	$\chi^2 = 3.41$	0.182
Age (mean, SD)	32.4 (1.72)	32.6 (1.03)	31.8 (1.42)	$\chi^2 = 0.174$	0.917
Unemployed, n (%)	17 (53)	52 (74)	22 (79)	$\chi^2 = 7.17$	0.306
Years of education (mean, SD)	13.0 (0.35)	13.2 (0.32)	12.3 (0.40)	$\chi^2 = 2.209$	0.331
IQ (mean, SD)	101.0 (1.81)	96.5 (1.35)	97.2 (2.13)	F = 1.83	0.165
Methamphetamine and other drug use					
Frequency of use (mean, SD)	–	21.7 (1.21)	23.5 (1.58)	z = –0.56	0.579
Age of Onset (mean, SD)	–	24.3 (1.07)	24.3 (1.82)	z = –0.036	0.972
Severity of Dependence (SDS) (mean, SD)	–	10.1 (0.43)	11.2 (0.67)	z = –1.67	0.096
Cannabis Dependence, n (%)	–	15 (21.13)	7 (24.14)	$\chi^2 = 0.11$	0.742
Alcohol Dependence, n (%)	–	5 (7.04)	2 (6.90)	$\chi^2 = 0.00$	0.979

**HC, Healthy Controls MNP; Methamphetamine use, no psychotic symptoms MAP; Methamphetamine use, psychotic symptoms.*
[1]Omnibus test for comparison between three groups, chi² for categorical variables and ANOVA for continuous, normally distributed; Kruskal Wallis test for continuous, non-parametric; t-test, chi², or Mann–Whitney U for comparison between two groups.

TABLE 2 | Cognitive performance across groups.

Cognitive test	Groups	Mean ± SD	P[1]	Post-hoc Test[2]					
				HC-MAP Z	P	HC-MNP Z	P	MAP-MNP Z	P
Decision-Making (Iowa Gambling Task net score)	HC	22.75 ± 32.84	0.006	–2.79	0.003	2.86	0.002	0.477	0.317
	MNP	2.94 ± 22.34							
	MAP	0 ± 28.95							
Impulsivity (DDT k score)	HC	0.10 ± 0.11	0.027	–1.52	0.064	–2.81	0.003	0.94	0.173
	MNP	0.15 ± 0.10							
	MAP	0.14 ± 0.10							
Facial emotion recognition (Ekman's Test Total Score)	HC	46.50 ± 5.86	0.007	–2.60	0.005	–0.02	0.494	3.02	0.001
	MNP	45.86 ± 7.53							
	MAP	42.76 ± 4.86							

[1]Kruskal Wallis rank sum test.
[2]Post-hoc Dunn test.

emotion recognition performance between the MNP and HC groups.

In terms of accuracy of identification of discrete emotions, individuals in the MAP group were specifically impaired in recognition of anger (OR 0.56) and sadness (OR 0.57) compared to HC participants (**Table 3**). The MNP group had no significant differences in recognition of any discrete emotions with reference to the HC group.

DISCUSSION

In this study examining cognitive deficits among methamphetamine users with and without past-month psychotic symptoms and a matched sample of healthy controls, we found that MAP was associated with poor emotion recognition, particularly for anger and sadness. In contrast, impairments in emotion recognition were absent in the MNP group, suggesting that deficits in social cognition may be specific to MAP rather than being associated with methamphetamine use per se. Indeed, we found that deficits in steeper delay discounting, which are suggestive of impulsive choices, appear to be more general to methamphetamine use. These differences in cognitive performance were not accounted for by differences in patterns of methamphetamine use, or other potential confounds (age, gender, and IQ).

In contrast with other studies that have investigated emotion recognition in MA-using samples, we specifically examined the influence of psychotic symptoms on performance. In our sample, there were no differences in MA use parameters between the MAP and MNP participants (including age of onset, frequency of use or severity of dependence). As such, our results do not support the concept of emotion recognition deficits as a common correlate of both methamphetamine use and psychosis, but rather, as a more specific correlate of psychotic symptoms in methamphetamine-using individuals.

Our findings are consistent with that of the broader literature of non-drug psychosis, including studies of early-psychosis or first episode psychosis samples where deficits in emotion recognition are evident at first presentation (16, 32). The specific finding of impaired recognition of anger has implications for

TABLE 3 | Discrete emotion recognition across groups.

	HC (n = 32)		MAP (n = 29)		MAP (n = 29)			OR (95% CI) (compared to HC group)	P value
	M	SD	M	SD	M	SD			
Anger	7.75	0.32	7.14	0.21	6.59	0.38	MNP	0.73 (9.48–1.09)	0.121
							MAP	0.56 (0.35–0.91)	0.018
Disgust	7.13	0.38	7.14	0.26	6.48	0.30	MNP	1.01 (0.65–1.56)	0.188
							MAP	0.74 (0.48–1.16)	0.972
Fear	6.44	0.41	6.45	0.27	6.00	0.47	MNP	1.01 (0.67–1.52)	0.978
							MAP	0.83 (0.50–1.38)	0.474
Happiness	9.75	0.11	9.54	0.12	9.52	0.15	MNP	0.53 (0.19–1.46)	0.216
							MAP	0.51 (0.17–1.47)	0.210
Sadness	7.13	0.36	7.04	0.28	5.86	0.33	MNP	0.96 (0.62–1.48)	0.856
							MAP	0.57 (0.37–0.88)	0.012
Surprise	8.31	0.28	8.52	0.19	8.31	0.24	MNP	1.17 (0.72–1.90)	0.528
							MAP	1.00 (0.60–1.66)	0.995

M, Mean; SD, Standard deviation; OR, Odds ratio.

understanding how people with methamphetamine-associated psychosis interact with others. For instance, this could serve as a mechanism underpinning aggressive behavior in methamphetamine-using populations which has been reported in previous studies (33). Positive psychotic symptoms have an established association with violence (34) and if this is associated with poorer emotion recognition in methamphetamine users, this could lead to misinterpretation of threat, resulting in individuals responding pre-emptively in an aggressive manner to benign social stimuli (33). Importantly, there is a dearth of evidence to guide de-escalation for aggression in psychosis, with a recent Cochrane review failing to identify any trials in this area (35). Our finding of poorer recognition of anger in relation to psychotic symptoms in methamphetamine-using individuals has important clinical implications for treatment providers in emergency and acute health settings, where particular attention may need to be paid to non-verbal and facial communication skills to support more effective de-escalation.

These findings suggest that psychotic symptoms may play a role in influencing social cognition in people who use MA and provide preliminary insights into the relationship between social cognition and methamphetamine-associated psychosis. Although the cross-sectional design was appropriate for between-group comparisons, other limitations of this study design are relevant (36), and we were unable to confirm the direction of association between cognitive impairment and psychotic symptoms. It is possible that impairments in cognition (including deficits in emotion recognition) pre-existed methamphetamine use and/or psychosis, reflecting a vulnerability to psychosis in this population. In this case, the presence of facial emotion recognition deficits may serve as a marker for psychosis vulnerability amongst people who use methamphetamine, and hence may be useful in identifying peopl e who would benefit from early intervention for psychosis. Conversely, it is possible that these social cognition deficits are a consequence of MAP, for example, as neuroadaptation associated with MA use may lead to cognitive impairment and psychosis (17). It is also thought that the process of psychosis itself may lead to cognitive impairment, and this would indicate that the prevention of MAP (e.g., through harm reduction and drug treatment) may also attenuate the cognitive deficits associated with chronic methamphetamine use. Further research to elucidate the chronology of cognitive deficits in relation to MAP may help reveal whether impaired social cognition is a vulnerability marker or a consequence of psychosis.

In line with recent evidence from a meta-analysis of cognition in methamphetamine dependence (17), we found performance on reward-based decision making was impaired in methamphetamine users (both MNP and MAP groups), whereas verbal memory performance was similar across all three groups. There was a significant difference in impulsivity (delay discounting) between the MNP and control group, whereas only trend-level differences were noted between MAP and control participants, suggesting that the presence of psychotic symptoms may decrease impulsivity. Heightened impulsivity has been characterized across substance use disorder groups, particularly in those with stimulant and opioid use disorders, and this may represent a premorbid trait or a consequence of substance use itself (37). Greater impulsivity has a demonstrated impact on clinical outcomes in methamphetamine-using adults, predicting poorer engagement in treatment in early recovery, and poorer quality of life (38, 39).

Strengths of this study included the use of a diagnostic interview (SCID I/P) to exclude pre-existing psychotic disorders, strengthening the interpretation that the symptoms observed in the sample were related to methamphetamine use. This is a key difference in comparison to a substantial number of studies in this area (40). We utilized the Brief Psychiatric Rating Scale (BPRS) (18), a well validated dimensional psychotic symptom measure that has been widely used in other studies of methamphetamine-associated psychosis (19, 41) and primary psychotic disorders (42).

A limitation of the study was that we did not diagnose methamphetamine-induced psychotic disorder, and we did not

distinguish between symptoms that were limited to periods of acute intoxication and those that occurred otherwise, so we cannot assume that psychotic symptoms co-occurred with methamphetamine use. However, given the almost-daily patterns of methamphetamine use reported in our sample, and considering that past research has found a strong temporal relationship between methamphetamine use and symptoms of psychosis (19), it is highly probable that symptoms were concurrent with methamphetamine use in most cases. In addition, the study did not include biological verification of methamphetamine use. This approach is consistent with that used in other studies of similar populations, and self-report has been found to be a valid and reliable indicator of drug use, particularly when there is no perceived gain or benefit associated with under-reporting of drug use (43, 44), and the Timeline Followback method used in our study has demonstrated concordance with urinalysis for amphetamines (23).

Being a naturalistic study, participants engaged in the use of other substances, most often cannabis, alcohol and prescription drug use, which could have impacted on cognitive performance. Although there were no differences between measures of alcohol and cannabis dependence between the MAP and MNP groups, non-dependent patterns of substance use may have contributed to impairments in cognitive performance. This is particularly relevant for alcohol use which is shown to impact on emotion recognition (45). Although participants were requested to abstain on the day of the assessment and were seen by clinically-trained researchers experienced in assessing signs of intoxication, we cannot completely exclude the possibility that unmeasured confounds, including acute intoxication, were responsible for cognitive impairments. Finally, although we assessed general cognitive ability using IQ, we did not have a measure of pre-morbid intelligence which may have provided a better measure of this potential confound.

CONCLUSION

Although there is a growing body of evidence that stimulant-using individuals present with impairment in social cognition (36, 46), we have shown that such deficits are related to experiencing psychotic symptoms within the past month. However, whether this is a vulnerability marker or a consequence of psychosis requires further elucidation. Nevertheless, these findings contribute to furthering our understanding of the MAP phenotype, and its overlap with other psychotic disorders, as well as having implications for the clinical management of people with this condition.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. Consent was not provided for public availability of data.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Monash University Human Research Ethics Committee (CF15/40- 2015000222). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SA, AV-G, RM, and DL contributed to study design and protocol. SA, AR and RF contributed to data collection and analysis. SA drafted and refined the manuscript. AV-G, RM and DL provided supervision of the study and edited the manuscript. All authors have reviewed the final version of the manuscript.

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Transgenic Analyses of Homer2 Function Within Nucleus Accumbens Subregions in the Regulation of Methamphetamine Reward and Reinforcement in Mice

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Problems associated with the abuse of amphetamine-type stimulants, including methamphetamine (MA), pose serious health and socioeconomic issues world-wide. While it is well-established that MA's psychopharmacological effects involve interactions with monoamine neurotransmission, accumulating evidence from animal models implicates dysregulated glutamate in MA addiction vulnerability and use disorder. Recently, we discovered an association between genetic vulnerability to MA-taking and increased expression of the glutamate receptor scaffolding protein Homer2 within both the shell and core subregions of the nucleus accumbens (NAC) and demonstrated a necessary role for Homer2 within the shell subregion in MA reward and reinforcement in mice. This report extends our earlier work by interrogating the functional relevance of Homer2 within the NAC core for the conditioned rewarding and reinforcing properties of MA. C57BL/6J mice with a virus-mediated knockdown of Homer2b expression within the NAC core were first tested for the development and expression of a MA-induced conditioned place-preference/CPP (four pairings of 2 mg/kg MA) and then were trained to self-administer oral MA under operant-conditioning procedures (5–80 mg/L). Homer2b knockdown in the NAC core augmented a MA-CPP and shifted the dose-response function for MA-reinforced responding, above control levels. To determine whether Homer2b within NAC subregions played an active role in regulating MA reward and reinforcement, we characterized the MA phenotype of constitutive *Homer2* knockout (KO) mice and then assayed the effects of virus-mediated overexpression of Homer2b within the NAC shell and core of wild-type and KO mice. In line with the results of NAC core knockdown, *Homer2* deletion potentiated MA-induced CPP, MA-reinforced responding and intake, as well as both cue- and MA-primed reinstatement of MA-seeking following

extinction. However, there was no effect of Homer2b overexpression within the NAC core or the shell on the KO phenotype. These data provide new evidence indicating a globally suppressive role for Homer2 in MA-seeking and MA-taking but argue against specific NAC subregions as the neural loci through which Homer2 actively regulates MA addiction-related behaviors.

Keywords: Homer2, place-preference, self-administration, nucleus accumbens, adeno-associated virus, knock-out

INTRODUCTION

Amphetamine-type stimulants, including methamphetamine (MA), are the most highly abused psychostimulants in the world, with an estimated 29 million users worldwide in 2017 (1) . Despite the prevalence and severity of MA Use Disorder, the lack of knowledge regarding the neurobiological substrates underlying risk, development and severity impedes therapeutic progress. MA reinforcement and psychomotor activation involves monoamine release and reuptake inhibition, particularly within dopaminergic neurons from the ventral tegmental area (VTA) to the nucleus accumbens (NAC) (2)., Accumulating evidence supports the role of glutamate transmission, especially glutamatergic projections from the prefrontal cortex (PFC) to the NAC, in both MA addiction vulnerability and the long-term neuroplasticity maintaining the MA-addicted state (3–6).

It has been known for decades that binge-like, high-dose (> 4 mg/kg) MA exposure induces glutamate-dependent neurotoxicity within the dorsal striatum (7). However, subchronic administration of subtoxic MA doses (< 2 mg/kg) can also elevate extracellular glutamate within the NAC (3, 8). In addition, such exposure is sufficient to increase the expression/function of mGlu1/5 glutamate receptors and their associated scaffolding protein Homer2 within this region (8). Indeed, a survey of the extant literature on animal models of MA abuse supports a correlative link between potentiated indices of glutamate signaling and addiction-related behavior, including self-administration, MA-induced reinstatement of drug-seeking after abstinence or extinction, incubation of MA-craving, and conditioned place-preference (CPP) (8–17).

Supporting a link between NAC glutamate and MA addiction vulnerability, drug-naïve mice selectively bred for high MA intake (MAHDR) exhibit several glutamate anomalies within the NAC, relative to MALDR mice selectively bred for low MA drinking (18–22). These differences include elevated basal and MA-induced increases in extracellular glutamate, increased expression of Homer2 and mGlu5, and decreased expression of the EAAT3 glutamate transporter responsible for clearing synaptic glutamate (3, 8). Further, NMDA glutamate receptor antagonists attenuate MA-conditioned reward and behavioral sensitization (14), while pharmacological manipulations of extracellular glutamate in the NAC bidirectionally regulate the expression of MA-conditioned reward in B6 mice (8). These results provide causal evidence for a relationship between glutamate and MA-induced behavior. Finally, small hairpin RNA (shRNA)-mediated knockdown of Homer2 expression in the shell subregion of the NAC reduces the magnitude of both a MA CPP and oral MA intake during operant-conditioning procedures (8), indicating for the first time a causal role for Homer2, at least within the NAC shell, in regulating the rewarding and reinforcing properties of MA.

The present study sought to extend our earlier results in the NAC shell (8) to the NAC core subregion and to probe the bidirectionality of the effects of transgenic manipulations of NAC Homer2 expression on MA addiction-related behaviors. The core and shell subregions of the NAC have distinct functions, connectivity, and pharmacology that are still being characterized within the context of addiction (23). Current theories argue that the NAC core is embedded within subcircuits involved in decision-making by signaling the motivational value of expected goals to guide drug-seeking in drug-experienced animals. In contrast, the NAC shell appears to be more involved in the initial affective valence of the drug during early drug experience (23). As Homer2 expression within both subregions is correlated with MA addiction vulnerability in mouse models (8), we first examined the effects of knocking down Homer2 expression in the NAC core on MA-induced CPP and the acquisition of oral MA self-administration in inbred C57BL/6J (B6) mice. The combined results of our knockdown studies suggest opposing roles for Homer2 within the NAC shell and core in regulating MA reward and reinforcement. To determine whether Homer2 contributes to the development of MA CPP and oral intake, we also determined the effects of upregulating Homer2 expression in both NAC subregions on the behavior expressed by constitutive *Homer2* knockout (KO) mice and their wild-type (WT) counterparts.

MATERIALS AND METHODS

Subjects

The knockdown studies employed adult, male C57BL/6J (B6) mice (~8 weeks of age; The Jackson Laboratory, Sacramento, CA). The remaining studies used both male and female adult (6–8 weeks of age) *Homer2* KO and wild-type (WT; on a mixed 129X1/svJ X C57BL/6J background) mice [see (24)] that were bred in-house from the mating of heterozygous breeder pairs in the Psychological and Brain Sciences vivarium at UCSB. Animals were housed in groups of 3–5 mice in standard ventilated polycarbonate cages, under standard, reverse-light, housing

conditions in an AAALAC-accredited vivarium (lights on/off: 2200/1000 h), with *ad libitum* access to food and water. All behavioral procedures were conducted during the dark phase of the circadian cycle. All procedures were consistent with NIH guidelines and approved by the Institutional Animal Care and Use Committee of UCSB.

General Experimental Design

Homer2 within the NAC regulates both cocaine- (25) and alcohol-induced (26–30) changes in behavior in murine models, but the subregional specificity of Homer2's role in MA-related behavior has received relatively little experimental attention (8). Thus, two experiments were conducted to further address the role for NAC Homer2 expression in gating the rewarding and reinforcing properties of MA. The first experiment in this report sought to extend the results of a prior study of the NAC shell (8) to the NAC core by determining whether or not Homer2 expression within the NAC core is necessary for MA reward/reinforcement. To accomplish this, the first experiment in this report employed a similar experimental design and approach as that described in our previous report (8), which involved knocking down Homer2b expression in the NAC core of B6 mice using an adeno-associated viral vector (AAV) carrying a small hairpin RNA (shRNA) against *Homer2b*. Control animals were infused with an AAV carrying green fluorescent protein (GFP). The details of the AAV-shRNA construct and the control AAV are provided in Klugmann and Szumlinski (31) and Cozzoli etal. (29) and the details of the specific procedures employed in this shRNA study are provided in the subsections below. A time-line of the procedures is provided in **Figure 1A**.

Combined, the results of our prior shRNA study of the NAC shell (8) and those of the present study of the NAC core (see Results below) argued that Homer2 expression within the NAC shell and core plays opposing roles in gating MA reward/reinforcement, with Homer2 in the shell promoting, and Homer2 in the core, suppressing MA addiction-related behaviors. Thus, a follow-up experiment was conducted to determine whether or not mimicking a MA-induced increase in Homer2 expression within the NAC shell and core (8) would be sufficient to respectively promote and suppress MA-induced place- and operant-conditioning. To address this question, we employed an AAV *Homer2b*-cDNA strategy similar to that used in previous studies from our laboratory (25, 26, 32). As in our earlier work [e.g., (25)], we infused a *Homer2b* AAV-cDNA construct [see (25) and (31) for details of the cDNA construct] into the NAC shell or core of *Homer2* WT and constitutive KO mice, the latter of which enabled determination of an active role for Homer2 within each subregion in gating behavior. As the effects of constitutive *Homer2* deletion upon MA addiction-related behaviors had yet to be characterized, we first compared the MA place- and operant-conditioning phenotypes of *Homer2* KO and WT mice on a mixed B6-129 hybrid genetic background. Then, we replicated the experiment in a second cohort of *Homer2* KO and WT mice infused with either the AAV-cDNA or -GFP control. A time-line of procedures is presented in **Figure 5A**.

Surgeries and AAV Infusion

The surgical procedures to infuse the AAVs carrying either shRNA-Homer2b, cDNA-Homer2b, or cDNA-GFP were consistent with those previously described by our laboratory (8, 29, 33). For B6 mice, we used the following stereotaxic coordinates from Bregma (in mm): for core, AP: +1.3; ML: ± 1; DV: −4.3; for shell, AP: +1.3; ML: ± 0.5; DV: −4.8. Based on our experience conducting craniotomies on B6-129 hybrid mice [e.g., (25, 29, 33)], the following stereotaxic coordinates were used for *Homer2* KO and WT mice: for core, AP: +1.4; ML: ± 1; DV: −4.3; for shell, AP: +1.4; ML: ± 0.5; DV: −4.6. Mice were anesthetized with 1.5% isoflurane and positioned on the stereotaxic apparatus. Thirty gauge microinjectors (12 mm) were lowered bilaterally, directly into the core or shell. AAVs were infused at a rate of 0.10 μl/min for 5 min (total volume/side = 0.50 μl), and injectors were left in place for an additional 5 min prior to closing the incision site with tissue adhesive. The shRNA and cDNA infusions procedures have been demonstrated previously to reduce and increase, respectively, Homer2b protein expression in mouse brain by approximately 50% (31, 33, 34). Animals were left in their home cages for a minimum of 3 weeks prior to behavioral testing to allow for maximal neuronal transduction (31).

Place-Conditioning and Locomotor Activity

MA place-conditioning procedures also followed those previously employed by our laboratory (8) and included three main phases: habituation/preconditioning test (day 1), MA/saline (SAL) conditioning (days 2–9), and a postconditioning test (day 10, post-test). The apparatus consisted of two distinct compartments—one with black and white marble-patterned walls and a textured floor, and the other with wood-patterned walls and a smooth Plexiglas floor. During the habituation and post-test sessions, mice were allowed free-access to both compartments for 15 min *via* a divider with a door. During conditioning, mice received 2 mg/kg MA intraperitoneal (IP) injections and were immediately confined to one of the compartments. On alternating days, mice were injected with an equivalent volume of SAL (10 ml/kg) and confined to the other compartment. Each conditioning session was 15 min in duration and mice received four conditioning sessions for each unconditioned stimulus. Overall, mice did not exhibit a strong preference for one compartment vs. the other during the habituation session, so the time spent on the SAL-paired side during the post-test was subtracted from the time spent on the MA-paired side to calculate a CPP score (8, 35). This CPP score served to index the direction and magnitude of the MA-conditioned reward. During each 15-min session, the locomotor activity of the animals was recorded by digital video cameras, interfaced with a PC-type computer equipped with ANY-Maze software (Stoelting), recorded the distance traveled (in m) during each of the sessions. As in our prior studies [e.g., (8)], MA-induced locomotor sensitization was measured by subtracting the distance travelled during the first 15-min MA-conditioning session from that on the fourth/last MA-conditioning session.

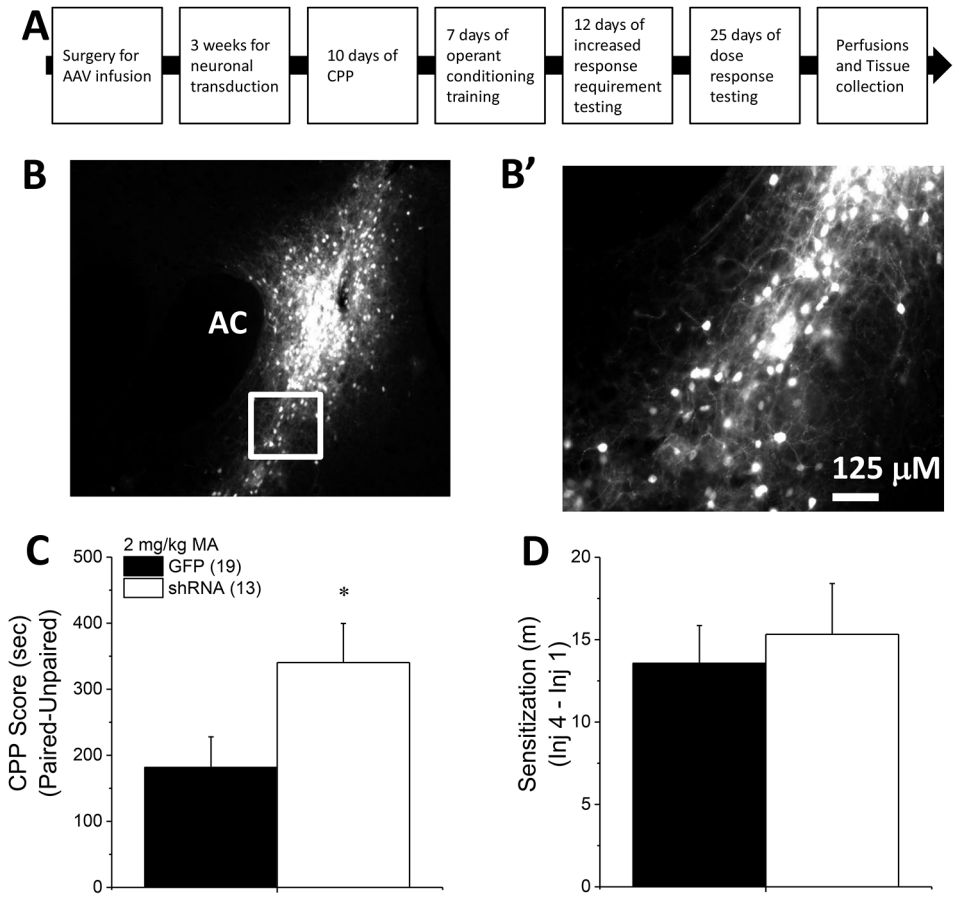

FIGURE 1 | Homer2b knockdown in the nucleus accumbens (NAC) core potentiates a methamphetamine (MA)-induced CPP. **(A)** The procedural timeline for the study examining the effects of shRNA-mediated knock-down of Homer2b within the NAC core. Representative micrographs of the neuronal transduction within the NAC core by green fluorescent protein (GFP)-tagged adeno-associated viral vector (AAV)-shRNA against Homer2b at 10 X magnification **(B)** and 40 X magnification **(B')**. AC, anterior commissure. **(C)** shRNA infusion potentiated MA-induced place conditioning, without altering the magnitude of locomotor sensitization that developed during conditioning **(D)**. The data represent the means ± SEMs of the number of mice indicated in Panel **B**. *$p < 0.05$ vs. GFP.

Operant-Conditioning

In our prior study of the effects of Hoemr2 knock-down in the NAC shell (8), the generalization of a place-conditioning phenotype to operant-conditioning for MA reinforcement was determined using a within-subjects design. To the best of our knowledge, a parametric analysis of the effects of prior behaviorally non-contingent MA upon subsequent drug-taking has not been performed. Thus, we cannot speak to any potential effects our place-conditioning procedures might have upon the MA self-administration of the mice. However, we do know from our prior study of B6 mice, that a mere history of non-contingent MA treatment (four injections of 2 mg/kg MA, as employed in the present study) does not necessarily promote subsequent MA reinforcement/intake as MA-injected mice self-segregate into high versus low MA-taking phenotypes when allowed to orally self-administer the drug (8). To be consistent with our prior study (8), following place-conditioning procedures, mice were trained in daily 1-h sessions to nose-poke for delivery of unadulterated MA solutions (prepared in tap water; reinforcer volume = 20 μl). Standard mouse operant-conditioning chambers (MedAssociates, St Albans, VT, USA) were used to measure instrumental responding for MA. Operant chambers were fitted with two nose-poke holes, with a liquid receptacle located in-between and chambers were housed in ventilated, sound-attenuated chambers. Responses in the active (MA-associated) hole resulted in the activation of the infusion pump, delivery of 20 μl MA into the receptacle, and the presentation of a 20-s light/tone compound stimulus. During the 20-s MA-delivery period, further responding in the active hole was recorded but had no programmed consequences. Throughout the session, responding in the inactive hole had no programmed consequences but was recorded to assess the selectivity of responding in order to determine reinforcer efficacy. Mice were first trained for 7 days to nose-poke for delivery of a 10-mg/L MA solution under an FR1 schedule of reinforcement. Animals that did not reach the acquisition criteria of at least 10 active nose-pokes during the 1-h session, with greater than 65% of their total nose-pokes directed at the active

hole were excluded from the study. Using these criteria, 9/48 mice were excluded from the shRNA study and 20/114 mice were excluded from the cDNA studies. As in our prior study of the NAC shell (8), we next progressively increased the number of nose-pokes required for delivery of the 10 mg/L MA reinforcer (maintaining the 20-s time-out) over subsequent days (4–5 days/schedule). We then conducted a dose-response study of MA reinforcement and intake (5–80 mg/L) under the initial FR1 (20-s time-out) reinforcement schedule (5 days/dose) as data indicated an inverse relationship between MA intake and reinforcement schedule (see Results). Given the inverse relationship between operant-responding and reinforcement schedule, we opted to forego this phase of testing in the cDNA study and animals proceeded from training directly into dose-response testing. In the operant-conditioning study of *Homer2* WT and KO mice, technical issues interfered with the testing of 13 of the 21 WT mice at the 80 mg/L concentration. As such, the data from this concentration were analyzed separately from the rest of the dose-response function.

At the end of each 1-h operant session, the volume of solution remaining in the receptacle was determined by pipetting. Mice were returned to the colony room and left undisturbed until the next day. Total MA intake was calculated each day by subtracting the volume of MA remaining in the receptacle from the total volume delivered to determine the total volume of MA consumed. The volume consumed was converted into mg consumed based on the concentration of the solution and then amount of MA intake was expressed as a function of body weight (in mg/kg), which was measured weekly (8).

Extinction and Reinstatement of the Operant Response

In the cDNA study, the strength of the conditioned operant response was established by repeatedly testing mice in daily operant sessions in a MA-free state, with no light/tone stimulus, until the number of active nose-pokes in a 1-hr session dropped to 25% of initial MA-free responding (i.e., extinction). Animals that did not reach these extinction criteria within 30 days were excluded from the remainder of the study. Two additional mice from the cDNA studies were excluded for failing to reach extinction criteria. This extinction procedure was conducted immediately upon the completion of dose-response testing (see above). Following extinction, AAV-infused mice were then subjected to a series of reinstatement of MA-seeking tests in which responding in the active hole resulted in the presentation of only the light/tone stimulus previously predictive of MA delivery (i.e., MA reinforcement was withheld during reinstatement testing). For reinstatement testing, mice were administered a once-daily IP injection of 0.0 (SAL), 0.5 or 0.25 mg/kg MA, with doses increased across days, to examine the degree of cue- and MA-induced reinstatement of the conditioned response. Immediately following injection, mice were placed into the operant-conditioning chamber for a period of 1 h, at which time they were removed and returned to their home cages and the number of active versus inactive nose-pokes were recorded.

Histology

The goal of this study was to determine the subregional specificity of the effects of AAV-mediated Homer2 manipulations within the NAC for MA addiction-related behavior. As such, we deemed it important to determine the neuroanatomical specificity of AAV infusion and thus, employed immunohistochemical, *in lieu* of immunoblotting, procedures to localize neuronal transduction within the NAC shell versus core. For this, animals were euthanized with an overdose of Euthasol (Virbac AH, Fort Worth, TX, USA) and transcardially perfused with phosphate-buffered saline (PBS), followed by 4% paraformaldehyde. Brains were then removed and cold-stored in PBS until slicing. Tissue was sectioned (40 μm) along the coronal plane on a vibratome at the level of the NAC. As in our recent work (8), localization of the transfection of neurons by our shRNA-Homer2b, as well as by our GFP control viruses, was examined using an anti-GFP antibody (Invitrogen, Carlsbad, CA, USA; 1:200 dilution) and fluorescence microscopy. As in our prior work (8, 25, 26), tissue from cDNA-Homer2b infused mice was stained with a mouse antihemagglutinin (HA) primary antibody (Biolegend, San Diego, CA, USA; 1:1,000 dilution) to visualize the viral construct, followed by a biotinylated antimouse secondary IgG (Vector Laboratories, Burlingame, CA, USA; 1:2,000 dilution), and visualized with 3,3'-diaminobenzidine (DAB). Poststaining, all tissue was mounted on slides and cover-slipped. Slides were viewed using a Nikon Eclipse E800 microscope equipped with a Hamamatsu CCD camera (model C4742-95) and MetaMorph imaging software (Molecular Devices, Sunnyvale, CA, USA). Only mice exhibiting localized neuronal transduction within the NAC shell and core subregions were included in the statistical analyses of the results.

Statistical Approaches

The effects of Homer2b knockdown in the NAC core upon place-conditioning related measures were analyzed using t-tests. The operant-conditioning data were analyzed using multivariate ANOVAs, with the between subjects factors of Sex and AAV (GFP vs. shRNA or GFP vs. cDNA) and/or Genotype (WT vs. *Homer2* KO) and the within-subjects factors of Day, FR schedule, and Dose, when appropriate. As initial analyses of the data for both place- and operant-conditioning in *Homer2* WT and KO mice indicated no main Sex effects or interactions, the data were collapsed across sex prior to reanalyses. As described above, the data for *Homer2* WT/KO mice tested for the self-administration of 80 mg/L MA were analyzed separately using t-tests. Two-tailed Pearson correlational analyses were also conducted to relate dependent measures with CPP score. α = 0.05 for these analyses. The effects of *Homer2* KO on the dose-response function for MA-induced place-conditioning were analyzed using ANOVAs, with the between-subjects factors of Genotype (WT vs. KO) and Dose (0.5–4.0 mg/kg MA, 4 levels). All data was analyzed using SPSS ver 12 (IBM) and for all ANOVAs, the homogeneity of variance was confirmed. Alpha was set at 0.05 for all analyses.

RESULTS

Homer2 Knockdown in the NAC Core Augments a MA CPP in B6 Mice

To extend recent results for the NAC shell (8) to the core subregion, B6 mice were infused with an AAV carrying shRNA to knockdown *Homer2b* in the NAC core and then tested for MA-induced CPP. Expression of the AAV was confirmed as confined to the NAC core using fluorescence microscopy (**Figures 1B, B'**). shRNA-infused mice exhibited higher CPP following four pairings of 2 mg/kg MA than GFP-infused controls (**Figure 1C**) [$t(30) = 2.14$, $p = 0.04$]. The shRNA-Homer2b NAC core infusion did not affect the acute locomotor response to MA [data not shown; $t(30) = 0.39$, $p = 0.70$], nor did it alter the magnitude of MA-induced locomotor sensitization that developed over the course of the conditioning (**Figure 1D**) [$t(30) = 0.47$, $p = 0.64$]. These data indicate that Homer2 within the NAC core normally suppresses the positive affective and motivational valence of MA, independent of effects upon without interfering with the locomotor-activating effects of the drug.

Homer2 Knockdown in the NAC Core Augments Oral MA Reinforcement Intake in B6 Mice

During the first 5 days of self-administration training under an FR1 reinforcement schedule, both GFP and shRNA animals exhibited a similar pattern of active nose-pokes (**Figure 2A**) [Day effect: $F(1,29) = 28.33$, $p < 0.0001$; AAV effect, interaction: p's > 0.10], ratio of active vs. inactive responding (**Figure 2B**)

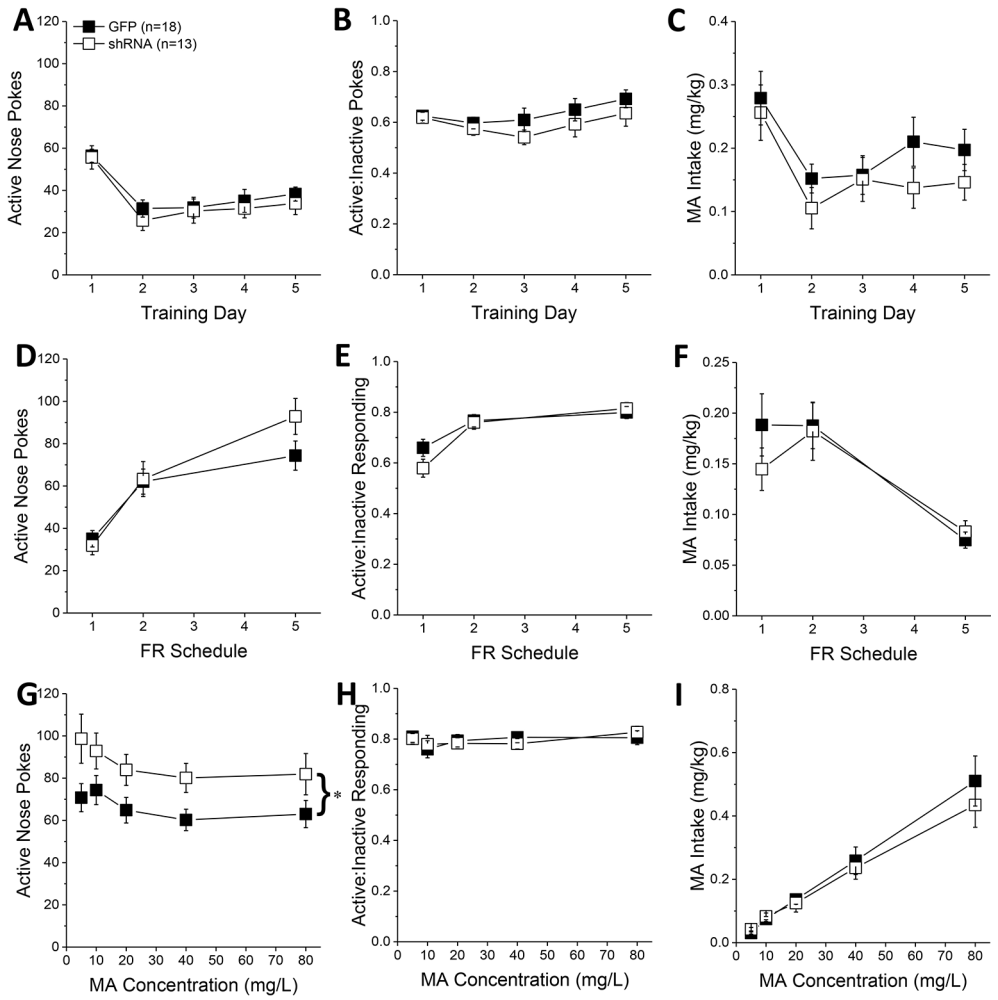

FIGURE 2 | Homer2b knockdown in the nucleus accumbens (NAC) core increases methamphetamine's (MA's) reinforcing efficacy without altering MA intake. shRNA against Homer2 did not influence: **(A)** the number of active nose pokes, **(B)** the relative responding on the active versus inactive hole or **(C)** MA intake during the first 5 days of self-administration training (10 mg/L MA as reinforcer). **(D–F)** shRNA infusion also did not alter these measures when mice were tested under increasing response requirements on an FR schedule of reinforcement. **(G)** shRNA infusion shifted the dose-response function for active hole poking upwards of green fluorescent protein (GFP) controls but did not affect the dose-response functions for **(H)** response allocation or **(I)** MA intake. The data represent the means ± SEMs of the number of mice indicated in Panel **A**. *$p < 0.05$ vs. GFP [main adeno-associated viral vector (AAV) effect].

[Day effect: F(1,29) = 2.56, p = 0.04; AAV effect and interaction, p's > 0.20], and MA intake (**Figure 2C**) [Day effect: F(1, 29) = 12.20, p = 0.002; AAV effect, interaction: p's > 0.10]. When tested under increasing response requirements, responding on the active lever increased (**Figure 2D**) [FR effect: F(1,29) = 76.00, p < 0.0001], the ratio of active vs. inactive responding increased (**Figure 2E**) [FR effect: F(1,29) = 25.32, p < 0.0001], and MA intake decreased (**Figure 2F**) [FR effect: F(1,29) = 20.17, p < 0.0001], but there was no effect of Homer2b knockdown on any of these measures (**Figures 2D–F**; AAV effects and interactions, all p's > 0.20). Thus, Homer2 within the NAC core is not necessary for the acquisition of oral MA self-administration or MA demand, at least when behavior is reinforced by a low, 10 mg/L MA concentration.

In contrast, Homer2b knockdown in the NAC core shifted upwards the dose-response function for active nose-poking behavior (**Figure 2G**) [AAV effect: F(1,29) = 5.31, p = 0.03; Dose effect: F(1,29) = 4.65, p = 0.002; interaction, p = 0.799], without impacting the ratio of active vs. inactive responding (**Figure 2H**; AAV X Dose ANOVA, p's > 0.35), or the dose-response function for MA intake (**Figure 2I**) [Dose effect: F (1,29) = 77.35, p < 0.0001; AAV effect, interaction, p's > 0.30]. These data indicate that Homer2 within the NAC core normally curbs the reinforcing efficacy of MA in mice with a history of self-administration, but this effect does not translate into a change in MA intake.

Constitutive *Homer2* KO Increases Ma-Induced CPP

The results of our shRNA study above indicate that Homer2 within the NAC core normally suppresses behavioral indices of MA reward and reinforcement, which is a finding opposite to that reported for Homer2 in the NAC shell (8). Thus, we employed a complementary AAV-cDNA strategy (25, 26, 29) in WT littermates and *Homer2* KO mice to determine whether Homer2 in the NAC shell promotes, while that in the core suppresses, MA place- and operant-conditioning. We know that *Homer2* KO mice exhibit greater sensitivity to the psychomotor-activating effects of MA (36); however, their MA reward/reinforcement phenotype has yet to be characterized. Therefore, we first assayed the effects of a constitutive *Homer2* KO on MA place- and operant-conditioning. A genotypic comparison of the dose-response function for the time spent in the MA-paired vs. -unpaired side during the post-test phase of place-conditioning indicated greater MA-induced CPP, irrespective of MA dose (**Figure 3A**) [Genotype effect: F(1, 86) = 14.83, p < 0.0001; Genotype X Dose: F(3, 86) = 2.54, p = 0.06], although the genotypic difference in MA-conditioned behavior was most obvious at lower MA concentrations. Despite exhibiting potentiated MA-conditioned reward, *Homer2* KO mice did not differ significantly from WT littermate controls regarding the acute locomotor stimulatory effects of MA during the first conditioning session (**Figure 3B**) (Genotype X Dose ANOVA, all p's > 0.14) or in the capacity of the four MA injections to elicit a dose-dependent sensitization of locomotion during the conditioning phase of the study, as determined by the difference in the distance traveled from the first to the forth injection (**Figure 3C**) [Dose effect: F(1,79) = 8.00, p < 0.0001; Injection: F(3,237) = 8.94, p < 0.0001; Dose X Injection: F(9,237) = 2.47, p = 0.01; Genotype X Dose: F(3,79) = 2.23, p = 0.09; all other p's > 0.30]. While this result contradicts our earlier report, these conditioning sessions were only 15-min long, while in Szumlinski et al. (36), the sessions were 1 h so the difference in duration of testing likely mitigated genotypic differences.

Constitutive *Homer2* KO Increases MA-Reinforcement and Intake

The number of active hole pokes emitted by KO mice progressively increased across training days, whereas the responding of WT mice fluctuated during early training (**Figure 4A**) [Genotype X Day: F(4, 140) = 5.71, p < 0.0001]. *Post hoc* analyses indicated greater active hole responding in KO versus WT mice on day 2, 3, and 5 of training (**Figure 4A**; t-tests, p's < 0.03). No genotypic differences were observed for the number of inactive hole pokes (data not shown; Genotype X

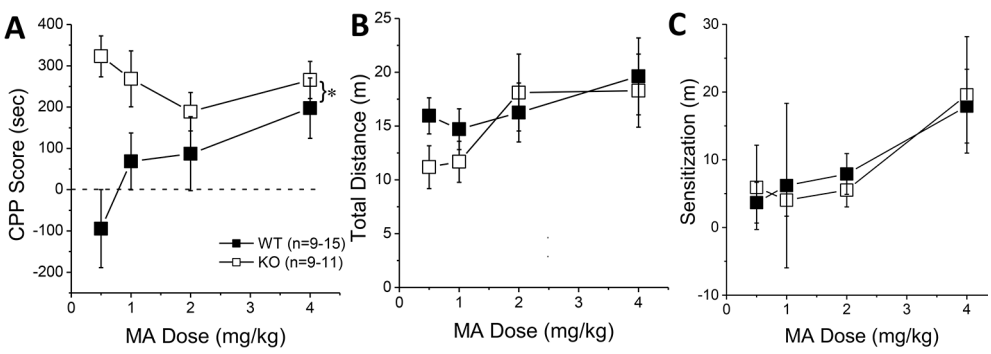

FIGURE 3 | Constitutive *Homer2* deletion augments a methamphetamine (MA)-induced conditioned place-preference (CPP). When compared to wild-type (WT) mice, *Homer2* knockout (KO) animals exhibited **(A)** a shift upwards in the dose-response function for a MA-induced CPP. In contrast, gene deletion did not alter the dose-response functions for **(B)** acute MA-induced locomotor activity or **(C)** the increase in locomotor activity from the first to the last MA-conditioning session (sensitization). The data represent the means ± SEMs of the number of mice indicated in Panel **A**. *p < 0.05 vs. WT (main Genotype effect).

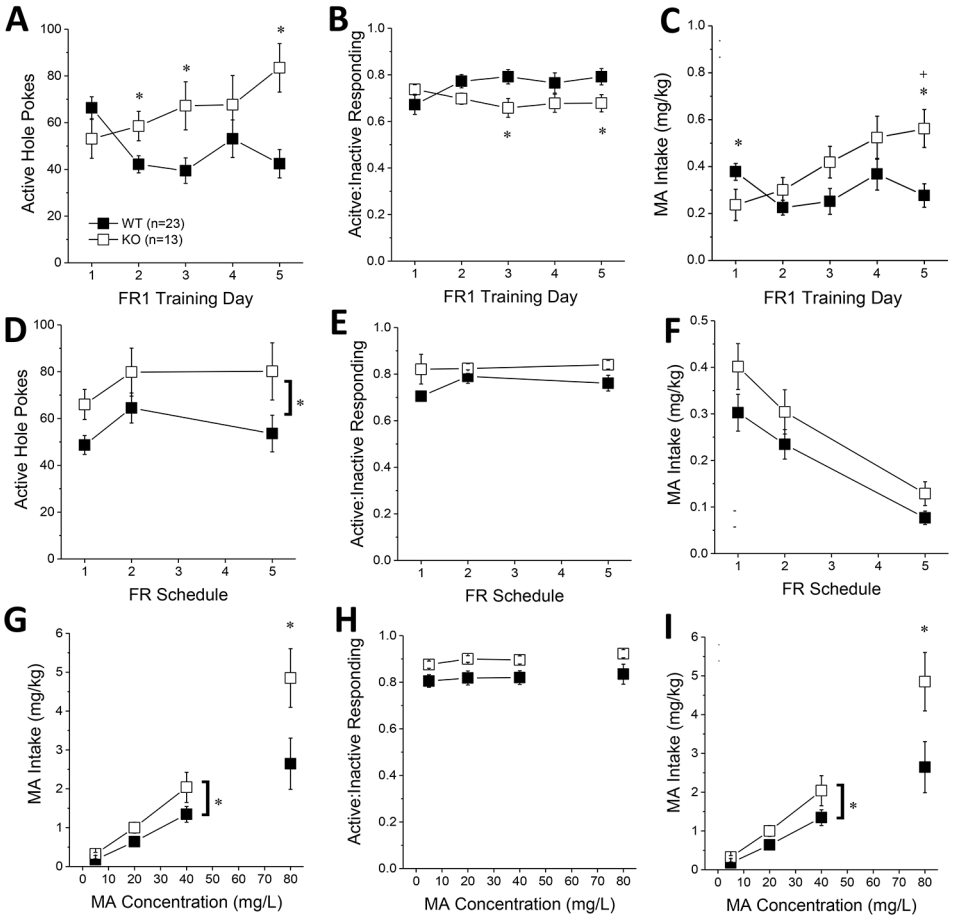

FIGURE 4 | Constitutive Homer2 deletion increases methamphetamine (MA) reinforcement and intake. When compared to WT mice, Homer2 knockout (KO) mice exhibited a greater: **(A)** the number of active nose pokes, **(B)** relative responding on the active versus inactive hole and **(C)** MA intake during the first 5 days of self-administration training (10 mg/L MA as reinforcer). **(D)** *Homer2* KO mice also exhibited more active hole responding under increasing response requirement but did not differ from WT mice regarding **(E)** response allocation or **(F)** MA intake during this phase of testing. Relative to WT mice, the dose-response function for active hole-responding was shifted upwards **(G)**, without a change in that for response allocation in the active hole **(H)**. **(I)** KO mice also consumed more MA than wild-type (WT) mice across the range of doses tested. The data represent the means ± SEMs of the number of mice indicated in Panel **A**. *p < 0.05 vs. WT (main Genotype effect).

Day, all p's > 0.25). However, KO mice tended to exhibit lower active vs. inactive responding than WT mice during early training (**Figure 4B**) [Genotype X Day, F(4,140) = 3.59, p = 0.008], with *post-tests* indicating significantly lower relative responding on Days 3 and 5 of training (t-tests, p's < 0.04). Despite the lower active nose-poke responding in KO, only the KO mice escalated their MA intake during early training (**Figure 4C**) [Genotype X Day: F(4, 140) = 5.98, p < 0.0001]. While *Homer2* KOs exhibited significantly lower MA intake than WT animals on the first training day [t(35) = 2.05, p = 0.05], their MA intake was significantly higher than WT animals by the 5th training day [t(35) = 3.18, p = 0.003]. Thus, constitutive *Homer2* deletion increases low-concentration MA reinforcement and intake during early training in a manner similar to shRNA-mediated knockdown of Homer2b expression within the NAC core.

When the response requirement for reinforcement by 10 mg/L MA progressively increased across days, KO mice exhibited more active hole responding, overall, than WT mice (**Figure 4D**) [Genotype effect: F(1,35) = 5.27, p = 0.03; interaction: p > 0.6]. The number of inactive hole pokes declined with increasing response requirement (data not shown) [Schedule effect: F(2,70) = 15.85, p < 0.0001] but was not influenced by genotype (all p's > 0.60). In contrast to the early acquisition phase (**Figure 4B**), KO mice exhibited slightly higher active hole response allocation than WT mice during this phase of testing (**Figure 4D**) [Genotype effect: F(2,70) = 3.63, p = 0.07; Day effect and interaction, p's > 0.15]. The MA intake of KO mice was also slightly higher than WT controls as response requirement increased (**Figure 4E**) [Genotype effect: F (1,35) = 3.26, p = 0.08; FR effect: F(2,70) = 43.48, p < 0.0001; interaction: p = 0.68]. These data provide some limited evidence

that constitutive *Homer2* deletion increases demand for a low-concentration MA solution.

The dose-response function (5–40 mg/L MA) for active hole pokes under the original FR1 schedule of reinforcement was shifted upward in KO mice, compared to WT mice [Genotype effect: $F(1,35) = 5.57$, $p = 0.02$; interaction, $p > 0.10$], an effect especially apparent at lower MA doses (**Figure 4F**). KO mice also tended to exhibit higher active hole responding for the 80 mg/L solution (t-test, $p = 0.09$). Inactive hole pokes declined as a function of MA concentration, but no genotypic differences were detected (data not shown) [5–40 mg/L MA: Dose effect: $F(2,70) = 4.19$, $p = 0.02$; Genotype effect and interactions, p's > 0.40; 80 mg/L: t-test, $p = 0.25$]. KO mice continued to show modestly higher relative responding on the active versus inactive lever during dose-response testing, but genotypic differences were not statistically significant (**Figure 4H**; 5–40 mg/L: Genotype X FR ANOVA, p' > 0.10; at 80 mg/L, WT vs. KO: t-test, $p = 0.06$). Finally, in contrast to Homer2 knockdown (**Figure 2I**), the MA dose-intake function was shifted upwards in KO versus WT mice (**Figure 4I**) [5–40 mg/L: Genotype effect: $F(1,35) = 4.70$, $p = 0.04$; Dose effect: $F(2,70) = 50.73$, $p < 0.0001$; Genotype X Dose: $p = 0.17$; 80 mg/L: $t(22) = 2.16$, $p = 0.04$]. These latter data indicate that the potentiation of MA reinforcement and intake by constitutive *Homer2* deletion extends across a relatively broad dose-range.

Homer2b Overexpression in the NAC Core, But Not Shell, Augments a MA-Induced CPP

The final series of experiments examined the effects of Homer2b overexpression within the NAC core and shell of *Homer2* WT and KO mice upon MA-induced place- and operant-conditioning. Immunohistochemical staining for the HA-tag indicated neuronal transduction within the NAC core (**Figure 5B**) that was comparable to that observed in prior reports from our group (e.g., 25, 28). Intriguingly, similar to NAC core knockdown of Homer2b (**Figure 1C**) and constitutive *Homer2* deletion (**Figure 3A**), Homer2b overexpression within the NAC core also potentiated the magnitude of a CPP induced by the repeated pairing of 2 mg/kg MA (**Figure 5D**) [AAV effect: $F(1,33) = 7.18$, $p = 0.01$]. While the initial dose-response study failed to support genotypic differences in the magnitude of the conditioned response elicited by pairing with 2 mg/kg MA (**Figure 3A**), the CPP elicited by this dose in the cDNA study was lower overall in KO versus WT mice (**Figure 5D**) [Genotype effect: $F(1,33) = 6.20$, $p = 0.02$; interaction: $p = 0.74$]. Homer2b overexpression within the NAC core did not influence the acute locomotor-response to 2 mg/kg MA (**Figure 5E**; Genotype X AAV ANOVA, p's > 045) nor did it influence the sensitization of this response during conditioning (**Figure 5F**; Genotype X AAV ANOVA, p's > 0.20). Thus, curiously, overexpressing Homer2b within the NAC core produces an effect on MA-conditioned reward akin to that observed upon either constitutive gene deletion (**Figure 3A**) or protein knockdown within this region (**Figure 1C**).

Immunohistochemical staining indicated robust neuronal transfection within the NAC shell, with no overt signs of infection or tissue damage (**Figure 5C**). Thus, we were surprised that the level of MA-induced place-conditioning was lower overall in the mice infused with GFP/cDNA into the NAC shell (**Figure 5G**), than that observed for the other place-conditioning experiments in this report. This low level of conditioning may have precluded our ability to detect group differences in the MA-conditioned response (Genotype X AAV, all p's > 0.15). Despite lower CPP Scores, the locomotor response to an acute injection of 2 mg/kg MA was comparable to that observed in the other studies herein and was not affected by either *Homer2* deletion or intra-shell cDNA infusion (**Figure 5H**; Genotype X AAV ANOVA, all p's > 0.07). Although intra-NAC shell cDNA infusion appeared to augment the difference in MA-induced locomotor activity observed from the first to the forth conditioning session (sensitization), this effect was not statistically significant (**Figure 5I**; Genotype X AAV ANOVA, all p's > 0.06). These data do not support an active role for Homer2b within the NAC shell in gating MA-induced locomotion or -conditioned reward under place-conditioning procedures.

Homer2b Overexpression Within NAC Subregions Does Not Influence the Acquisition of Oral MA Self-Administration

Based on the above results, we predicted that the effects of Homer2b overexpression upon place-conditioning would translate to operant-conditioning procedures. However, we found that Homer2b-cDNA infusion into either the NAC core (**Figures 6A–C**) or shell (**Figures 6D–F**) had no significant effect on any measure during the first 5 days of training under operant-conditioning procedures. A significant Genotype X Day interaction was detected for active hole responding in mice infused intra-NAC core (**Figure 6A**) [$F(4,120) = 2.83$, $p = 0.03$] that reflected a differential time-course of acquisition between WT and KO mice as *post hoc* comparisons between WT and KO mice failed to indicate genotypic differences in responding on any training day (t-tests, p's > 0.15). In neither genotype did NAC core Homer2b overexpression alter active hole responding during the first 5 days of self-administration training (AAV effect and interactions, p's > 0.20). In mice infused intra-NAC core, response allocation increased progressively during early training (**Figure 6B**) [Day effect: $F(4,120) = 4.2$, $p = 0.003$] and KO mice exhibited overall greater MA-appropriate responding than WT mice during this phase of study [Genotype effect: $F(1,30) = 4.34$, $p = 0.05$]. However, this measure was not altered by Homer2b overexpression within the NAC core (no AAV effect or interactions, p's > 0.10). Finally, KO mice tended to consume more MA during the first 5 days of training (**Figure 6C**; Genotype X Day: $p = 0.09$), but there was no effect of intra-NAC core infusion of Homer2b cDNA upon MA intake during early training (AAV effect and interactions, p's > 0.25). Taken together, these data do not support an effect of Homer2b overexpression within the NAC core in regulating initial MA reinforcement or intake.

Initial active hole responding was lower in mice infused with Homer2b-cDNA into the NAC shell than that typically observed

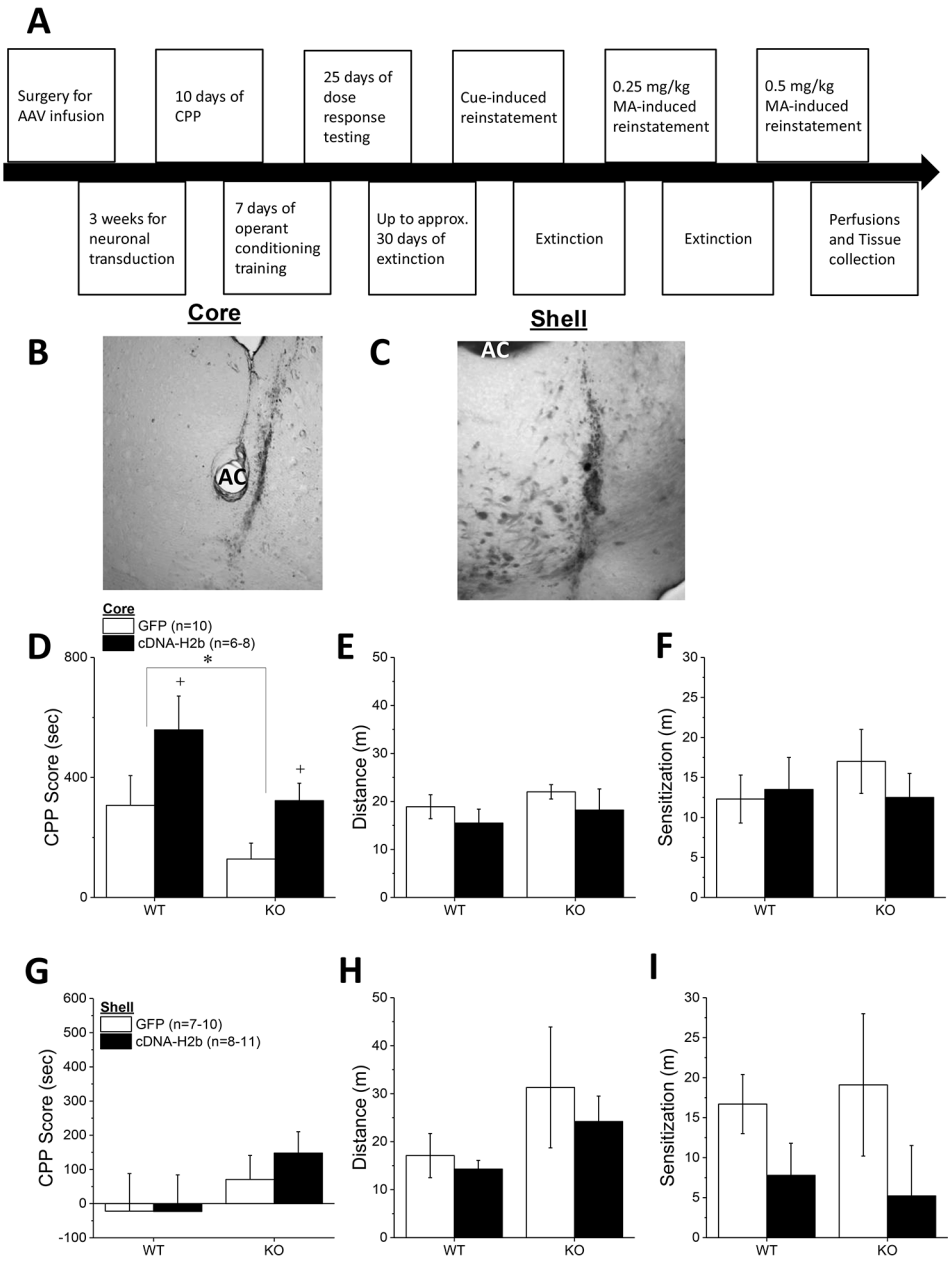

FIGURE 5 | Homer2b overexpression in the nucleus accumbens (NAC) core, but not NAC shell, potentiates a methamphetamine (MA)-induced conditioned place-preference (CPP). **(A)** The procedural time-line for the study examining the effects of cDNA-mediated overexpression of Homer2b within the NAC core and shell. Representative micrographs of the neuronal transduction within the NAC core **(B)** and NAC shell **(C)** by antihemagglutinin (HA)-tagged adeno-associated viral vector (AAV)-cDNA encoding Homer2b (images at 20 X magnification). AC, anterior commissure. **(D)** The magnitude of a MA-induced CPP was lower in Homer2 knockout (KO) mice versus wild-type (WT) controls and cDNA infusion into the NAC core potentiated MA-induced place conditioning in both genotypes, without affecting the **(E)** acute or **(F)** sensitized locomotor response to MA. No genotypic difference or cDNA effect were apparent for **(G)** MA-induced CPP, **(H)** the acute locomotor response to MA or **(I)** the magnitude of MA-induced locomotor sensitization, when the cDNA was infused into the NAC shell. The data represent the means ± SEMs of the number of mice indicated in Panel **C** for NAC core and Panel **F** for NAC shell. $^{*}p < 0.05$ vs. WT; $^{+}p < 0.05$ vs. GFP.

under our oral MA operant-conditioning procedures (**Figure 6D**) and the Genotype X Day interaction failed to reach statistical significance [Day effect: $F(4,128) = 4.79$, $p = 0.001$; Genotype X Day, $p = 0.095$]. However, as observed for the NAC core, intra-NAC shell cDNA infusion did not alter active hole responding (AAV effect and interactions, p's > 0.22). In mice infused intra-NAC shell, response allocation progressively increased across day, irrespective of the genotype or AAV treatment (**Figure 6E**) [Day effect: $F(4,128) = 8.80$, $p < 0.0001$; no interactions with the Day factor, p's > 0.25]. However, in

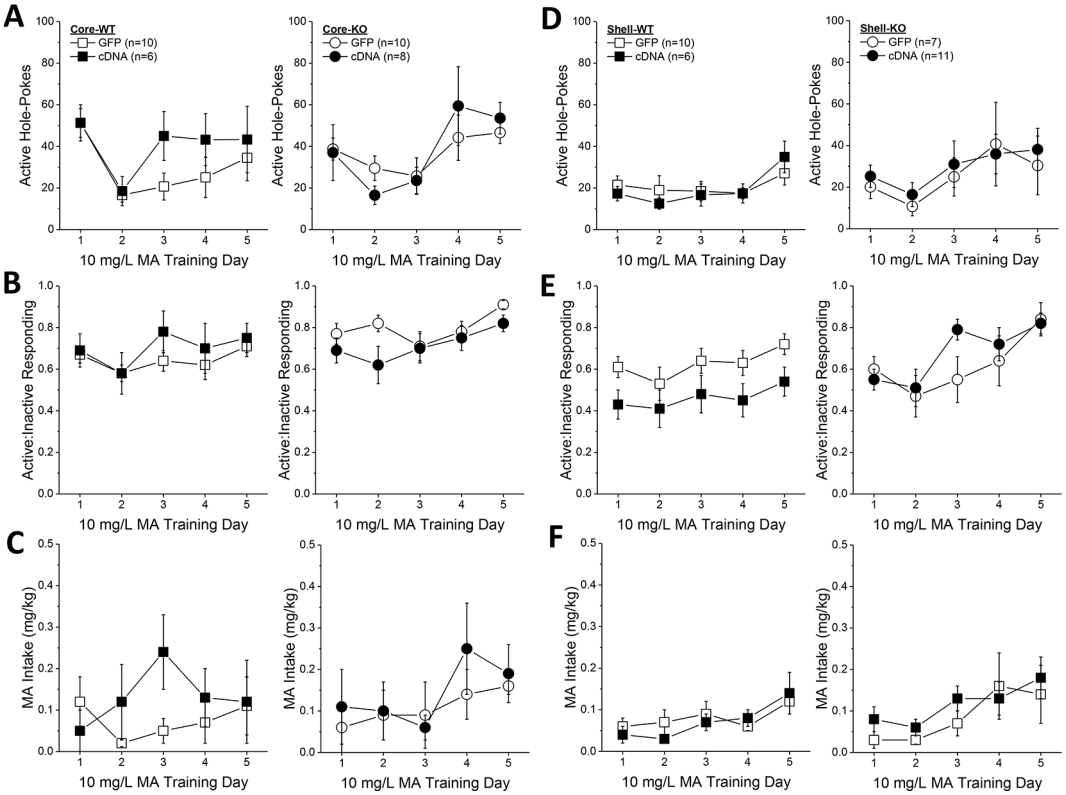

FIGURE 6 | Homer2b overexpression does not alter methamphetamine (MA) reinforcement and intake during early training for MA self-administration. When compared to WT (left) and Homer2 knockout (KO) (right) mice infused with green fluorescent protein (GFP), cDNA infusion into the nucleus accumbens (NAC) core did not alter: **(A)** active hole responding, **(B)** response allocation or **(C)** MA intake during the first 5 days of self-administration training. **(D–F)** Similarly, cDNA infusion into the NAC shell did not affect any measure of self-administration during early training. The data represent the means ± SEMs of the number of mice indicated in Panel **A** (NAC core) and Panel **D** (NAC shell).

contrast to the data for the NAC core (**Figure 6B**), a significant Genotype X AAV interaction was detected for the ratio of active to inactive hole pokes exhibited by mice infused with AAV into the NAC shell (**Figure 6E**) [Genotype X AAV: $F(1,32) = 5.0$, $p = 0.03$]. Averaging across the 5 training days, this interaction reflected a cDNA-induced reduction in the response ratio in WT mice [$t(16) = 3.29$, $p = 0.005$], but no effect in KO animals (t-test, $p = 0.83$). Finally, MA intake fluctuated during early training in the mice infused intra-NAC shell (**Figure 6F**) [Day effect: $F(4,128) = 8.08$, $p < 0.0001$]. However, we detected no effect of gene deletion or intra-NAC shell cDNA infusion during the early training period (Genotype X AAV X Dose ANOVA, other p's > 0.25).

Homer2b Overexpression Within the NAC Shell Reduces the Efficacy of Oral MA to Serve as a Positive Reinforcer

Homer2b-cDNA infusion into the NAC core (**Figures 7A–C**) did not influence any self-administration measure as a function of the concentration of the MA reinforcer. The dose-response function for active hole-poking was relatively flat in mice infused intra-NAC core with our AAVs and there was no effect of *Homer2* deletion or AAV infusion upon this measure (**Figure 7A**; Genotype X Dose X AAV ANOVA, all p's > 0.12). Although KO mice tended to exhibit a higher ratio of active versus inactive responding during dose-response testing (Genotype effect, $p = 0.07$), no significant group differences were detected for this measure at any MA dose tested (**Figure 7B**; Genotype X Dose X AAV ANOVA, other p's > 0.15). In this experiment, *Homer2* deletion shifted the dose-response for MA intake (**Figure 7C**) [Genotype X Dose: $F(4,120) = 3.04$, $p = 0.02$], but *post hoc* tests failed to confirm genotypic differences at any MA dose (t-tests, p's > 0.07) and no AAV effects or interactions were detected (p's > 0.40). Taken together, these cDNA data argue against an active role for Homer2b within the NAC core in regulating MA intake or sensitivity to its reinforcing effects.

In contrast to the NAC core, Homer2b-cDNA infusion into the NAC shell altered the dose-response function for active nose-poking behavior (**Figure 7D**) [AAV X Dose: $F(4,120) = 2.89$, $p = 0.03$]. Although inspection of **Figure 7D** suggested that this interaction was driven by the results from the WT mice, there was no genotype effect or interactions with the genotype factor (Genotype effect: $p = 0.10$; all interactions with Genotype factor: p's > 0.40). Collapsing the data across genotype, *post hoc* analyses did not indicate any significant GFP-cDNA difference at any of the MA concentrations tested (p's > 0.25), arguing that the AAV X Dose interaction reflected the distinct shapes of the dose-response

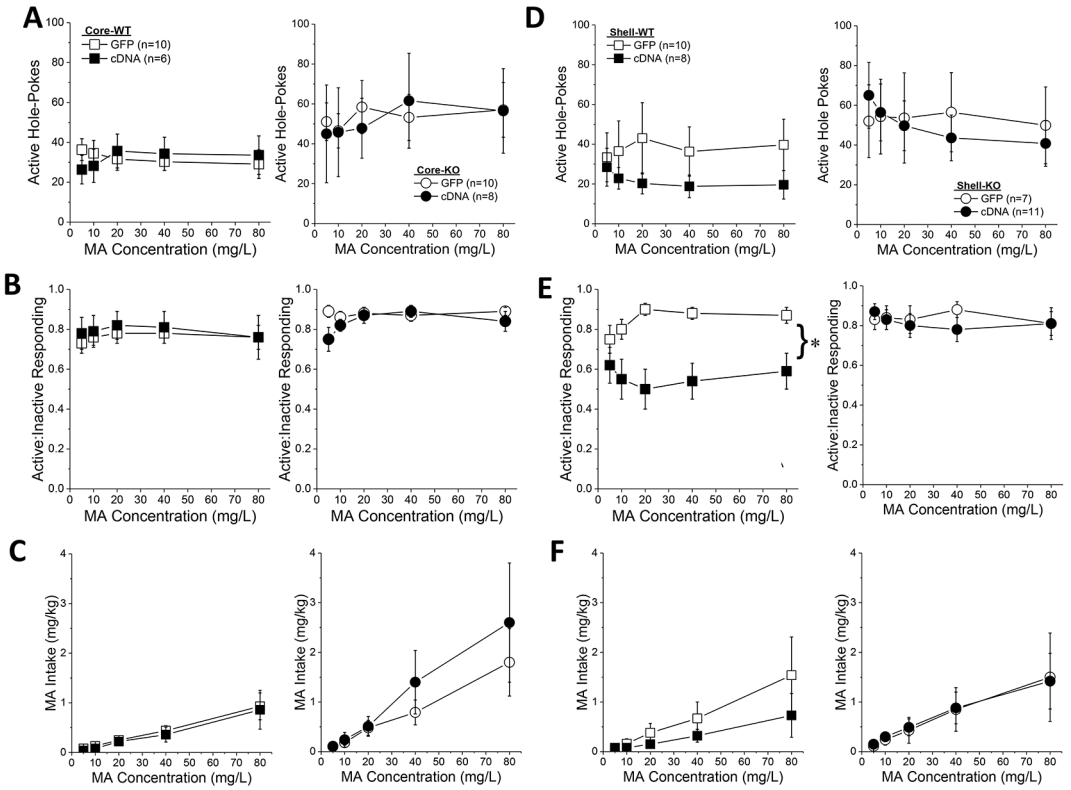

FIGURE 7 | Homer2b overexpression in the nucleus accumbens (NAC) shell blunts methamphetamine (MA) reinforcement only in wild-type (WT) mice. When compared to WT (left) and Homer2 knockout (KO) (right) mice infused with green fluorescent protein (GFP), cDNA infusion into the NAC core did not alter the dose-response functions for: **(A)** active hole responding, **(B)** response allocation or **(C)** MA intake. **(D)** cDNA infusion into the NAC shell caused a declining dose-response function for active hole-responding in both WT and KO mice, **(E)** lowered the dose-response function for response allocation in the active hole in WT mice, but **(F)** did not significantly alter the dose-response function for MA intake. The data represent the means ± SEMs of the number of mice indicated in Panel A (NAC core) and Panel **D** (NAC shell). *p < 0.05, main AAV effect. Main Genotype effects are not indicated for clarity but are described in the text.

functions for GFP- versus cDNA-infused mice (respectively, flat vs. descending). Homer2b-cDNA into the NAC shell also altered the dose-response function for the ratio of active versus inactive responding (**Figure 7E**) [AAV X Dose: $F(4,120) = 2.89$, $p = 0.03$] - an effect driven by the shift down-wards in the dose-response response produced by cDNA infusion in the WT mice (**Figure 7E**) [Genotype X AAV: $F(1,30) = 4.20$, $p = 0.05$]. While it appeared that an intra-NAC shell infusion of Homer2b-cDNA lowered MA intake selectively in WT mice (**Figure 7F**), no group differences were observed with respect to the MA dose-intake function [Dose effect: $F(1,124) = 12.73$, $p < 0.0001$; all other p's > 0.40]. Taken together, these data argue that Homer2b overexpression within the NAC shell lowers the efficacy of MA to serve as a reinforcer, without significantly impacting MA intake.

Homer2b Overexpression Within NAC Subregions Does Not Alter the Extinction or Reinstatement of MA-Seeking

Although Homer2b-cDNA infusion into the NAC core appeared to reduce the number of trials to reach extinction criterion in both WT and KO mice (**Figure 8A**), no group differences were detected for this measure (Genotype X AAV ANOVA, p's > 0.09). Likewise, neither *Homer2* deletion nor Homer2b-cDNA infusion into the NAC shell altered the time taken to extinguish responding in the active hole (**Figure 8B**; Genotype X AAV ANOVA, p's > 0.31). A comparison of active hole responding during the last day of extinction with that elicited by presentation of the MA-associated cue or a priming injection of 1 or 2 mg/kg MA indicated greater responding, overall, in *Homer2* KO versus WT mice, irrespective of the AAV infused into the NAC core (**Figure 8C**) [Test effect: $F(3,81) = 6.31$, $p = 0.001$; Genotype effect: $F(1,27) = 5,26$, $p = 0.03$; no AAV effect and no interactions, p's > 0.25]. Inspection of **Figure 8C** suggested that cDNA into the NAC core differentially affected the magnitude of cue-induced reinstatement (0 mg/kg MA), while exerting no effect on MA-primed responding. However, a direct comparison of responding on the cued reinstatement test and the extinction baseline failed to detect any interaction with the AAV factor [AAV effect and interactions, p's > 0.30; Genotype X Test: $F(1,28) = 5.91$, $p = 0.02$]. Akin to the findings for the NAC core, cDNA infusion into the NAC shell also did not significantly influence active hole responding during the tests for reinstatement of drug-seeking (**Figure 8D**; no AAV effect or

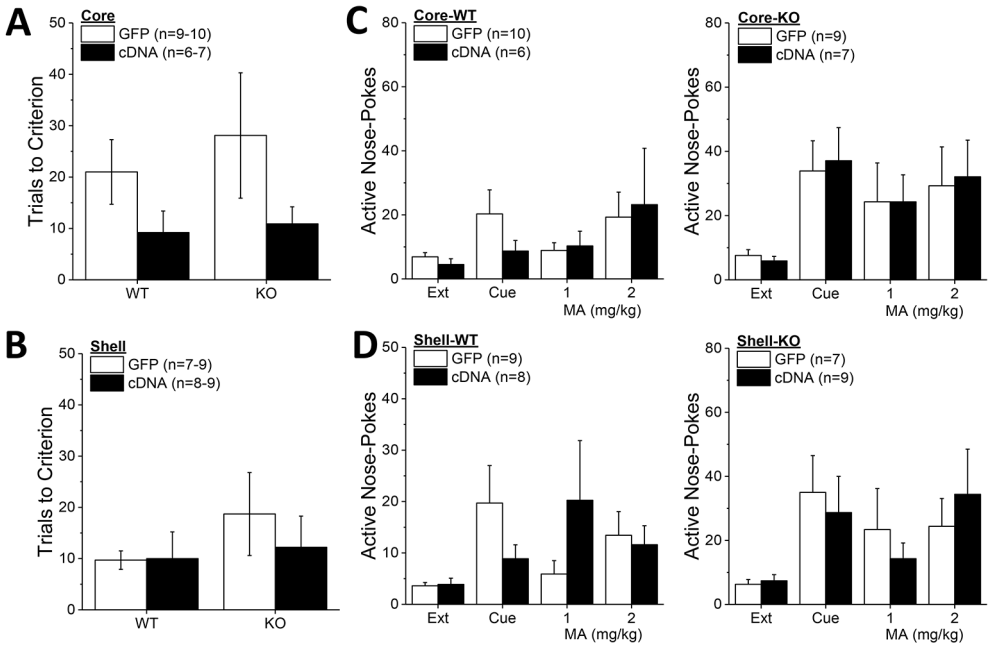

FIGURE 8 | Homer2b overexpression in nucleus accumbens (NAC) subregions does not significantly alter genotypic differences in responding under extinction-reinstatement procedures. Although it appeared that cDNA infusion into the NAC core reduced the number of trials taken to reach extinction criterion in both wild-type (WT) and Homer2 knockout (KO) mice, no cDNA effect was observed on this measure when infused into either the NAC core **(A)** or the NAC shell **(B)**. **(C)** Homer2 KO mice exhibited greater cue- and MA-primed reinstatement of active hole responding than WT mice, but NAC core infusion of cDNA did not affect responding in either WT (0left) or KO animals (right). **(D)** cDNA infusion into the NAC shell also did not alter the genotypic difference in reinstatement. The data represent the means ± SEMs of the number of mice indicated in their respective panels. Main Genotype effects are not indicated for clarity but are described in the text. The sample sizes in this figure are lower than those indicated in **Figures 6** and **7** as some animals were euthanized following MA self-administration procedures due to illness.

interactions, p's > 0.17), but again, *Homer2* KO mice exhibited greater responding overall, compared to WT mice [Genotype effect: $F(1,27) = 4.40$, $p = 0.04$]. These data for the extinction and reinstatement of MA-seeking argue a suppressive role for Homer2 in regulating behavior but do not support either NAC subregion as the active loci of these effects.

DISCUSSION

Homer2 is a postsynaptic scaffolding protein regulating the localization and function of glutamate receptors [c.f., (37–44)] and its expression within the NAC plays a necessary and active role in behavioral sensitivity to both cocaine and alcohol [c.f., (27, 37)]. In more recent work (8), idiopathic, genetic, and MA-induced vulnerability to MA addiction-related behaviors was found to be associated with increased indices of glutamate signaling within the NAC, including elevated Homer2 expression. More specifically, the magnitude of a MA-induced CPP is highly correlated with Homer2 expression within both the shell and core subregions of the NAC, arguing a potential role for Homer2-dependent neuroadaptations within both subregions in the motivational valence of MA. However, in both genetically vulnerable MAHDR and MA-sensitized B6 mice, increased behavioral sensitivity to MA was associated with elevated Homer2 expression within the NAC shell only, suggesting some subregional specificity may exist within the NAC regarding the relationship between Homer2-dependent signaling and MA-induced behaviors. Using an shRNA strategy to selectively knockdown the major rodent isoform of Homer2 [Homer2b; (45)] within the NAC shell, we demonstrated previously little to no effect upon the magnitude of a MA-CPP, but a marked reduction in responding for oral MA reinforcement and for MA intake when the same mice were assayed under operant-conditioning procedures. Such data argued a necessary role for Homer2b within the NAC shell for MA reinforcement/intake and suggested that idiopathic or MA-induced increases in NAC shell Homer2b expression promotes a MA addicted phenotype (8). Herein, we extended the results of this prior study to the NAC core.

Further, to determine whether Homer2b within either NAC subregion actively regulates MA-induced changes in behavior, we also applied our cDNA-Homer2b strategy [e.g., (25, 26, 28, 34)] in both WT and constitutive *Homer2* KO mice to upregulate Homer2b expression. The results show that constitutive *Homer2* deletion potentiated MA-CPP, oral MA reinforcement/intake under operant-conditioning procedures, and the reinstatement of MA-seeking following response extinction. A subset of these

KO effects was recapitulated by Homer2b knockdown in the NAC core, providing new evidence that Homer2b within the NAC shell and core oppositely regulate MA reinforcement. While the present shRNA findings argue a suppressive role for NAC core Homer2b expression in regulating MA reward/reinforcement, cDNA-Homer2b infusion within this subregion also potentiated a MA-CPP, without affecting measures of MA reinforcement/intake/reinstatement. Opposite our expectations (8), Homer2b overexpression within the NAC shell reduced indices of MA reinforcement but did not affect other behavioral measures. Below, we discuss these effects of bidirectional manipulations of Homer2b within the NAC in the context of animal models of MA reward and reinforcement. The data collected during this study are summarized in **Table 1**.

Constitutive Homer2 Deletion Tends to Promote MA Reward/Reinforcement

Constitutive *Homer2* deletion potentiated: MA-conditioned reward (**Figure 3A**), responding for oral MA reinforcement and MA intake under operant-conditioning procedures (**Figures 4** and **7**), and the number of trials required to extinguish MA-seeking behavior (**Figure 8A**). Additionally, *Homer2* deletion increased the magnitude of both cue- and MA-primed reinstatement of MA-seeking behavior following extinction (**Figures 8C, D**). Further, the increased MA reinforcement and intake observed in *Homer2* KO mice was apparent early during self-administration training (**Figures 4A–C**) and persisted across a range of MA doses in MA-experienced mice (**Figures 4G–I**). Such data argue a suppressive role for Homer2 in both gating vulnerability to early MA abuse and maintaining an addicted phenotype. Although genotypic differences in MA-induced locomotor activity were not observed in the present study (**Figures 3B, C**), we reported previously that the dose-response function for acute MA-induced locomotor activity is shifted upwards in *Homer2* KO mice versus WT controls (36). Thus, it is possible that the increased MA reinforcement and intake exhibited by *Homer2* KO mice herein relates to the greater efficacy of the drug to induce psychomotor activation. The precise reason for the present failure to replicate genotypic differences in MA-induced locomotion is not entirely clear but likely reflects procedural differences between the studies. First and foremost, the two studies were conducted in two distinct research institutions (Medical University of South Carolina vs. University of California Santa Barbara); thus a host of environmental differences may have contributed to the differential results to include the fact that the mice in the present study were bred in-house, while those in our earlier study were obtained from the laboratory of Dr. P.F. Worley at Johns Hopkins University School of Medicine. Also, the present experiments employed both a shorter testing period (15 vs. 60 min) and a smaller testing arena than our prior report. Additionally, mice in the present study underwent saline-conditioning sessions on the days intervening between MA injections, while mice in the prior study were injected with MA only (36). Nevertheless, the present data for MA reward/reinforcement in *Homer2* KO mice aligns well with those reported for cocaine reward/reinforcement (25), providing new evidence for a generalization of a "proaddictive" phenotype of *Homer2* KO mice across different psychomotor stimulant drugs of potential relevance for the neurobiology of psychomotor stimulant abuse liability and/or MA-cocaine coabuse.

Drawbacks of a constitutive KO approach for studying the neurobiology of behavior relate to the lack of developmental and neuroanatomical specificity of gene deletion. There exist three different Homer isoforms, with Homer1 and Homer2 isoforms expressed in midbrain and forebrain regions highly implicated in addiction neurobiology (45). Further, distinct Homer1 isoforms differentially regulate spontaneous and stimulant-induced changes in behavior (32, 36), with imbalances in the relative expression of Homer1 versus Homer2 isoforms within mPFC gating cocaine-conditioned reward (34) and the reinstatement of cocaine-seeking behavior (46). Although extant correlative evidence does not support a relationship between Homer1 protein expression within either NAC subregion or within the mPFC and MA behavioral sensitivity (4, 8), such findings do not preclude the possibility that compensatory changes in Homer1 expression/function may contribute to the "proaddictive" phenotype of *Homer2* KO mice.

Subregional Selectivity in the Effects of *Homer2b* Knock-Down Within NAC Upon MA Reward/Reinforcement

In brain, Homer2 expression is regulated in a regionally selective manner by prior MA experience in inbred B6 mice, with increases in protein expression observed selectively within the NAC shell (4, 8). Further, increased Homer2 expression within the NAC shell, but not core, is a biochemical correlate of genetic vulnerability to consume MA in mice on a heterogeneous genetic background (8). Providing causal evidence that Homer2 functions to alter MA reward/reinforcement in a subregionally distinct manner, Homer2b knockdown in the shell reduces (8), while knockdown in the core increases, both the magnitude of a MA-CPP and responding for a MA reinforcer (**Figures 1** and **2**). Thus, the effects of constitutive *Homer2* deletion upon MA reward/reinforcement/intake (**Figures 3** and **4**) are recapitulated, albeit incompletely, by Homer2b knockdown within the NAC core (**Figures 1** and **2**; **Table 1**). Given the neuroanatomical nature of our research question, we deemed it more critical to decipher the site of AAV transduction within NAC subregions than quantify the efficiency of our shRNA construct to alter Homer2b protein expression. The fact that the phenotype produced by Homer2b knockdown in the NAC core did not fully recapitulate that of the *Homer2* KO mouse is perhaps not surprising as we know from prior work that our shRNA-Homer2b infusion procedure consistently reduces protein expression by 40%–50% *in vivo* (31, 33, 34, 47) and does not completely eliminate protein expression as is the case for gene deletion. Further, in humans, MA addiction is associated with anomalies in the function of many brain structures that were not targeted herein (48–50). Indeed, lower Homer2 expression within the mPFC of mice is associated with both genetic and idiopathic

TABLE 1 | Summary of the results of the present experiments.

Behavioral Measure	Core Knockdown	Constitutive KO	Core Over-expression: Effects of KO	Core Over-expression: Effects of cDNA	Shell Over-expression: Effect of KO	Shell Over-expression: Effect of cDNA
CPP	↑	↑	↓	↑	–	–
Locomotor Sensitization	–	–	–	–	–	–
Self-Administration Training	–	↑	–	–	–	–
Increasing Response Requirement	–	↑	N/D	N/D	N/D	N/D
Self-Administration Dose Response Curve	↑	↑	–	–	–	↓
Trials to Extinction	N/D	N/D	–	–	–	–
Cue- & MA-induced reinstatement of self-administration	N/D	N/D	↑	–	–	

↑ denotes an increase in behavior relative to control. ↓ denotes a decrease in behavior relative to control. – denotes no effect of manipulation relative to control. N/D denotes not determined.

vulnerability to express a MA-CPP, and to respond for/consume the drug under operant-conditioning procedures (4). Thus, it is highly likely that Homer2 within other structures embedded within putative addiction neurocircuits functions also to regulate MA-conditioning, MA-seeking and MA-taking behavior and contribute to the robust MA phenotype of *Homer2* KO mice. Although Homer2b knock-down in the NAC core does not fully recapitulate the effect of constitutive gene deletion, it is interesting to note that the phenotype produced by Homer2b knock-down in the NAC core predominates in the *Homer2* KO mouse (**Table 1**).

In our limited experience using shRNA to target Homer2 expression within both NAC subregions (29) and to the best of our knowledge of the extant Homer2 literature, our shRNA-Homer2 findings for MA reward/reinforcement [(8); present study] are the first to demonstrate opposing roles for Homer2b within NAC subregions in regulating addiction-related behavior. We know through studies of constitutive *Homer2* KO mice and of the effects of intracranial shRNA-Homer2b infusion that intact Homer2 expression is important for: maintaining basal extracellular glutamate levels within both the NAC and mPFC (25, 34, 47), cocaine- and alcohol-stimulated glutamate release (25, 26, 32, 33), and the expression/function of glutamate receptors, transporters, and signaling molecules within these regions (25, 26, 34). However, we are unaware of any study that has directly compared the effects of either *Homer2* deletion or Homer2b knockdown upon any biochemical measure *between* NAC subregions to inform the mechanisms underpinning the opposing MA effects of Homer2b knockdown observed herein. That being said, we do know from studies of the mPFC that shRNA-Homer2b (and cDNA-Homer2b) infusion can produce not only local effects upon basal and drug-stimulated changes in extracellular glutamate, in addition to changes in the expression of Homer2 and glutamate receptor-related proteins, but can also alter these biochemical measures within NAC, intriguingly in a direction sometimes *opposite* that observed at the site of infusion (34). As striking examples, intra-mPFC infusion of cDNA-Homer2b elevates basal extracellular glutamate content and Homer2 expression, in addition to blunting drug-stimulated glutamate release at the site of infusion, but lowers the glutamate content and expression of both Homer1/2 and mGlu1/5 and potentiates drug-stimulated glutamate release within the NAC. Further, intra-mPFC infusion of shRNA-Homer2b reduces Homer2 and mGlu5 expression at the infusion site, but elevates markedly the expression of GluN2b, without affecting extracellular glutamate or the expression of Homers or mGlu1/5 within the NAC (34). These adaptations within NAC cannot be readily explained by anterograde transport of the AAVs and argue that the opposing effects of shRNA-Homer2b infusion into the NAC shell and core observed herein could reflect yet uncharacterized distinctions in local changes in extracellular glutamate and/or glutamate receptor function/expression that differentially alter the activation of efferents or could reflect yet uncharacterized biochemical alterations within those efferent structures (e.g., ventral pallidum).

Inconsistent Effects of Increasing *Homer2b* Expression Within the NAC Shell and Core Upon MA Reward/Reinforcement

The observed effects of intra-NAC core/shell shRNA-Homer2b infusion argued that Homer2b expression within the NAC core suppresses, while that in the NAC shell promotes, certain MA addiction-related behaviors in mice [**Figures 1** and **2**; (8)]. However, when this hypothesis was tested directly using well-established AAV-cDNA approaches that increase local Homer2b expression by approximately 50% (25, 26, 28, 34, 47), we found no supporting evidence for either notion. If anything, the results from our cDNA study were opposite those predicted from our shRNA experiments. For one, intra-NAC shell infusion of cDNA-Homer2b lowered the dose-response functions for MA-reinforced/appropriate responding in WT mice (**Figures 5F**, **6D, E**)—an effect qualitatively similar to (albeit more robust than) that observed upon Homer2b knockdown in this subregion of B6 animals (8). Also, an intra-NAC core infusion of either shRNA-Homer2b in B6 mice or cDNA-Homer2b in B6-129 hybrid WT mice produced a quantitatively similar increase in the magnitude of a MA-CPP (**Figure 1D** vs. **Figure 5E**). Despite baseline differences in responding, Homer2b overexpression and underexpression within NAC core produces similar effects upon

the MA-conditioned reward expressed in each experiment. Finally, within the context of operant-conditioning, in no instance did cDNA-Homer2 infusion into either NAC subregion significantly alter, let alone reverse, the MA phenotype of *Homer2* KO mice (**Figures 7** and **8**).

These null data are in stark contrast to our earlier reports demonstrating a complete reversal of the behavioral and/or neurochemical phenotype of *Homer2* KO mice by site-directed infusions of our cDNA-Homer2b construct (25, 26, 34). In only one instance did the data for cDNA-Homer2b infusion align with our predictions and this was observed within the context of extinction/reinstatement procedures. Although the results failed to reach statistical significance, cDNA-Homer2b infusion into the NAC core facilitated the extinction of operant-behavior (an effect observed in both WT and KO mice; **Figure 8A**) and blunted the capacity of the MA-associated cues to reinstate responding in WT mice (**Figure 8B**). That being said, cDNA-Homer2b infusion into the NAC shell produced a comparable reduction of cue-induced reinstatement as that observed in mice infused intra-NAC core (**Figure 8A** vs. **Figure 8B**). Such null results argue strongly against an active and autonomous role for Homer2 within either NAC subregion in regulating MA-conditioned reward or self-administration. Alternatively, these data could also suggest that any dysregulation in Homer2 expression, be it overexpression or underexpression, is sufficient to perturb normal glutamate transmission within NAC subregions to affect MA reward/reinforcement. Which, and how, specific signal transduction pathways are affected by increasing versus decreasing Homer2 expression within different NAC subregions remains to be determined and are important research questions for future studies aimed at understanding more precisely the role played by this scaffolding protein in regulating MA addiction-related behaviors.

Additional Caveats of the Current Study

Table 1 summarizes the major findings from this study, which are complicated to interpret to say the least. Adding to the interpretational difficulty is the notable fact that the baseline behavior of the control animals varied considerable across the different experiments. For instance, the baseline CPP behavior of GFP-infused B6 mice in the shRNA study of the NAC core was approximately half that of the WT B6-129 mice in the cDNA study of this region (**Figure 1C** vs. **Figure 5D**). These experiments were conducted over a year apart; thus, we cannot decipher from the current experimental design whether or not this difference in baseline CPP reflects environmental factors (e.g., differences in laboratory or animal care personnel) or strain differences in behavioral sensitivity to MA. Indeed, marked strain differences are reported between C57BL/6J mice and DBA2/J mice with respect to MA intake, with C57BL/6J mice exhibiting significantly lower MA intake than DBA2/J mice [e.g., (51–53)]. To date, we have yet to directly compare MA CPP, reinforcement or intake between B6 mice and mice on a mixed B6-129 background so we cannot rule out the potential contribution of background strain to our findings. However, arguing more in favor of environmental factors as contributors to the differences in baseline CPP, the 2 mg/kg MA dose elicited negligible CPP in the B6-129 mice infused with cDNA into the NAC shell (**Figure 5G**), despite these animals exhibiting similar acute and sensitized locomotor responses to the drug as those infused with cDNA into the NAC core (**Figures 5E, F** vs. **Figures 5H, I**). The MA self-administration behavior of the B6-129 mice infused with cDNA into the NAC shell was also lower than that exhibited by their NAC core counterparts, particularly during the training phase of the experiment (**Figure 6**). Such behavioral differences cannot be attributable to differences in genetic background.

Further, we would like to be forthcoming and report that, unfortunately, during the year we were conducting the NAC shell cDNA study, building renovations were occurring on the level beneath our laboratory. While arrangements were in place to minimize the noise and vibration during the daylight hours when the animals were being tested, we cannot rule out the possibility that the construction conducted during the evening hours affected the behavior of the animals nor did we have any control over, or ability to predict, any construction that took place during the day. For this very reason, the cDNA study of the NAC shell was conducted in 3 distinct cohorts of 21–25 B6-129 mice, spaced 1–3 months apart in accordance with the limited information we were provided regarding heavy construction/demolition. However, despite our best attempts to avoid this confound, we were unsuccessful at eliciting a CPP in this experiment. Indeed, the number of mice exhibiting a conditioned place-aversion [CPP Score <–100 s; see (8)] in each cohort of the cDNA study of the NAC shell was higher than that observed in the cDNA study of the NAC core (shell: 3–5/cohort vs. core: 2–3/cohort), with more mice exhibiting place-ambivalence. It is also possible that the AAV-GFP infusion into the NAC shell might have inadvertently affected the behavior of the B6-129 mice, although we observed no overt signs of infection or tissue damage. However, we deem this unlikely as we have conducted numerous experiments in which this AAV was infused into the NAC shell, to include studies of MA- (8), alcohol- (26, 28), and cocaine-induced place-conditioning (25) and observed no obvious off-target effects of the AAV upon the expression of the conditioned response. Thus, we surmise that factors related to building renovations likely confounded data interpretation from the cDNA study of the NAC shell.

Concluding Remarks and Future Directions

Considerable neuropharmacological, chemogenetic, and optogenetic work has established that the NAC shell and core are embedded within distinct neural subcircuits that differentially contribute to aspects of drug-conditioning, drug-taking, and drug-seeking behavior, the most well characterized of which are the relatively dense afferents from, respectively, the infralimbic (IL) and prelimbic (PL) subregions of the mPFC [e.g., (54, 55)]. The majority of data argue that PL-NAC (core) projections are involved in driving or executing operant behavior in the context of drug self-administration, whereas IL-NAC (shell) projections are more critical for suppressing or inhibiting responding [e.g., (56, 57)]. This being said, there is overlap in the PL and IL projections to specific NAC subregions

(55, 58) that can bear on how specific corticoaccumbens projections might influence responding for drugs and natural reinforcers [see (54, 59, 60)]. Thus, while the available data pertaining to Homer2 regulation of MA addiction-related behavior in mice do not reliably support an active role for Homer2 within NAC subregions for gating MA addiction-related behaviors, our AAV findings do not negate a role for this Homer isoform within NAC afferents, in particular those from the mPFC, in this regard. Although repeated MA does not alter Homer2 expression in samples from the entire PFC (to include PL, IL, and anterior cingulate), reduced PFC Homer2 expression is associated with both genetic and idiopathic MA addiction vulnerability in mouse models (4). Given the importance of mPFC-NAC subcircuits for gating drug-taking and drug-seeking behavior and based on our earlier cocaine studies of Homer2 function within mPFC (34), one goal of future work is to characterize the neuroanatomical selectivity of MA-induced changes in Homer2/glutamate signaling within PFC subregions and to interrogate the role played by distinct mPFC-NAC subcircuits and Homer2 expression within these subcircuits in MA-taking and MA-seeking behavior.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Care and Use Committee of the University of California Santa Barbara.

AUTHOR CONTRIBUTIONS

CNB, TK, CDB, and KS designed the experiments. CNB, JS, EF, AP, DF, SF, and EL composed initial drafts of experimental write-ups. CNB and KS conducted the data analyses, consolidated findings, and composed the final manuscript. CNB, JS, EF, AP, DF, EL, SR, and SF performed the experiments and GJ provided and consulted on the viruses. All co-authors edited the manuscript.

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Decision-Making by Patients With Methamphetamine Use Disorder Receiving Contingency Management Treatment: Magnitude and Frequency Effects

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Background: Individuals with substance use disorders exhibit maladaptive decision-making on the Iowa Gambling Task (IGT), which involves selecting from card decks differing in the magnitudes of rewards, and the frequency and magnitude of losses. We investigated whether baseline IGT performance could predict responses to contingency management (CM) by treatment-seeking individuals with methamphetamine use disorder (MA Use Disorder) in Cape Town, South Africa.

Methods: Twenty-nine individuals with MA Use Disorder underwent an 8-week, escalating reinforcement, voucher-based CM treatment in a study on the suitability of CM therapy for the South African context. Along with 20 healthy control participants, they performed a computerized version of the IGT before starting CM treatment. Seventeen participants maintained abstinence from methamphetamine throughout the trial (full responders), and 12 had an incomplete response (partial responders). Performance on the IGT was scored for magnitude effect (selection of large immediate rewards with high long-term loss) and for frequency effect (preference for frequent rewards and avoidance of frequent losses). Group differences were investigated using linear mixed-effect modeling.

Results: Partial responders made more selections from decks providing large, immediate rewards and long-term losses than healthy controls [$p = 0.038$, $g = -0.77$ (-1.09: -0.44)]. Full responders showed a greater, nonsignificant preference for frequent rewards and aversion to frequent losses than partial responders [$p = 0.054$, $g = -0.63$ (-0.95: -0.29)].

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Conclusions: A predilection for choices based on the size and immediacy of reward may reflect a cognitive strategy that works against CM. Pretesting with a decision-making task, such as the IGT, may help in matching cognitive therapies to clients with MA Use Disorder.

Keywords: decision-making, risk-taking, methamphetamine, methamphetamine use disorder, Iowa Gambling Task, contingency management

INTRODUCTION

Substance misuse is linked to maladaptive risk taking that typically results in long-term loss or foregone gain in the context of uncertainty (1, 2). Such decision-making deficits have been observed in individuals with substance use disorders using the Iowa Gambling Task (IGT), a laboratory test of adaptive decision-making (3–6), and on temporal discounting tasks, which evaluate a participant's devaluation of rewards as a function of delay (7, 8).

On the IGT, individuals who have or are at risk for drug use disorders demonstrate maladaptive decision-making by differentially favoring choices associated with large, immediate rewards over choices that produce long-term gain, as compared with individuals who do not use drugs of abuse or who are not at risk (3, 6, 9). This finding is consistent within methamphetamine-dependent samples [Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)] in particular Gonzalez et al. (5) and van der Plas et al. (2). The IGT has been used predominately to assess the influence of the *immediacy* and *magnitude* of rewards (and losses) on decision-making, but it has also been used to investigate the impact of the *frequency* with which rewards and losses are presented (10, 11). Chiu et al. (12) found that healthy individuals demonstrate a tendency to seek out gains that occur more *frequently* rather than exclusively seeking out long-term gains, as initially proposed by Bechara et al. (13). On a different task, Voon et al. (14) found that methamphetamine-dependent individuals (DSM-IV) made riskier choices for lower probability/frequency rewards and higher probability losses than healthy controls, suggesting that decision-making of methamphetamine use disorder (MA Use Disorder) patients may also be influenced by outcome frequency. However, this has yet to be investigated with respect to the IGT.

Decision-making deficits appear to vary depending on the substance in question. Ahn et al. (15) found that amphetamine-dependent (DSM-IV) individuals exhibit maladaptive decision-making that is characterized by a greater sensitivity to reward, whereas heroin-dependent individuals demonstrate less sensitivity to loss as compared with healthy individuals. Therefore, it is necessary to assess decision-making deficits by substance type. Decision-making deficits have also been shown to vary within same substance-using samples, with associated treatment implications (16, 17). Chen et al. (18) found that poorer performance on the IGT by methamphetamine-dependent (DSM-IV) individuals predicted dropout in cognitive behavioral therapy (CBT), while better performance on the IGT was related to greater treatment retention. Evidence of variability in decision-making deficits among individuals with substance use disorders and its links to treatment outcomes suggests the need for greater assessment of a potential spectrum of decision-making profiles *within* substance use disorder populations, but this relationship may also be specific to the type of treatment, and treatment outcome in question.

There is limited research into the relationship between maladaptive decision-making in MA Use Disorder and risk of relapse in the context of contingency management (CM). A behavioral treatment that rewards abstinence with rewards, often monetary, CM has greater short-term therapeutic efficacy than other treatments for MA Use Disorder, such as CBT (19). Maladaptive decision-making is particularly relevant to the context of CM treatment, which directly positions the reinforcing value of monetary rewards against the reinforcing value of drugs, measuring an individual's choices between monetary rewards for abstinence versus continued drug use, which lead to missed monetary rewards (20). The IGT was used at treatment entry to evaluate whether response to CM treatment corresponds with deficits in decision-making as measured by the task.

This project is a key part of a pilot study to evaluate mechanisms of CM therapy for MA Use Disorder patients in Cape Town, South Africa. The objective of this trial is to examine links between maladaptive decision-making using the IGT with CM treatment outcomes and to compare IGT responses for the MA Use Disorder patients with a comparable sample of healthy controls. We hypothesized that participants with MA Use Disorder who failed to respond completely to 8 weeks of CM (partial response) would demonstrate significant maladaptive decision-making at baseline relative to participants who responded completely (full response) or to healthy controls as measured by a "magnitude effect" (preference for riskier choices with larger, immediate rewards and long-term losses than for less risky choices). We also predicted that compared to participants with complete CM response and healthy controls, participants who showed partial response to CM would demonstrate greater preference for frequent rewards and avoidance of frequent losses, that is, a "frequency effect."

MATERIALS AND METHODS

Study Design and Participants

This study was part of a pilot project investigating the suitability of CM in treating MA Use Disorder in South Africa. It used a between-groups, cross-sectional design comparing outcomes to CM (complete response, partial response) among 29 individuals

diagnosed with MA Use Disorder (DSM-5) to 20 healthy control participants, see Okafor et al. (21). All participants completed neurocognitive and self-report measures, after which MA Use Disorder patients commenced an 8-week, escalating schedule, thrice-weekly, voucher-based CM intervention. The study protocol was approved by the Health Sciences Human Research Ethics committee of the University of Cape Town and UCLA in accordance with the Declaration of Helsinki. MA Use Disorder patients were recruited through local drug clinics (n = 20), and a combination of local newspaper advertisements and snowball sampling was used to recruit additional individuals with MA Use Disorder (n = 9) and all healthy control candidates (n = 20). Interested candidates provided informed, written consent and were screened for eligibility.

Recruits with suspected MA Use Disorder underwent a 2-week baseline screening period to determine whether they met DSM-5 criteria for MA Use Disorder [Structured Clinical Interview for DSM-5 (SCID) verified by a trained professional], to demonstrate ability to attend thrice-weekly scheduled appointments to provide scheduled urine tests and to confirm recent methamphetamine use, where participants were not made aware of the latter eligibility criterion. Of 269 recruits who were initially screened, 148 individuals were not eligible based on either one of the exclusion criteria outlined under *Screening Tools and Inclusion/Exclusion Criteria*, and a further 88 were excluded from the study due to nonattendance, which was the most common reason for exclusion. From the remaining 33 MA Use Disorder patients who were initially enrolled in CM treatment, four participants were additionally excluded from the CM trial for the following reasons: cocaine use not previously disclosed (n = 1), meningitis not previously disclosed (n = 1), brain structural abnormality (n = 1), and a MA-positive (methamphetamine-positive) urine test at the time of task assessment (n = 1). A total of 29 adult MA Use Disorder patients, 18–45 years of age, were enrolled (20 males) in the study.

Participants with MA Use Disorder were categorized according to their response to CM treatment as partial responders (n = 12) and full responders (n = 17). Full responders were defined as those participants who exclusively presented with MA-negative (methamphetamine-negative) urine samples during CM treatment, demonstrating that they maintained abstinence. Partial responders were defined as those participants who presented with at least one MA-positive or missed urine sample over the entire duration of CM treatment. In addition to verifying methamphetamine use before initiating treatment, urine tests were used to verify treatment response, as well as to verify abstinence from methamphetamine on the day of task assessment, as well as several other substances, including barbiturates, cocaine, opiates, and cannabis, in order to prevent any confounding acute effects of drugs on task performance. If on the day of task assessment a participant presented with a positive urine test for any of the tested substances, the assessment was rescheduled. Participants were abstinent on average 4.2 days before testing on the first day of treatment. Over the CM intervention, partial responders presented with an average of 13.17 negative (i.e., clean) urine samples out of a total of 24 (sd = 6.35), where the remaining 45% represented positive (including missed) urine samples, and 22% of total samples represented missed urine samples. A frequency-matched control group of 20 (13 male) participants who did not use substances of abuse, other than tobacco or occasional alcohol, was enrolled. Matching characteristics included age, education, gender, ethnicity, and broad intellectual function.

Screening Tools and Inclusion/Exclusion Criteria

All MA Use Disorder patients met diagnostic criteria for current and primary MA Use Disorder, as indicated by the research version of the SCID; secondary use, but not misuse, of cannabis and/or methaqualone (Mandrax) was accepted due to high prevalence of paired use of these substances with methamphetamine in Western Cape, South Africa (22). Tobacco and alcohol use were accepted for both MA Use Disorder and control groups, given typical use of such legal substances within low-socioeconomic communities (23). For methamphetamine-using and control groups, the presence of the following psychiatric comorbidities was exclusionary: non-primary MA Use Disorder or current/past primary substance use disorder involving a substance other than methamphetamine or tobacco, schizophrenia spectrum disorders, bipolar and related disorders, depressive and anxiety disorders not induced by MA Use Disorder, and obsessive–compulsive-related disorders. In addition, primary MA Use Disorder was an exclusion criterion for the control group. For both MA Use Disorder and control groups, antisocial personality disorder was accepted due to its high prevalence in low-socioeconomic status communities in South Africa (24). In addition, performance and verbal subscale scores of the Weschler Abbreviated Scale of Intelligence (WASI) were used to assess capacity to perform neurocognitive tasks. A score of 55 was the minimum requirement to establish competency in understanding task instructions according to local cultural standards (25). Additional exclusion criteria for MA Use Disorder and control groups included use of psychoactive medication that may have potential effects on the central nervous system, current or previous head injury or neurological illness, HIV-seropositive status using a pin-prick test, left-handedness, and limited comprehension of English. MA Use Disorder patients who were unavailable over a 10-week period or required inpatient treatment were not enrolled. As part of the requirements for the neuroimaging component in the broader study, other exclusion criteria for MA Use Disorder patients included current pregnancy, claustrophobia, pacemaker, and metal prosthesis or metal present in the body.

Contingency Management Intervention Setting

MA Use Disorder patients underwent CM treatment, which required thrice-weekly scheduled clinic visits to provide urine samples, which were analyzed using radioimmunoassay strips (CLIAwaived Inc., San Diego, California, United States) to detect methamphetamine in urine over the prior 48–72 h. Integrity of

urine test results was ensured by using supervised urine sample collection, which was further verified using temperature-sensitive strips on collection cups. Participants who provided MA-negative urine samples immediately received vouchers to be redeemed at a large supermarket (Pick n Pay). The value incrementally increased with each subsequent MA-negative urine test, demonstrating continued abstinence to a maximum of 4,850 Rand (USD $404) over the 8 weeks. If a MA-positive urine test was obtained, or if an appointment was missed with no attempt to reschedule the appointment to a future date that was within the number of days it takes to fully metabolize d-amphetamine, participants did not receive a voucher. The next MA-negative urine test following a positive was worth the starting 25 Rand. To sustain motivation, we used a "rapid reset" procedure to return participants to their prior position on the CM schedule following three consecutive scheduled MA-negative urine tests.

Iowa Gambling Task (IGT)

The Psychology Experiment Building Language (PEBL) 0.14 computerized version of the IGT was used (13). It consists of four virtual decks of cards, A, B, C, and D, each associated with a unique combination of short-term fixed rewards and probabilistic losses, in addition to an associated long-term net payout. Riskier decks (A and B) present short-term high-reward and high-loss contingencies, with consistent choices of such decks yielding low cumulative totals. In contrast, optimal decks (C and D) are linked to short-term low-reward and low-loss contingencies, yielding moderately high cumulative totals. The objective of the IGT is to maximize long-term cumulative payout earned on the task by learning to shift or avoid selection of riskier, disadvantageous decks A and B and favor safer, more advantageous decks C and D within 100 trials.

IGT Setting

For both MA Use Disorder and control groups, participants' vision was first tested using the Snellen chart before administering the IGT. The IGT was administered to participants *via* a desktop computer situated in a quiet, distraction-free room. Participants were instructed to select from four possible virtual decks on screen using a computer mouse, over a total of 100 trials, with the aim of maximizing net gains from the task. Participants were not time restricted, but took approximately 30–45 min to complete the task. Participants were provided with headphones during administration of the IGT in order to hear the sound effects associated with obtaining either a net gain or a net loss on each deck selection.

IGT Scoring: Magnitude Effect

The magnitude effect is represented by a greater selection of riskier decks A and B relative to decks C and D. This is indicative of both a greater preference for short-term rewards and an ability to withstand or otherwise lack the foresight of long-term associated losses. It is calculated by summing deck selections from disadvantageous decks and subtracting them from the sum of advantageous deck selections (C + D) – (A + B), with negative scores reflecting the magnitude effect. This net score was calculated for each of four blocks of 20 trials, excluding block 1 (26).

IGT Scoring: Frequency Effect

The frequency effect is defined as a greater selection of decks B and D, relative to decks A and C, and demonstrates a preference for frequent short-term rewards and infrequent losses over infrequent rewards and frequent losses (**Table 1**). The frequency effect is calculated as the sum of selections from decks with frequent rewards and infrequent losses minus decks with infrequent rewards and frequent losses (B + D) – (A + C), where higher scores demonstrate the frequency effect. As above, frequency effect scores were generated per block from blocks 2 to 5. Although a preference for frequent rewards and infrequent losses is arguably more optimal than that of infrequent rewards and frequent losses, the frequency effect does not explicitly account for long-term associated outcomes, like the magnitude effect, which is crucial to effective decision-making on the IGT. In turn, the frequency effect may act as a less optimal decision-making strategy, where frequent rewards are sought out and frequent losses avoided without consideration of long-term consequences.

In order to incentivize performance, a voucher with a flat rate value of 25 Rand, equivalent to USD $2, was offered to participants from both MA Use Disorder and control groups if an overall positive net payoff on the IGT was achieved.

Linear Mixed-Effect (LME) Modeling of Decision-Making

Magnitude and Frequency Effect

Utilizing the nlme package (27) on the R programming platform (28), an LME model was used to test for differences between partial responders, full responders, and controls in both the magnitude effect and frequency effect across blocks 2–5 on the IGT at baseline. LME modeling is advantageous as it allows for the estimation of fixed effects while simultaneously accounting for the clustered or hierarchical structure of data, namely, within-cluster relationships (the random effect). In this study, group differences (the fixed effect) were estimated in conjunction with within-subject variability (random effects), represented by repeated block scores per subject. The model assessed net block score as the unit of observation at level-1, accounting for its clustering within each participant, where the individual participant is specified as the unit at level-2. An LME

TABLE 1 | IGT deck outcome specifications.

	Deck A	Deck B	Deck C	Deck D
Reward magnitude	100	100	50	50
Loss magnitude	150- 350	1250	25-75	250
Long-term average	–250	–250	250	250
Absolute gain-loss frequency	10 gains 5 losses	10 gains 1 loss	10 gain 5 losses	10 gains 1 loss
Net gain-loss frequency	9 gains 5 losses	9 gains 1 loss	9 gains 5 draws	9 gains 1 loss

framework is particularly appropriate given previous findings of within-group heterogeneity in IGT performance of substance-using and healthy samples (1, 10). Each LME model was compared to a fixed-effect model (in absence of random effects) in order to confirm the presence of individual variability.

Post Hoc Contrasts of Group Differences

In order to minimize familywise error associated with multiple group comparisons, *post hoc* contrasts were conducted on all LME models to compare the groups using Tukey's p-adjustment correction method, carried out with the lsmeans r package (29). Hedges g effect size estimates were estimated using the compute.es r package (30), where hedges g estimation was presented due to its utility in generating unbiased estimates particularly within smaller samples. All hedges g confidence intervals were bootstrapped. Small, medium, and large effect sizes were represented by *g* values of 0.2, 0.5, and 0.8, respectively (31). Findings were considered significant with p-values < 0.05.

Covariates of Decision-Making

Several sociodemographic, individual, and drug use variables, including sex, education, broad intellectual function, and drug use history have been previously linked with IGT performance (32–38). In order to control for their potential effects on task performance, all covariates were entered as fixed effects into models of magnitude effect and frequency effect, but were only retained if the model was significantly improved with the inclusion of covariates, based on the likelihood ratio.

RESULTS

Sample Characteristics

The majority of MA Use Disorder patients and matched controls were self-reported as "colored" (27 and 19, respectively), where the term "colored" loosely describes an ethnic group of persons of mixed European and African or Asian descent, who makes up a substantial proportion of the Western Cape population, where the study took place. A minority of both MA Use Disorder patients and healthy controls were self-reported as "black" (2 and 1, respectively). The three groups (partial responders, full responders, controls) did not differ in sex, age, or broad intellectual function but differed in years of education, employment, and household income (**Table 2**); partial responders also had a longer history of methamphetamine use and demonstrated more problematic use of alcohol (at trend levels) than full responders. The inclusion of covariates did not explain significantly more variance than a model in absence of covariates for both the magnitude effect (likelihood ratio = 4.94, p = 0.293) and frequency effect (likelihood ratio = 5.39, p = 0.249), and the inclusion of covariates did not improve the precision of estimates. In turn, covariates were excluded, and simpler models were retained. Additional demographics of interest are included in **Table 2**.

TABLE 2 | Full sample characteristics (N = 49).

Variable	Partial responders (n = 12)	Full Responders (n = 17)	Healthy Controls (n = 20)	p
Sociodemographic characteristics				
Age, mean (SD)	34.83 (5.62)	33.76 (6.68)	34.95 (6.36)	0.835
Gender (M: F)	10:2	10:7	13:7	0.370
Education	9.58 (2.42)	11.11 (2.9)	12.25 (1.05)	0.001*
Employment (Y: N)	0:12	[a]4:12	12:8	0.002*
Household income (RAND), mean (SD)	40417 (27672)	14118 (19404)	22375 (21018)	0.011*
Cognitive characteristics				
WASI IQ, mean (SD)	87.33 (12.57)	91.47 (21.55)	86.35 (15.42)	0.653
Cigarette use				
Cigarettes smoked/day, mean (SD)	10.66 (9.33)	6.82 (6.02)	7.40 (6.67)	0.335
Nicotine dependence, mean (SD)	3.00 (1.63)	3.58 (2.69)	2.75 (2.22)	0.542
Methamphetamine (MA) use history				
Duration of MA use (years), mean (SD)	12.75 (3.54)	9.88 (4.48)	–	0.076+
Baseline MA negative, %	58.20 (22.10)	63.70 (19.60)		0.483
Previous MA stop attempts (n), mean (SD)	2.91 (3.14)	3.70 (5.93)	–	0.678
MA and substance use severity				
MA use quantity (grams), mean (SD)	1.14 (0.71)	0.87 (0.48)	–	0.235
Drug use severity, mean (SD)	0.25 (0.06)	0.26 (0.09)		0.995
Alcohol use severity, mean (SD)	0.10 (0.01)	0.08 (0.02)	–	0.074+
Other substance use and concurrent treatment				
Secondary substance (Methaqualone &/or cannabis: none)	9:3	[a]8:8	–	0.342
Concurrent outpatient treatment (Y: N)	9:3	9:8	–	0.413

*MA = methamphetamine. Employment = Binary (yes or no) variable representing current employment. a = missing value/s in total sample. Household income = Yearly household income variable (R14: $1 US) derived from an ordinal 5 income category variable, where average income was extracted from the income range reflected within an income category. WASI IQ = aggregate score derived from both verbal and performance subsets of the Weschler-abbreviated scale of intelligence test. Nicotine dependence = measured using the Fagerström test. Baseline MA negative= proportion of MA-negative tests during baseline period prior to CM treatment. Previous MA stop attempts = Frequency of previous attempts to abstain from MA. Drug (and Alcohol) use severity = composite scores derived from the addiction severity index. Secondary substance = binary variable (Methaqualone &/or cannabis or none) indicating presence or absence of use of specific secondary substances besides MA. Concurrent outpatient treatment = binary variable (yes or no) indicating concurrent participation in motivational interviewing and/or group therapy alongside CM. F tests were utilized to assess potential group differences in Age, Education, Household income, WASI IQ, Cigarettes smoked/day, Nicotine dependence, Duration of MA use, Baseline MA negative, Previous MA stop attempts, MA use quantity as well as Drug and Alcohol use severity. Fisher's exact tests were conducted on count factors including; gender and employment, whilst chi-squared tests were conducted on Concurrent outpatient treatment and Secondary substance. +p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001*

Magnitude Effect

An LME model of magnitude effect demonstrated significantly greater fit over a fixed-effect model (likelihood ratio = 49.62, $p < 0.001$), suggesting the impact that individual variability plays in estimating the magnitude effect. Group contrasts from the LME magnitude effect model demonstrated a significant difference between partial responders and healthy controls in magnitude effect, with a large effect size. More specifically, partial responders favored decks tied to large, short-term reward and withstood long-term loss more than healthy controls (**Figure 1** and **Table 3**). Partial responders also appeared to favor large, immediate rewards and withstood future losses more than full responders, although this finding was at trend level. Conversely, full responders did not differ from healthy controls in magnitude effect. Interestingly, while partial responders performed most poorly in magnitude effect on average [mean (SE) = -5.87 (1.79)], full responders and healthy controls did not score above chance level [mean (SE) = -0.52 (1.50) and -0.15 (1.38), respectively], with an average net gain around zero. See Appendix A of **Datasheet 1 (Supplementary Material)** for LME model estimates.

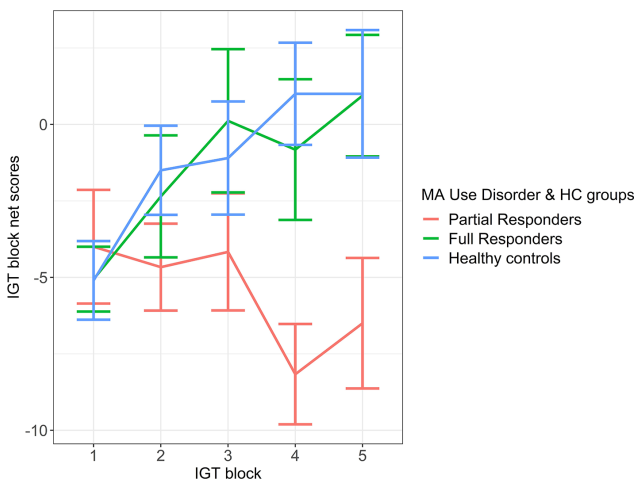

FIGURE 1 | Magnitude Effect. IGT net scores by block for partial responder, full responder and control groups. HC, healthy control. Displays relative mean group differences in Magnitude Effect (where error bars represent standard error), measured by the preference for large, short term rewards over long term gains across the entire duration of the IGT. Lower block scores represent a higher Magnitude Effect, where riskier choices associated with large, immediate rewards are favoured whilst higher block scores represent a lower Magnitude Effect, illustrated by a greater tendency to avoid risky choices and select safer decks tied to lower, short term rewards but higher long-term gains.

Frequency Effect

An LME model of the frequency effect was significantly improved over a fixed-effect model (likelihood ratio = 38.35, $p < 0.001$). On the LME frequency effect model, a group difference in frequency effect was exhibited between full responders [mean (SE) = 5.18 (1.11)] and partial responders [mean (SE) = 1.04 (1.33)], where full responders demonstrated a greater tendency than partial responders to favor frequent rewards and avoid frequent losses (**Figure 2**). However, this difference was at trend level with a moderate effect size (**Table 4**). Healthy controls [mean (SE) = 3.23 (1.03)] did not differ from full responders or partial responders on the frequency effect. See Appendix B of **Datasheet 1 (Supplementary Material)** for LME model estimates.

DISCUSSION

Individuals with MA Use Disorder, who did not respond fully to CM treatment, demonstrated maladaptive decision-making that was characterized by a greater preference for risky choices associated with large, immediate rewards and long-term losses,

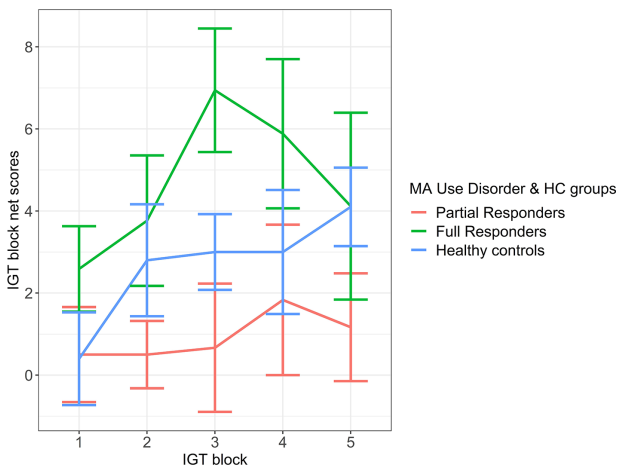

FIGURE 2 | Frequency effect: IGT net scores by block for partial responder, full responder and control groups. HC, healthy control. Displays relative mean group differences in Frequency Effect (where error bars represent standard error), measured by the preference for frequent rewards and avoidance of frequent loses across the entire duration of the IGT. Higher block scores represent higher Frequency Effect, where frequent rewards are favoured and frequent losses are avoided, whilst lower block scores represent a lower Frequency Effect. Illustrated by a relatively diminished tendency to favour frequent rewards and avoid frequent losses.

TABLE 3 | Group contrasts from LME Magnitude Effect model on baseline IGT.

Contrasts	Mmd	g (CI)	p
Partial responders– Controls	-5.72	-0.77 (-1.09: -0.44)	0.038*
Full responders – Controls	-0.37	-0.04 (-0.38: 0.26)	0.981
Partial responders – Full responders	-5.34	-0.67 (-1.05: -0.35)	0.067^{+}

*mmd, marginal mean difference between groups. g = hedges g effect size. Tukey's p-adjustment used to correct for multiple comparisons. +p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001.*

TABLE 4 | Group contrasts from LME Frequency Effect model on baseline IGT.

Contrasts	Mmd	g (CI)	p
Partial responders– Controls	-2.18	-0.42 (-0.74: -0.08)	0.401
Full responders – Controls	1.95	-0.30 (-0.01: 0.66)	0.409
Partial responders – Full responders	-4.13	-0.63 (-0.95: -0.29)	0.054^{+}

*mmd = marginal mean difference between groups. g = hedges g effect size. CI = confidence interval. Tukey's p-adjustment used to correct for multiple comparisons. $^{+}$p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001.*

over safer choices that were associated with greater long-term gain, relative to healthy controls. This finding points to the importance of the *immediacy* and *size* of reward outcomes, in conjunction with a lack of consideration for and/or limited ability to hold long-term consequences in mind, and their links to maladaptive decision-making and ultimately poor performance, otherwise referred to as the magnitude effect. Moreover, our findings are supported by literature findings of poor IGT performance in samples of individuals with drug use problems other than methamphetamine (1, 3, 4), as well as those who suffer from MA Use Disorder (2, 5).

Given that the magnitude effect incorporates the potential influence of the *magnitude* as well as the *immediacy* of the outcome on decision-making, impaired performance on the IGT could be driven by a prepotent drive for large, immediate gains in spite of both short-term and long-term negative consequences (1), or an insensitivity to future consequences despite the valence, as demonstrated in patients with ventromedial prefrontal cortical lesions (13). Using a modified IGT version, Bechara et al. (3) found that impaired performance by substance users is typically driven by a desire to seek rewards rather than an insensitivity to future consequences. This view is supported by findings that MA Use Disorder patients exhibit greater temporal discounting of reward value than healthy controls, illustrating a preference for immediate gains (8, 39). In turn, findings regarding temporal discounting suggest that maladaptive decision-making by partial responders is likely to be predominately driven by the tendency to favor large, immediate rewards in particular. Future studies with larger sample sizes should address the impact of *immediacy* and *magnitude* subcomponents of the IGT on decision-making.

Healthy controls and individuals who fully responded to CM performed at chance level (net zero gain) with respect to the magnitude effect, which is in contrast to previous studies of IGT performance by healthy individuals in particular, where healthy individuals were found to be able to obtain net positive gains on the IGT (1, 3). This contrast in findings may be explained by differing sample characteristics, where previous studies predominately consisted of university-educated healthy individuals, while the current study consisted of education-matched healthy controls with a lower, secondary-level education on average.

Decision-making among healthy samples is also influenced by the frequency with which rewards and losses are presented (10, 11). In this study, healthy controls did not differ from full responders or partial responders in the frequency effect, but full responders appeared to favor frequent rewards and avoided frequent losses more often than partial responders. This observation suggests that full responders and partial responders may present with differing decision-making profiles. In the context of the IGT where optimal decision-making is represented by a tendency to favor long-term gains in spite of small, immediate rewards, a tendency to favor frequent rewards and avoid frequent losses represents a kind of suboptimal decision-making strategy. Favoring of the frequency effect might be somewhat maladaptive in the context of the IGT, although full responders' task-based preference to receive frequent rewards and to avoid frequent losses in this pilot study may correspond with a responsiveness toward frequent positive reinforcement with monetary vouchers from sustained abstinence from methamphetamine.

Baseline IGT performance differences associated with response to CM indicate that an individual's cognitive strategy for balancing reward and potential loss can be an important factor to consider in deciding whether CM is the best treatment for a particular client. The very nature of CM, which involves forgoing immediate gain (from drug use) for a greater long-term gain (vouchers for abstinence), is consistent with greater therapeutic success of clients who can avoid immediate, large rewards that carry the risk of long-term loss. The findings also point to the influence of the frequency with which such decision alternatives arise. Future work confirming links between maladaptive decision-making and outcomes of CM treatment for MA Use Disorder might offer quick, affordable methods to separate persons most likely to fully respond from those who respond relatively less so to CM.

There are several limitations in this study. Sample size was small, but hypothesized meaningful findings were still obtained, and so was sufficient in size to test hypotheses. Groups were not perfectly matched against all potentially relevant sociodemographic, cognitive, and drug-use factors that may covary with performance, and models were run in absence of any covariates, which could lead to under- or overestimation of model estimates in small samples. Steps were taken to increase the precision of model estimates with use of LME models, which account for potential confounding effects of individual differences in performance. Moreover, groups were not examined on executive functioning capabilities, which have been strongly tied to performance on IGT (2, 5). As such, group differences in performance may partly be explained by executive functioning differences. However, a review by Toplak et al. (40) found that performance on the IGT was weakly related to various cognitive capabilities. A flat rate monetary incentive was used for task performance, instead of a performance-sensitive monetary incentive, due to logistical limitations of obtaining customized monetary vouchers. However, this flat rate was consistently applied across partial responder, full responder, and controls groups. Lastly, IGT findings cannot necessarily be uniquely tied to CM treatment, and future studies should compare the relationship between IGT performance and CM to that of other treatment types.

CONCLUSION

Partial responders to CM exhibited maladaptive decision-making as compared with healthy controls, reflected by the favoring of large, immediate rewards over long-term gains—the magnitude effect. Partial responders and full responders also appeared to differ in frequency effect, where full responders demonstrated a greater preference for frequent rewards and avoided frequent losses more than partial responders. Evidence

of group differences in magnitude effect and frequency effect suggests a difference in decision-making profiles, with different associated implications for treatment response on CM. In particular, the finding that the magnitude effect was more linked to lowered response to CM whereas the frequency effect was associated with positive response suggests that the magnitude effect is a risk factor for relapse during CM treatment, whereas the frequency effect may act as a cognitive strategy that predicts greater CM treatment success in the form of sustained abstinence.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Health Sciences Human Research Ethics committee of the University of Cape Town and UCLA Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML conceived the study focus with support from JI. SS conceived the broader study design with additional contributions from LN, EL, and DS. LN project managed the broader study and was in charge of data acquisition with assistance from ML. ML conducted analysis of data. ML interpreted findings of data with assistance from JI. ML wrote up the paper; revisions were obtained from all authors, with the biggest contributions from EL, ST, and SS. Final approval of the manuscript was obtained from all authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00022/full#supplementary-material

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BRIEF RESEARCH REPORT
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Effectiveness of the First German-Language Group Psychotherapy Manual to Accompany Short-Term Treatment in Methamphetamine Dependence

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Background: Methamphetamine abuse is expanding in Europe, leading to a shortfall in medical care for related disorders in many regions. Research focusing on the effectiveness and feasibility of methamphetamine-specific treatment programs is scarce, especially in short-term settings.

Methods: To this end, we treated 31 patients with methamphetamine dependence using a new group psychotherapy manual added to standard psychiatric care. Trained research assistants recorded demographic, illness and treatment variables using a standardized interview at baseline and a follow-up visit 3 months later. Outcome and process variables for this intervention encompassing 15 modules for qualified detoxification and motivation of patients with methamphetamine dependence are reported.

Results: Retention and abstinence rates as well as acceptance and feasibility in daily routine were assessed positively. Patients with an unsuccessful outcome were characterized by longer regular methamphetamine use ($t = -2.513$, df $= 29$, $p = 0.018$) and a shorter abstinence period at baseline (U $= 74.500$, $z = -1.808$, $p = 0.072$). Among the demographic and clinical variables, the only predictor significantly increasing the odds of a successful outcome was a shorter period of regular methamphetamine use (OR $=$ 1.318, CI 95% for OR $=$ 1.021–1.700, b $= 0.276$, SE $= 0.130$, $p = 0.034$).

Conclusions: This freely available therapy manual can help counter the shortfall in available psychotherapeutic interventions for patients with methamphetamine dependence in German-speaking countries. The routinely assessed parameters duration of regular methamphetamine use and abstinence before treatment were associated with outcome and may be used to personalize therapeutic strategies.

Keywords: methamphetamine, psychotherapy, manuals, effectiveness, prognosis, predictors, Germany

INTRODUCTION

Methamphetamine dependence is a growing global problem with major regional differences. Due to these differences, the availability of methamphetamine has affected certain cultures more than others. The annual prevalence of (meth-)amphetamine use in the European general public was 0.7% in 2012, with adults between the ages of 25 to 29 exhibiting a 12-month prevalence as high as 2.4% (1). Care providers in the German states of Bavaria, Saxony, Saxony-Anhalt and Thuringia (2) were particularly challenged in the past decade (3) due to the proximity of these states to the Czech Republic, which has a comparatively long history of methamphetamine consumption and production (5–10 tons per year) (4). A meta-analysis has shown that psychosocial interventions for substance use disorders are effective (5), yet the transferability of these interventions for the treatment of methamphetamine dependence may be limited due to rewarding effects concerning sexual drive (6), euphoria (7) and a greater likelihood for developing major psychiatric disorders compared with other drugs (8). However, there has been little research focusing on the effectiveness and feasibility of methamphetamine-specific treatment programs.

In the German healthcare system, treatment of drug-related disorders is divided into acute therapy, i.e., inpatient qualified withdrawal treatment for 3–4 weeks, and seamless post-acute management spanning from 3 to 12 months delivered either as outpatient, semi-inpatient or inpatient treatment (8). In post-acute long-term settings, the Matrix Model—a methamphetamine-specific, group-based treatment program consisting of cognitive behavioral therapy, family therapy and self-help sessions—demonstrated higher retention and completion rates than non-specific inpatient post-acute management programs (9). Following this rationale we adopted and translated the manual by Lee et al. (10), which is in line with the quality standards recommended by the German treatment guidelines for methamphetamine-related disorders (8). The original manual has been proven effective in treating methamphetamine use disorders compared with other treatment options (11), and the version adapted by our department has demonstrated good feasibility in daily clinical routine (12).

The aim of the present study was to evaluate the effectiveness of the first German-language group psychotherapy manual specifically developed for treating patients with methamphetamine dependence, using a short-term approach in a real-world setting. Based on other studies focusing on the Matrix Model, we expected similar retention rates of approximately 40%. Moreover, we explored if participant characteristics at baseline were associated with outcome to identify predictors for a successful treatment.

METHODS

This is a real-world study testing the effectiveness of the first German-language group psychotherapy manual using short-term treatment in patients with methamphetamine dependence. The methods were performed according to relevant national and institutional guidelines and regulations as approved by the institutional review board of the Technische Universität Dresden. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Intervention

The German manual is available free of charge from the corresponding author and has been described in detail elsewhere (12). In summary, it features a methamphetamine-specific relapse prevention program based on motivational interviewing, which comprises 15 modules: [1] introduction to treatment rationale including functional analysis of last methamphetamine consumption, [2+6] motivational clarification and enhancement (if necessary also in further course of therapy), [3−5] understanding and managing of cravings, [7−9] the role of the social environment and role-play training of strategies to resist drug use, [10+11] awareness of seemingly irrelevant decisions, [12+13] identifying and dealing with other high-risk situations, [14] drafting a personal crisis plan, [15] coping with problems after the end of therapy. The 15 sessions lasted 50 min each and were delivered to groups of up to 6 participants by a psychotherapist twice a week. Patients could join the program at any module, but received an individual session before in which the program was introduced.

Study Procedure

To ensure a naturalistic study sample, all patients using either an in- or outpatient treatment between the ages of 18 to 65 diagnosed with methamphetamine abuse or dependence according to the International Classification of Diseases (ICD-10) were offered study participation. Patients were eligible to participate after symptoms of intoxication and withdrawal subsided and they maintained abstinence from any drug for at least 2 days, proven by negative urine results (Drug-Screen Multi 4TL-AC-A, nal von minden, Moers, Germany) for amphetamines, methamphetamines, methylenedioxymethamphetamine (MDMA), opioids, tetrahydrocannabinol (THC), benzodiazepines and tricyclic antidepressants. Any condition (e.g., psychotic or severe affective symptoms, cognitive impairment and reduced mobility) that would have interfered with the capability to attend group psychotherapy led to exclusion from the study.

Trained research assistants recorded demographic, illness and treatment variables using a standardized interview at baseline and a follow-up visit approximately 3 months later. Outcome was classified as successful if patients (a) attended at least 8 out of 15 group sessions or enrolled in a post-acute management program and (b) had no more than 1 methamphetamine relapse until the follow-up visit indicated by drug tests, provided the relapse was admitted and self-critically processed. Inpatients were tested unannounced at least once a week, whereas outpatients were randomized unannounced with a 1/6 probability of urine screens between Monday and Friday. Urine was collected under direct observation followed by temperature measurement to minimize manipulation.

Statistics

We used SPSS Statistics 25 (IBM, Armonk, NY, USA) and assumed 2-tailed significance at $p < 0.05$ for all analyses. All tests were based on the whole study sample ($N = 31$) and data were complete on all implicated variables (i.e., no missing values). Histograms and normal quantile-quantile plots were used to judge normality. Descriptive analyses were conducted to characterize demographic, illness and treatment variables as well as treatment outcome. We compared participant characteristics and the number of group sessions attended according to treatment outcome (successful vs. unsuccessful) using Pearson's chi-square test for categorical variables, applying Fisher's exact test if needed and the independent *t*-test for continuous variables, applying the Mann Whitney *U*-test if needed. Variables that considerably differed between outcome groups (successful vs. unsuccessful) were correlated across groups and reported as Pearson's r or Spearman's ρ as appropriate. To identify predictors for a successful outcome, all participant characteristics reported in **Table 1** were explored by logistic regression analyses with forward stepwise selection, using natural log transformations of abstinence durations at baseline to meet the assumptions of parametric testing.

RESULTS

Participant Flow and Retention

We offered study participation to 48 in- and outpatients from the Carl Gustav Carus University Hospital in Dresden, Germany of which 10 patients were not interested and 7 patients did not meet the eligibility criteria. Of the 31 patients enrolled from March to December 2017, 15 were classified as having a successful outcome (48.4%), 5 of whom were referred to a post-acute management program before completing group psychotherapy. Twenty of 31 participants attended the follow-up visit (64.5%), including 3 of the referred patients and 7 of the 16 participants who were classified as having an unsuccessful outcome. Patients with successful outcome participated in more group psychotherapy sessions (mean ± SD = 8.33 ± 5.21, without referred patients: 10.10 ± 5.32) than patients with an unsuccessful outcome (4.88 ± 2.99) (U = 69.000, $z = -2.028$, $p = 0.045$, test based on $N = 31$).

Participant Characteristics and Outcome Prediction

Demographic and clinical characteristics were comparable between patients with a successful and with an unsuccessful outcome, except for sex distribution and the duration of regular methamphetamine use (see **Table 1**). Current psychiatric comorbidities were depressive episodes ($N = 6$), harmful use of THC ($N = 5$), alcohol dependence ($N = 4$), attention-deficit hyperactivity disorder ($N = 4$), drug-induced psychotic disorder ($N = 3$, subsided before start of psychotherapy), borderline personality disorder ($N = 2$), dissocial personality disorder ($N = 1$), posttraumatic stress disorder ($N = 1$) and schizophrenia ($N = 1$). While sex was almost equally distributed in the group with successful outcome, participants with an unsuccessful outcome were predominantly male (81.3%) and characterized by longer regular methamphetamine use ($t = -2.513$, df = 29, $p = 0.018$) and a shorter abstinence period at baseline (U = 74.500, $z = -1.808$, $p = 0.072$). Correlational analysis revealed that regular methamphetamine use was longer in men across groups ($r = 0.362$, $p = 0.046$). Although only reaching trend-level significance, we were interested in whether such a relationship also existed for abstinence. However, abstinence period was not significantly correlated with sex ($\rho = -0.083$, $p = 0.656$; numerically shorter in men) or with the duration of regular methamphetamine use ($\rho = -0.116$, $p = 0.535$) across groups. Among the demographic and clinical variables, the only predictor significantly increasing the odds of a successful outcome was a shorter period of regular methamphetamine use (OR = 1.318, CI 95% for OR = 1.021–1.700, b = 0.276, SE = 0.130, $p = 0.034$).

TABLE 1 | Participant characteristics at baseline.

	Successful outcome	Unsuccessful outcome	Statistics
Sample size	15 (48.4)	16 (51.6)	
Demographics			
Sex			$X^2 = 4.045$, df = 1, $p = 0.044$*
Women	8 (53.3)	3 (18.8)	
Men	7 (46.7)	13 (81.3)	
Age [years]	27.53 ± 5.29	30.75 ± 7.73	$t = -1.343$, df = 29, $p = 0.190$
Romantic relationship	7 (46.7)	6 (37.5)	$X^2 = 0.267$, df = 1, $p = 0.605$
Children	9 (60.0)	10 (62.5)	$X^2 = 0.020$, df = 1, $p = 0.886$
Lower secondary school leaving certificate or less	9 (60.0)	14 (87.5)	$X^2 = 3.058$, df = 1, $p = 0.113$
Unemployed	9 (60.0)	13 (81.3)	$X^2 = 1.697$, df = 1, $p = 0.252$
Clinical data			
Methamphetamine dependence	15 (100.0)	16 (100.0)	
Age of first methamphetamine use [years]	18.20 ± 4.31	19.81 ± 5.91	$U = 139.000$, $z = 0.760$, $p = 0.470$
Regular methamphetamine use [years]	5.17 ± 2.58	8.69 ± 4.81	$t = -2.513$, df = 29, $p = 0.018$*
Abstinence [days]	33.73 ± 69.23	5.63 ± 4.50	$U = 74.500$, $z = -1.808$, $p = 0.072$
Abstinence confidence for the next 3 months[A]	8.07 ± 2.09	7.06 ± 1.73	$U = 82.000$, $z = -1.534$, $p = 0.140$
Current psychiatric comorbidity[B]	10 (66.7)	7 (43.8)	$X^2 = 1.642$, df = 1, $p = 0.200$
First or second degree family history of mental disorders[C]	7 (46.7)	6 (37.5)	$X^2 = 0.267$, df = 1, $p = 0.605$

*All tests are based on the whole study sample (N = 31) and complete data on all variables. Data are number (%) or mean ± SD. [A]Likert scale, from 1 = not very safe to 10 = very safe, [B]according to ICD-10, [C]according to (15), *significant at $p < 0.05$.*

DISCUSSION

We aimed to evaluate the effectiveness of the first German-language group psychotherapy manual specifically designed

for short-term treatment in patients with methamphetamine dependence in a real-world setting. Almost half of the participants were classified as having a successful outcome, which was based on abstinence, group psychotherapy attendance and enrollment in a post-acute management program. Women were found to be significantly more successful compared to men with shorter periods of regular methamphetamine use at baseline than those with an unfavorable outcome. A shorter period of regular methamphetamine use was the only significant predictor of a successful outcome.

Methamphetamine-Specific Psychotherapy

A comparison between short- and long-term interventions led to heterogeneous results. Additionally, differentiation between in- and outpatient settings is of interest. Concerning interventions for methamphetamine-related disorders, observation periods varied between 3 weeks and 6 months, with retention rates between 90% (9, 13, 14, 16) and 30% (17). In China, Srisurapanont et al. (16) enrolled 48 students with methamphetamine abuse or dependence in a randomized controlled trial in an outpatient setting comparing a methamphetamine-specific brief intervention consisting of two 20-min sessions with one 15-min psychoeducation session. The brief intervention appeared to reduce the days of methamphetamine use at the 8-week endpoint (1.97 days to 1.09 days, $p = 0.04$). Dropout rates were 50 and 30% for the brief intervention and psychoeducation group, respectively. The most studied methamphetamine-specific outpatient program is the cognitive behavioral therapy based 16-week Matrix Model (18). Whereas retention rates did not statistically differ between the Matrix Model (65%) and a complex inpatient treatment routine based on a therapeutic community model (51%) in 115 patients in Thailand (19), a higher short-term retention was achieved in the US comparing the Matrix manual with non-methamphetamine-specific treatment as usual in 978 patients (9). Of note, this superiority leveled off in 2 post-treatment time points. Recently, a German work group found no significant differences in dropout rates (41% across groups) between 2 inpatient programs for post-acute management of 108 patients with methamphetamine abuse (20). Interestingly, retention rate was higher ($p = 0.001$) in the treatment-as-usual group (171 vs. 128 days), but this may be due to structural differences between treatment facilities assuming a better treatment allegiance in the treatment-as-usual facility (20). On a broader scale, a Cochrane review including 52 trials (6,923 participants) reported a dropout rate of 32% for all individuals involved in psychostimulant misuse (21). Nevertheless, because of the heterogeneity of the results, it is unlikely that there is a one-size-fits-all approach. With this in mind, the present study supports the finding in contemporary substance abuse literature that all treatment conditions are associated with comparable levels of improvement.

Predictors of Favorable Outcome

A systematic review including 199,331 participants of 122 addiction treatment studies concluded that consistent predictors for dropout were younger age, personality disorders and low treatment alliance, with younger age being the most robust predictor (22). It is important to emphasize that research focusing on stimulant use disorders has been scarce. In cocaine dependence ($N = 286$), younger patients who did not complete high school and had more days of cocaine use in the previous month were less likely to complete 1 week of abstinence at the beginning of treatment (23). In another study, drug use variables did not predict time to dropout, but younger African American patients and unemployed patients were more likely to drop out earlier of psychosocial treatment for cocaine dependence (24). Furthermore, psychiatric severity was associated with women dropping out sooner but not in men. In methamphetamine dependence, injection drug use (20), history of drug injecting, employment status and multiple sexual partners (25) were identified as predictors for an unfavorable outcome. We did not assess drug injection use or sexual behavior in our study, but age, being in a romantic relationship or employed did not considerably differ between outcome groups. By contrast, methamphetamine use before treatment was longer in patients with an unsuccessful outcome and was also found to be a significant predictor. Of note, those patients were predominantly male with substantially longer regular methamphetamine use in men across groups. Since abstinence period at baseline tended to be shorter in these patients without being significantly correlated with sex across groups, sex and drug use variables seem to have at least a partially independent influence on treatment success. Taken together, our data indicate that a longer duration of regular methamphetamine use and a shorter abstinence period before treatment are linked to a more difficult course of treatment. As these parameters are easy and take little time to collect, they can be utilized to identify specific patients, who may benefit from this manual or are even at risk for an unsuccessful outcome. If necessary, individual treatments could then be escalated quickly, e.g., through augmenting the program with individual psychotherapy sessions.

The different predictors found across studies may be explained by differences in sample characteristics, possibly reflecting country-dependent patterns of addiction or broader cultural themes. Of note, our study may have lacked statistical power to detect predictors of smaller effect sizes. Moreover, we did not test for differences in single psychiatric comorbidities between outcome groups due to an insufficient number of cases.

Strengths and Limitations

To our knowledge, this work represents the first study evaluating the effectiveness of a German-language group psychotherapy manual to accompany short-term treatment in patients with methamphetamine dependence. The study of a naturalistic sample demonstrated the transferability of this program into the real world. Given the external validity, our findings concerning clinical markers are of direct importance for day-to-day patient care. Yet since country-dependent epidemiological research addressing consumers and their consumption patterns is non-existent, our results may not be generalizable. Moreover, our study is limited by a rather small sample ($N = 31$), the

lack of a control group with a non-methamphetamine-specific intervention and a follow-up restricted to 3 months.

CONCLUSION

We positively evaluated the effectiveness of the first German-language group psychotherapy manual to accompany short-term treatment in patients with methamphetamine dependence in a real-world setting. The manual is available free of charge from the corresponding author and can be implemented easily into the daily clinical routine and help counter the shortfall in available psychotherapeutic interventions for patients with methamphetamine dependence in German-speaking countries. Male patients and patients with a longer regular methamphetamine use before treatment should receive particular attention when applying this program as these factors were associated with an unfavorable outcome. Since treatment success was only 48% similar to other psychological interventions with different outcome predictors associated with different programs, it emphasizes that we still know little about what works for whom. Large-scale head-to-head studies are needed to further our understanding of the active ingredients of psychological interventions for patients with methamphetamine dependence.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the Technische Universität Dresden. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP and MS designed the study. MP obtained funding. CG delivered group psychotherapy. CG, HH, BW, and MP collected the data. JP analyzed the data, wrote the methods and results and contributed to the introduction and discussion. JP, MP, BW, NB, MB, and TB interpreted the data. BW wrote the introduction and discussion. MP, TB, NB, MS, MB, CG, and HH revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Psychopathy and Corticostriatal Connectivity: The Link to Criminal Behavior in Methamphetamine Dependence

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Methamphetamine use and psychopathy are associated with criminal behavior; however, it is unclear how methamphetamine use and psychopathy interact to promote violent, economic and drug offenses. Abnormalities in corticostriatal functional connectivity are exhibited in both psychopathic and methamphetamine dependent individuals, which may contribute to criminal behavior through maladaptive and impulsive decision-making processes. This study shows that psychopathic traits contribute to weaker corticostriatal connectivity in methamphetamine dependence and contributes to an increase in criminal behavior. As the propensity to engage in criminal activity is dependent on a number of factors, a hierarchical regression identifies the contribution of the impulsive antisocial domain of psychopathy, anxiety, years of methamphetamine use and corticostriatal connectivity on different types of criminal offenses. Methamphetamine use and psychopathic traits reduce treatment responsiveness and increase the likelihood of recidivism, and it is therefore important to understand the factors underlying the propensity to engage in criminal behavior.

Keywords: methamphetamine, resting state – fMRI, psychopathy (PPI-R), corticostriatal, ventral striatum

INTRODUCTION

Substance use is especially prevalent among individuals with co-occurring psychiatric conditions, including psychopathic personality traits. Although psychopathy only affects approximately 1% of the population, antisocial diagnoses are greater in individuals with substance-use disorders, and are associated with early onset of drug use (1) and with development of polysubstance dependence (2, 3). Psychopathy and addiction share common behavioral phenotypes, including poor behavioral control, impulsivity, novelty seeking and risk-taking (4–11), which may contribute to an increase in criminal activities in both populations (10, 12). Although all drugs of abuse are associated to some extent with criminal activities, methamphetamine (MA) users are more likely than other drug users

to commit acts of violence (10). MA users also exhibit heightened categorical and dimensional aspects of antisocial and psychopathic traits, including interpersonal violence, hostility, and aggression (13, 14). There have been no studies, however, investigating the complex interaction of psychopathy in MA use disorder and its effect on criminal behavior.

Results from neuroimaging studies on psychopathy and MA use disorder converge on a set of brain regions responsible for emotional processing and behavioral planning, including the insula, amygdala, dorsal/ventral striatum, anterior cingulate cortex, and the dorsolateral and orbital/ventral medial prefrontal cortex (PFC) (15, 16). Notably, abnormalities in ventral striatal function and corticostriatal resting-state functional connectivity (RSFC) are similar in psychopathy and addiction. Individuals with psychopathic traits and individuals with MA use disorder have increased ventral striatal response to reward during temporal discounting (9) and risky decision-making (5), respectively. Resting-state functional connectivity results also show similar patterns, where psychopathy and MA dependence are both associated with abnormalities in corticostriatal RSFC (5, 9, 17, 18). As disruptions in striatal function and corticostriatal connectivity are linked with poor behavioral regulation and impulsiveness (4), the integrity of these regions may be critical in controlling various signals that increase the propensity for aggression and violence and shape maladaptive criminal behaviors.

Psychopathic traits and the link to criminal behavior is important to understand, from both substance abuse treatment and criminal justice perspectives, as individuals with histories of antisocial behavior are more likely to re-offend and less likely to successfully complete substance abuse treatment (10). A number of studies have examined how different dimensions of personality may predispose individuals to engage in criminal activities. Results suggest that psychopathy and anxiety are common traits in criminal offenders, where high levels of anxiety, nervous tension, and distress on the Karolinska Scales of Personality (KSP) were reported in a group of 130 individuals convicted of serious criminal offenses (19). Similarly, a cohort of criminally convicted women reported significantly high levels of anxiety, irritability, hostility, and insecurity, and individuals convicted of murder self-report significantly high levels on anxiety measures and on obsessive and psychopathic traits (20). These studies suggest a strong link between criminal behavior and anxious and psychopathic traits, and although some studies find a negative association between psychopathy and anxiety, anxiety is positively related to the anti-social impulsive dimensions of psychopathy (8, 21, 22).

Taken together, these studies provide evidence for a link between criminal behavior, brain function, and personality traits, however there has been no systematic study on the mechanism by which these processes promote criminal behavior in MA use disorder. Given that inhibitory control deficits are linked to corticostriatal function, which is compromised in both psychopathy and addiction, this study aims to examine the associations between brain connectivity, psychopathy, generalized anxiety, and criminal behavior in individuals with MA dependence. Both psychopathy and MA use has been linked to a decrease in corticostriatal connectivity but an increase in mesolimbic dopamine function and activation of the ventral striatal in response to rewards (5, 9). We therefore expect that the MA group will exhibit a negative relationship between psychopathy scores and connectivity between the ventral striatum and prefrontal cortex. As anxiety and psychopathy are linked to criminal behavior, we hypothesize that the increase in criminal behavior in the MA group will be associated with higher levels of anxiety and psychopathic traits. A systematic evaluation of the association of criminal behavior with brain function and personality traits in MA dependence is critical in addressing the clinical course and response to appropriately matched treatments, which may reduce incarceration.

METHODS

Participants

Thirty-three volunteers diagnosed with MA dependence (DSM-IV), recruited from the VA Portland Healthcare System (VAPORHCS) and community substance abuse treatment programs and 38 healthy controls recruited with online advertisements, provided written informed consent, as approved by the VAPORHCS and Oregon Health & Science University Institutional Review Boards. Exclusion criteria, determined by medical history and laboratory blood tests were: systemic, neurological, cardiovascular, or pulmonary disease, head trauma with loss of consciousness, magnetic resonance imaging (MRI) contraindications, use of medications known to have dopaminergic mechanisms (e.g., antipsychotics, antidepressants, antiparkinsonian agents), sedative-hypnotics (barbiturates, benzodiazepines, zolpidem), or anticholinergics. Past or Current Axis I diagnoses, other than MA dependence (MA group) or nicotine dependence (either group), assessed with the Structured Clinical Inventory for DSM-IV-TR, were exclusionary. Urine testing on day of MRI scan verified abstinence from cocaine, methamphetamine, benzodiazepines, opiates, and cannabinoids. Participants were able to smoke cigarettes up to 1 h before scanning to minimize and balance the effects of recent smoking on brain function against the effects of nicotine withdrawal and craving.

Neuropsychiatric and Criminal History Interview

The Psychopathic Personality Inventory - Revised (PPI-R) is a 154-item self-report scale that assesses psychopathy by measuring 8 factors that index psychopathic personality traits including, Machiavellian Egocentricity, Rebellious Nonconformity, Blame Externalization, Carefree Nonplanfulness, Social Influence, Fearlessness, Stress Immunity, and Coldheartedness. The PPI-R is composed of two underlying latent factors; PPI-1: Fearless Dominance and PPI-2: Impulsive Antisocial. The PPI-1 is a composite score of Social Influence, Fearlessness, and Stress Immunity, and higher scores are associated with low levels of depression, anxiety and substance use. The PPI-2 is a composite score consisting of Machiavellian Egocentricity, Rebellious

Nonconformity, Blame Externalization, and Carefree Nonplanfulness, and higher scores reflect a tendency for substance abuse, reckless impulsivity, self-centeredness, and a heightened risk for major Axis 1 disorders including anxiety disorders.

The Generalized Anxiety Disorder 7-item (GAD-7) scale (23), a brief self-report questionnaire, was used to assess generalized symptoms of anxiety, and the Addiction Severity Index-lite (ASI-lite) (24, 25) was used to assess past 30-day substance use and criminal history. The criminal history data used in this study included questions relating to the number of arrests, which were grouped in three categories: Acquisitive Offenses, which included shoplifting, forgery and burglary/larceny; Drug Offenses, which included selling or acquiring drugs; and Violent Offenses, which included assault, rape, homicide, and robbery charges. Data on the total number of convictions and months of incarceration were also collected. Participants were informed that disclosure of certain offenses (e.g., child/elder abuse, homicide) would be reported to authorities.

MRI Imaging Acquisition

Imaging was performed on a subset of participants (18 controls and 16 MA) on a 3 Tesla Siemens TIM Trio MRI scanner (**Table 1**). A localizer scan was acquired in order to guide slice alignment during anatomical and functional scans. A T_2*- weighted echo-planar image (EPI) was acquired (24 slices, 4 mm thick, gap width = 1 mm, TR/TE/α = 2,000 ms/40 ms/80°, matrix=128 × 128, FOV=240 mm^2, 170 volumes, in-plane pixel size of 1.875 mm^2) while subjects stared at a white cross on a black screen. One high-resolution T1-weighted anatomical magnetically prepared rapid acquisition gradient echo (MPRAGE; 144 slices 1 mm thick, TR/TE/TI/α = 2,300 ms/4.38 ms/1,200 ms/12°, FOV = 208×256 mm) was acquired for co-registration with functional images and statistical overlay.

Resting-State Processing and Group-Level Analyses

Image analysis was performed using FSL 5.0.2.1 (www.fmrib.ox.ac.uk/fsl). Images were skull-stripped, spatially smoothed (5 mm FWHM Gaussian kernel) and realigned to compensate for motion (26). Automatic Removal of Motion Artifacts (AROMA) was then used to reduce motion-induced signal variation using independent component analysis (ICA) with a classifier that uses two temporal and two spatial features to remove motion artifacts. Images were further pre-processed to include additional nuisance regressors: average signal of cerebrospinal fluid and white-matter, and two metrics of motion-related artifact, specifically motion scrubbing with frame-wise displacement and a combination of the temporal derivative of the time series and root-mean-squared variance over all voxels (27) and high-pass temporal filtering (100s). Global signal regression was not applied. The EPI images were registered to the high-resolution MPRAGE image and then into standard Montreal Neurological Institute space, using a 12-parameter affine transformation. An anatomically-defined region of interest (ROI) from the Harvard-Oxford Subcortical atlas of the ventral striatum was used as a seed. The seeds were transformed into each subject's native space by applying the inverted transformation matrix of EPI to MPRAGE to standard space. The mean time series across all voxels within the striatum seed from pre-processed images were used as covariates in separate whole-brain, voxel-wise resting-state correlation analyses. For between-group mixed-effects analyses, PPI-R Total scores were included as regressors to test PPI-R by group interactions in whole-brain voxel-wise RSFC analyses with the ventral striatal seed. All whole-brain functional MRI (fMRI) statistics were corrected for multiple comparisons by using cluster-correction with voxel height threshold of $p < 0.001$ and cluster significance of $p < 0.05$.

Statistical Analysis

Student's t-tests, chi-squared tests, and Fisher's exact tests, where appropriate, were used to compare groups in baseline demographics, clinical variables and criminal history (**Table 2**). Parameter estimates from voxels within significant clusters of activation resulting from group and PPI-R Total score interactions were extracted to examine group interactions with RSFC and PPI-R latent factors of PPI-1 and PPI-2 in SPSS 22. Hierarchical multiple regression analysis was conducted within the MA group to examine the influence of PPI-2, PPI-1, years of MA use, average amount of daily MA use and anxiety on criminal offenses, with a second model incorporating RSFC connectivity values.

RESULTS

The healthy control group includes 38 subjects (12 women/26 men, 15 smokers, mean ± SD age of 34.61 ± 11.52 years). The

TABLE 1 | Participant characteristics included in imaging analysis.

	Control Group (n = 18)	MA Group (n= 16)	p-value
Age (years) [a]	37.12 ± 13.92	32.47 ± 9.19	0.281
Sex (M/F) [b]	11/7	11/5	0.287
Education	14.29 ± 1.69	12.33 ± 1.18	0.001
Number of smokers [b]	6	14	0.001
PPI- Total	46.88 ± 8.18	54.33 ± 7.17	0.011
PPI-1	154.06 ± 25.02	160.40 ± 21.14	0.448
PPI-2	186.53 ± 18.35	209.73 ± 32.89	0.018
Machiavellian Egocentricity	44.71 ± 7.47	50.00 ± 13.35	0.170
Rebellious Non-conformity	48.82 ± 6.77	52.67 ± 7.20	0.130
Blame Externalization	46.59 ± 8.18	52.67 ± 7.92	0.042
Carefree Non-planning	46.41 ± 9.17	54.50 ± 14.36	0.067
Social Influence	50.53 ± 9.20	52.00 ± 10.80	0.680
Fearlessness	49.00 ± 11.76	57.47 ± 8.81	0.030
Stress Immunity	54.53 ± 9.81	50.93 ± 9.67	0.306
Cold Heartedness	47.18 ± 9.93	48.13 ± 9.09	0.779
Total Convictions	0.53 ± 0.80	14.40 ± 15.57	0.001
Acquisitive offenses	0.12 ± 0.33	8.27 ± 12.47	0.011
Drug offenses	0.18 ± 0.39	3.87 ± 6.64	0.029
Violent offenses	0.24 ± 0.44	1.13 ± 3.04	0.238
Months Incarcerated	2.06 ± 7.27	35.87 ± 49.85	0.010
Anxiety Score (GAD-7)	2.41 ± 2.45	4.73 ± 4.45	0.073
Age of MA first use		18.73 ± 4.38	
Years of MA use		9.133 ± 5.76	
Average use (grams)/day		1.59 ± 1.09	

[a]*Data shown are means ± Standard Deviations.*
[b]*Data analyzed with Chi-squared test (X2).*

TABLE 2 | Participant characteristics.

	Control Group (n = 38)	MA Group (n= 33)	p-value
Age (years) [a]	34.61 ± 11.52	32.39 ± 7.98	0.358
Sex (M/F) [b]	26/12	25/8	0.493
Education	14.16 ± 2.06	11.94 ± 1.56	0.000
Number of smokers [b]	15	31	0.001
PPI- Total	48.14 ± 8.432	55.82 ± 9.10	0.001
PPI-1	157.94 ± 20.67	157.55 ± 19.72	0.935
PPI-2	186.44 ± 26.55	217.09 ± 34.48	0.000
Machiavellian Egocentricity	45.61 ± 9.61	51.21 ± 12.55	0.040
Rebellious Non-conformity	49.14 ± 8.82	54.58 ± 9.85	0.018
Blame Externalization	47.94 ± 10.27	56.52 ± 9.93	0.001
Carefree Non-planning	43.75 ± 9.98	54.79 ± 11.94	0.000
Social Influence	52.03 ± 8.48	52.67 ± 10.64	0.783
Fearlessness	50.83 ± 9.88	56.45 ± 9.39	0.018
Stress Immunity	55.08 ± 8.98	48.42 ± 9.79	0.004
Cold Heartedness	47.78 ± 9.84	48.91 ± 9.27	0.625
Total Convictions	0.55 ± 0.76	11.64 ± 14.79	0.000
Acquisitive offenses	0.13 ± 0.41	7.15 ± 13.21	0.002
Drug offenses	0.18 ± 0.46	3.00 ± 4.77	0.001
Violent offenses	0.16 ± 0.37	0.79 ± 2.10	0.074
Months Incarcerated	2.38 ± 7.37	44.45 ± 65.38	0.000
Anxiety Score (GAD-7)	2.13 ± 2.65	5.39 ± 4.75	0.001
Age of MA first use		18.58 ± 6.04	
Years of MA use		10.30 ± 6.58	
Average use (grams)/day		1.57 ± 1.16	

[a]*Data shown are means ± Standard Deviations.*
[b]*Data analyzed with Chi-squared test (X2).*

MA group includes 33 subjects (8 women/25 men, 31 smokers, mean ± SD age of 32.39 ± 7.98 years), who report using MA for a mean ± SD of 10.30 ± 6.58 years and 1.57 ± 1.16 grams per day and abstinent for 52.18 ± 22.18 days. There are no significant group differences in age or sex but there are significant differences in education ($p < 0.001$), cigarette smoking status ($p = 0.001$), and levels of anxiety ($p = 0.001$) (**Table 2**). There are significant group differences in PPI-R Total scores ($p < 0.001$) and PPI-2 scores ($p < 0.001$), with the MA group showing higher scores, and no group differences in PPI-1 scores ($p = 0.935$). Post-hoc tests of group differences on PPI-R subscales show group differences in 6 of the 8 PPI-R subscales ($p < 0.05$) (**Table 2**). The MA group report more total convictions and months of incarceration than the control group (p's < 0.001) and report more acquisitive and drug offenses (p's < 0.002) (**Table 2**). Exploratory analysis of sex differences show no significant differences within the MA group for years or amount of daily MA use. There were also no significant effect of sex or interactive effects of sex and group on PPI-R Total, PPIR-1 or PPIR-2 scores.

RSFC and PPI-R Total Scores

Independent of PPIR scores, the MA group exhibit greater RSFC between the ventral striatum and right middle frontal gyrus than the control group (whole-brain corrected). For group analyses with PPIR- Total scores, there is a significant Group x PPI-R Total score interaction where the MA group exhibits a negative relationship between PPI-R Total scores and RSFC between ventral striatum and middle and inferior frontal gyrus, left anterior insula and cingulate gyrus with the control group showing the opposite effect (whole-brain corrected, **Figure 1**). The connectivity values from the functional ROI of the middle and inferior frontal gyrus show significant group interactions ($p = 0.002$) with PPI-2 (**Figure 1**), with a negative relationship in the MA group and a positive relationship in the control group. Within the MA group, the negative relationship remains significant after controlling for days abstinent.

PPI-R Scores, Criminal Convictions, and RSFC

There is a significant group interaction with PPI-R Total scores on total number of convictions ($p = 0.034$), however the results did not retain significance after excluding a MA participant with a high number of convictions and PPI total score. The limited range in the control group for total number of convictions, and

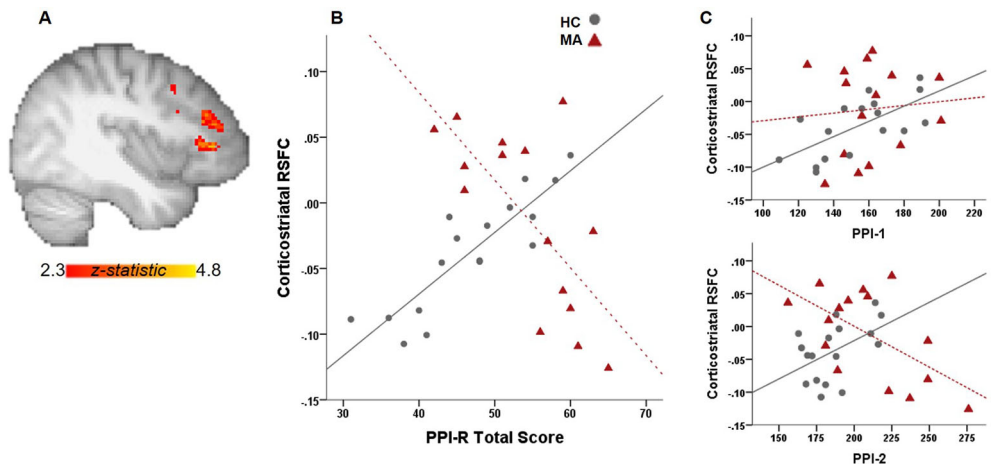

FIGURE 1 | Relationship between PPI total scores and RSFC. **(A)** Whole-brain connectivity analysis with a ventral striatal seed show significant group interactions with PPI-R total scores on corticostriatal connectivity. **(B)** Scatter plot illustrates the relationship between RSFC and PPI-R total scores for each group. **(C)** Significant group interactions on corticostriatal RSFC with PPI-R subscales.

for acquisitive, drug and violent offenses, however, limits the interpretation of any group interactions on criminal offenses. The hierarchical multivariate analysis of criminal history is, therefore, only examined in the MA group after excluding an outlier. For total convictions, ventral striatal-PFC RSFC is significantly associated with total number of convictions and the addition of RSFC in the model increases R^2 by 0.169. PPI-2 and amount of average daily MA use are both significant predictors for total number of convictions after accounting for ventral striatum-PFC RSFC, where an increase in PPI-2 scores and daily MA use are associated with a greater number of convictions (**Figure 2A**). Ventral striatum-PFC RSFC does not account for additional variability in violent offenses and only accounts for a.012 change in R^2 value. However, PPI-2 and years of MA use contribute to the number of violent offenses, where lower PPI-2 scores and more years of MA use is associated with more violent offenses but only years of MA use remains significant after accounting for RSFC (**Figure 2B**). For acquisitive crimes, ventral striatum-PFC RSFC improves model fit and accounts for 37% more variability than the model with only PPI-1, PPI-2, years, and amount of MA use and anxiety scores. An increase in RSFC and an increase in the amount of daily MA use are associated with higher numbers of acquisitive offenses (**Figure 2C**). For drug offenses, PPI-2 is only a significant predictor when RSFC values are excluded from the model (**Figure 2D**).

DISCUSSION

This study examined the extent to which psychopathic personality traits, MA use and associated brain connectivity confers predisposition to criminal involvement. We used the PPI-R, a self-report measure of psychopathy, and found that the MA group exhibited higher levels of psychopathy and reported significantly greater numbers of criminal offenses and convictions. The impulsive antisocial dimension of psychopathy (PPI-2) was a significant predictor in total convictions, violent offenses, and drug offenses, while amount of daily MA use were factors in total convictions and acquisitive crimes and years of MA use were associated with violent offenses. We also report different patterns of corticostriatal connectivity as a function of psychopathy total scores between MA-dependent individuals and controls with similar patterns for PPI-2, the impulsive antisocial dimension of psychopathy. Corticostriatal RSFC, however, was only a significant predictor for total

A Total Convictions

Model	R^2	R^2 Change		Beta	t	p-value
1	0.591	_	PPI-2	0.35	0.95	0.37
			PPI-1	0.12	0.43	0.67
			Years of MA Use	-0.03	-0.13	0.90
			Average daily MA use	0.70	3.02	0.15
			GAD Scores	-0.04	-0.11	0.91
2	0.760	0.169	PPI-2	0.73	2.17	0.05
			PPI-1	0.44	1.68	0.13
			Years of MA Use	0.01	0.04	0.97
			Average daily MA use	0.65	3.41	0.01
			GAD Scores	0.24	0.81	0.44
			Corticostriatal RSFC	0.65	2.38	0.05

B Violent Offenses

Model	R^2	R^2 Change		Beta	t	p-value
1	0.656	_	PPI-2	-0.80	-2.38	0.04
			PPI-1	0.12	0.43	0.32
			Years of MA Use	-0.03	-0.13	0.02
			Average daily MA use	0.70	3.02	0.38
			GAD Scores	-0.04	-0.11	0.10
2	0.668	0.012	PPI-2	-0.69	-1.75	0.12
			PPI-1	-0.19	-0.59	0.57
			Years of MA Use	0.60	2.81	0.02
			Average daily MA use	0.18	0.81	0.44
			GAD Scores	0.65	1.85	0.10
			Corticostriatal RSFC	0.17	0.54	0.60

C Acquisitive Offenses

Model	R^2	R^2 Change		Beta	t	p-value
1	0.385	_	PPI-2	0.16	0.35	0.74
			PPI-1	0.03	0.09	0.93
			Years of MA Use	-0.24	-0.89	0.40
			Average daily MA use	0.56	1.97	0.08
			GAD Scores	0.17	0.41	0.70
2	0.753	0.368	PPI-2	0.73	2.11	0.07
			PPI-1	0.51	1.88	0.10
			Years of MA Use	-0.19	-1.04	0.33
			Average daily MA use	0.48	2.51	0.04
			GAD Scores	0.58	1.92	0.09
			Corticostriatal RSFC	0.95	3.45	0.01

D Drug Offenses

Model	R^2	R^2 Change		Beta	t	p-value
1	0.613	_	PPI-2	0.86	2.43	0.04
			PPI-1	0.12	0.44	0.67
			Years of MA Use	0.16	0.73	0.48
			Average daily MA use	0.41	1.84	0.10
			GAD Scores	-0.62	-1.89	0.09
2	0.653	0.04	PPI-2	0.67	1.66	0.14
			PPI-1	-0.04	-0.12	0.91
			Years of MA Use	0.14	0.65	0.54
			Average daily MA use	0.43	1.91	0.09
			GAD Scores	-0.75	-2.11	0.07
			Corticostriatal RSFC	-0.32	-0.97	0.36

FIGURE 2 | Hierarchical multiple regression analysis to predict criminal offenses. The model includes factors hypothesized to contribute to a history of criminal convictions in the MA group. Model 1 includes PPI-1 and PPI-2 scores, Years of MA use, Average daily MA use and GAD-7 anxiety scores. Model 2 includes variables listed in Model 1 plus corticostriatal RSFC values. **(A)** Total Convictions: RSFC values improved the model by 1.69%. The most significant predictors are PPI-2 scores, daily MA use and corticostriatal RSFC. **(B)** Violent Offenses: RSFC values only improved the model by 1.2% and the most significant predictors of violent offenses are PPI-2 and years of MA use. **(C)** Acquisitive Crimes: RSFC values increased the model by 36.8.5% and indicates that greater daily MA use and greater corticostriatal RSFC are significant predictors of acquisitive crimes. **(D)** Drug Offenses: The independent variables accounted for the least amount of variance associated with drug offenses with greater PPI-2 scores associated with more drug offenses.

convictions and acquisitive crimes but did increase the predictive validity of PPI-2 for total convictions.

Similar to other studies showing greater RSFC in MA groups compared to control groups (5, 17, 18), the MA group exhibit greater RSFC between ventral striatum and right middle frontal gyrus compared to controls independent of PPI-R scores. These results are consistent with studies that suggest MA-induced abnormalities in corticostriatal circuits, which may manifest in poor decision-making, impulsivity, and behavioral phenotypes associated with addiction. The results with PPI-R total scores are also consistent with other studies that report heightened levels of psychopathy in drug-dependent groups (1, 28), and here we extend the literature to show that MA use disorder is also associated with significantly higher levels of psychopathy total scores and in the impulsive antisocial dimension of psychopathy (PPI-2). The MA group also exhibited significantly more criminal offenses than controls, which is in line with a report that MA use is a significant predictor in criminal behavior and recidivism (7). There were no significant interactions of group and psychopathy on total number of convictions; however, the limited range of convictions in the control group prevents definitive interpretation.

There is a high prevalence of MA addiction among those incarcerated (Office of National drug control policy 2006), however, the relationship between MA use, psychopathic traits and crime is complex and moderated by a number of factors. Here we investigated the relationship between psychopathy and functional connectivity of the ventral striatum. Higher total psychopathy scores were significantly related to weaker corticostriatal connectivity in the MA group, while the opposite was true for the control group. In addition, the impulsive antisocial dimension of psychopathy (PPI-2) showed similar group interactions. As cortical modulation of striatal activity is thought to promote adaptive and goal-directed behavior, abnormalities in corticostriatal connectivity associated with psychopathic traits in MA-use disorder may promote impulsivity and enhance maladaptive behavior in those with higher levels of psychopathy. This is consistent with other studies showing that corticostriatal and striatal connectivity is related to cognitive impulsivity and reward-driven behavior in MA use disorder (5, 18) and to temporal discounting in psychopathy (9).

This study extends previous studies in MA use disorder by showing that PPI-R scores and corticostriatal RSFC are significant predictors for the number of total convictions and acquisitive crimes. This agrees with a study showing that psychopathy is related to weaker corticostriatal RSFC, which is a predictor for a greater number of criminal convictions (9). In addition, we extend these results to show that average daily MA use contributes to total convictions. Similarly, average daily MA use and corticostriatal RSFC predict in an increase in acquisitive crimes. Interestingly, the regression shows that an increase in average MA use and stronger corticostriatal RSFC predicts a greater number of acquisitive crimes. As offenders of acquisitive crimes exhibit better cognitive function indexed by performance on measures of working memory, mental flexibility, capacity to plan action, and control of interference (29), greater corticostriatal RSFC coupled with an increase in MA use may contribute to impulsive behavior and enable those with MA-use disorder to execute goal-directed action. Although speculative, this notion is supported by results showing that MA users with greater striatal RSFC exhibit greater cognitive impulsivity (18), which differs from behavioral impulsivity in that it requires mental control, the ability to shift mental set or reasoning and is required in acquisitive crimes to a greater extent than violent behavior (29). In addition, there is an interaction between cognitive impulsivity and executive function, where higher cognitive impulsivity and low cognitive functioning is associated with more violent behaviors, while acquisitive crimes are linked to high cognitive impulsivity and functioning (29, 30). These results are interesting in the context of discussions on strengthening corticostriatal connections to promote adaptive decision-making in addiction. Although the goal of various treatment approaches is to enhance executive function through talk therapy or through functional connections with pharmacotherapies, these results highlight the importance of addressing impulsive and antisocial personality traits and the amount of MA use that could reinforce maladaptive behavior.

Consistent with studies showing that psychopathy predict higher levels recidivism (31), our results show that the impulsive antisocial dimension of psychopathy are associated with drug and violent offenses. Interestingly, the significance of PPI-2 as a predictor of these offenses are no longer significant after accounting for corticostriatal connectivity. However, years of MA use remains significantly associated with violent offenses after controlling for RSFC. Violent aggressive crimes have been linked to the pharmacological effects of MA, as psychosis and paranoia associated with intoxication leads to behavioral inhibition and criminal activity (11). Although this study did not assess whether violent offenses were associated with intoxication, we show that years of MA use is only associated with violent offenses, which accords with the association between violent offenses and more severe histories of substance use (32). Despite a number or studies reporting the link between anxiety and criminal activity and the link between MA use and anxiety, this study found no significant effects of anxiety on criminal offenses or convictions. Although dimensions of psychopathy are associated with anxiety (21), there is limited work describing the in interaction of anxiety and crime in MA use disorder and future studies addressing these two personality factors may provide important insight to reduce criminal offenses and recidivism and improve treatment outcomes in MA use disorder.

Criminal behavior in MA dependence is, however, conditional on many factors (6), some of which may be premorbid to MA use. The use of MA and related neural deficits can also contribute to criminal behavior through the lack of inhibitory/behavioral control, maladaptive decision-making processes and difficulties in interpersonal communication and emotion regulation (4, 6). However, it is unclear the extent to which MA use, independent of PPI-R is a factor in criminal offenses. A post-hoc analyses was therefore conducted to examine the regressions without PPIR scores, which show that daily MA use is still associated with Total

convictions and Acquisitive offenses, while years of MA use is still significantly associated with Violent offenses. However, a number of personal and contextual characteristics accompany addiction and motivate criminal behavior, gaining an understanding of neurobiological factors paired with personality and environmental variables may aid in developing future effective psycho- and pharmacotherapies.

LIMITATIONS

Although this study begins to detail the complex interactions of MA use, neurobiological dimensions of psychopathy to predict criminal behavior, it is not without limitations. Self-reports were used to assess criminal offenses and it is possible that the number of offenses were either inflated or underreported. Future studies should consider obtaining official records for accurate criminal history data. In addition, a more detailed description of violent offenses would help dissociate violent behavior resulting from MA intoxication from predisposing factors for violence. The small sample sizes preclude the examination of sex and other demographic variables in the analysis and results should be interpreted with caution. The limited number of offenses in the control group also limits the interpretation of group interactions on criminal history and future studies would benefit from recruiting control participants with greater variability in criminal convictions. In addition, differentiating first-time offenses from that of re-offenses may provide insight aimed to reduce recidivism in MA use disorder. Lastly, it cannot be determined to what extent brain connectivity, psychopathy and anxiety is premorbid to MA use or to what extent MA use exacerbates these outcome variables.

CONCLUSIONS

Despite these limitations, these results extend previous studies examining the association between brain function and psychopathy by providing evidence for the interaction of substance use and psychopathic traits on brain connectivity. This study also highlights the complex relationship between MA use, personality traits and criminal behavior and suggests that although brain function is an important component in a subset of criminal activity, therapies should focus on impulsivity/antisocial dimensions of personality to reduce criminal convictions.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by VAPORHCS and Oregon Health & Science University Institutional Review Boards. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WH designed and implemented the study. LD and HM managed and oversaw the study implementation. MK conducted the analysis and drafted the manuscript. MK, MJ, and AH contributed to data interpretation. SS participated in data collection. All authors took part in the revision of the manuscript and approved the article.

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Dark Times: The Role of Negative Reinforcement in Methamphetamine Addiction

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Methamphetamine use is associated with substantial adverse outcomes including poor mental and physical health, financial difficulties, and societal costs. Despite deleterious long-term consequences associated with methamphetamine, many people use drugs for short-term reduction of unpleasant physical or emotional sensations. By removing these aversive states, drug use behaviors are negatively reinforced. Abstinence from methamphetamine can then result in a return to previous aversive emotional states linked to withdrawal and craving, often contributing to an increased likelihood for relapse. This negative reinforcement cycle is hypothesized to be a motivating and maintaining factor for addiction. Thus, this review highlights the current evidence for negative reinforcement mechanisms in methamphetamine use disorder by integrating studies of subjective experience, behavior, functional magnetic resonance imaging, positron emission tomography, and event-related potentials and examining the efficacy of treatments targeting aspects of negative reinforcement. Overall, the literature demonstrates that individuals who use methamphetamine have diminished cognitive control and process emotions, loss of reward, and interoceptive information differently than non-using individuals. These differences are reflected in behavioral and subjective experiments as well as brain-based experiments which report significant differences in various frontal regions, insula, anterior cingulate cortex, and striatum. Together, the results suggest methamphetamine users have an altered experience of negative outcomes, difficulties employing effective emotion regulation, and difficulty engaging in adaptive or goal-directed decision-making. Suggestions for future research to improve our understanding of how negative reinforcement contributes to methamphetamine addiction and to develop effective interventions are provided.

Keywords: methamphetamine, negative reinforcement, emotion regulation, depression, anxiety, substance use disorder, neuroimaging, treatment

THE ROLE OF NEGATIVE REINFORCEMENT IN METHAMPHETAMINE ADDICTION

Methamphetamine is a commonly abused illicit substance due to its stimulating and euphoriant effects. However, its use is also associated with many consequences at the individual and societal level. For the individual, methamphetamine use can result in significant physical and mental health effects, including but not limited to cardiovascular/cerebrovascular dysfunction and mortality, depression, anxiety, cognitive deficits, psychosis, violence, and suicide (1, 2). In fact, suicide has been estimated to account for 18.2% of all methamphetamine-related deaths (3) and approximately 1/3 of adults addicted to methamphetamine report having attempted suicide one or more times (4). Additional public health concerns include high rates of crime and a significant burden on the health care system due to the deleterious physical effects of methamphetamine. According to the most recent National Survey on Drug Use and Health (5), methamphetamine use in the United States has increased since 2017, with approximately 1 million individuals using in the past month and over 1.8 million using in the past year. Given the severe consequences and increasing prevalence of methamphetamine use, it is important to understand reinforcing mechanisms that maintain and escalate symptoms of methamphetamine use disorder.

Drug use is commonly understood as providing immediate short-term reward. This acute positive effect of the substance (e.g., euphoria and/or high) can be seen behaviorally and within brain regions implicated in reward, including medial orbitofrontal cortex (OFC), rostral anterior cingulate cortex (ACC), and ventral striatum, in frequent users as well as substance-naïve individuals (6). When these positive feeling states outweigh the negative consequences and perpetuate use, drug-seeking behavior is said to be positively reinforced. However, methamphetamine use may also be reinforced by alleviating or removing uncomfortable or aversive states within the body. This principle, known as negative reinforcement, suggests that individuals continue to use drugs, despite negative consequences, because it alleviates uncomfortable states or sensations such as those associated with negative mood states, tension, arousal, craving, or withdrawal. For some individuals, these uncomfortable states and situations develop as a symptom of withdrawal following periods of prolonged use. For others, even initial use can be used as a maladaptive coping mechanism to alleviate aversive states that existed prior to drug use such as depression, anxiety, or reduced responsivity to reward.

A recent conceptualization describes addiction as a three-stage cycle of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation marked by varying dysfunction among motivation, reward, stress, and executive function systems (**Figure 1**) (7–9). The initial state of binge/intoxication is driven by the rewarding effects of drugs, in which an increased incentive salience is attributed to the drug and new drug-seeking habits develop. During the withdrawal/negative affect stage, the individual experiences increases in negative emotional states and an overall increased stress-response. The third stage of preoccupation/anticipation consists of increased drug-craving and deficits in executive functioning. These three stages are hypothesized to feed into one another, increase in intensity over time, and ultimately result in addiction (7). Addiction can therefore be thought of as an evolving process in which initial use is positively reinforced by the rewarding effects. However, with sustained use it becomes negatively reinforced as it relieves negative states including irritability, physical pain, emotional symptoms, such as depression and anxiety, and blunted responsivity to natural rewards [e.g., pleasant social interactions, food, water, monetary gain; Koob, (7)]. Negative reinforcement is therefore hypothesized to play a key role in the development and maintenance of addiction.

This conceptualization of addiction as a three-stage cycle can be demonstrated through findings from animal studies. During sessions of drug self-administration, animals will titrate their intake based on availability; as drug availability increases, animals significantly increase their self-administration of various drugs including methamphetamine, cocaine, nicotine, heroin, and alcohol (10–14). With continued administration, the drug's incentive salience increases and new motivations to seek the drug develop, reflecting the initial binge/intoxication stage of addiction. With increased drug-intake, reward thresholds also increase, resulting in reduced responsivity to natural rewards (9). This increase in reward threshold correlates with amount of drug intake and does not return to baseline after cessation of the drug administration session (15). With protracted abstinence, animals demonstrate symptoms of withdrawal, corresponding to the withdrawal/negative affect stage of addiction. These symptoms include negative emotional states as demonstrated by anxiety-like responses on behavioral tests (16) such as conditioned place aversion, wherein the animal avoids a place previously paired with an aversive state (17). Over time, animals with increased access to drugs of abuse demonstrate working memory impairments, as well as changes in neuronal density and functional connectivity of various frontal regions (e.g., prefrontal cortex, PFC; OFC), thereby contributing to a loss of control resulting in compulsive drug use, and ultimately progressing to a state of addiction (18, 19).

While our understanding of negative reinforcement in addiction has grown in recent years, the extent to which it plays a role in perpetuating addiction in humans is still not well established. Therefore, this review consists of two main aims: (1) to evaluate the evidence for negative reinforcement in methamphetamine addiction; and (2) to examine how treating negative affective symptoms impacts substance use outcomes related to abstinence and well-being, given the need for effective interventions for methamphetamine addiction. Although negative reinforcement is believed to play a role in addiction more generally, the present review focuses solely on methamphetamine given the recent resurgence of use and use-related problems. Data from the Center for Disease Control show that overdose deaths related to methamphetamine use tripled from 2011 to 2016 (20), highlighting the need for effective prevention and intervention options. Additionally, the role of negative reinforcement has commonly been examined within the

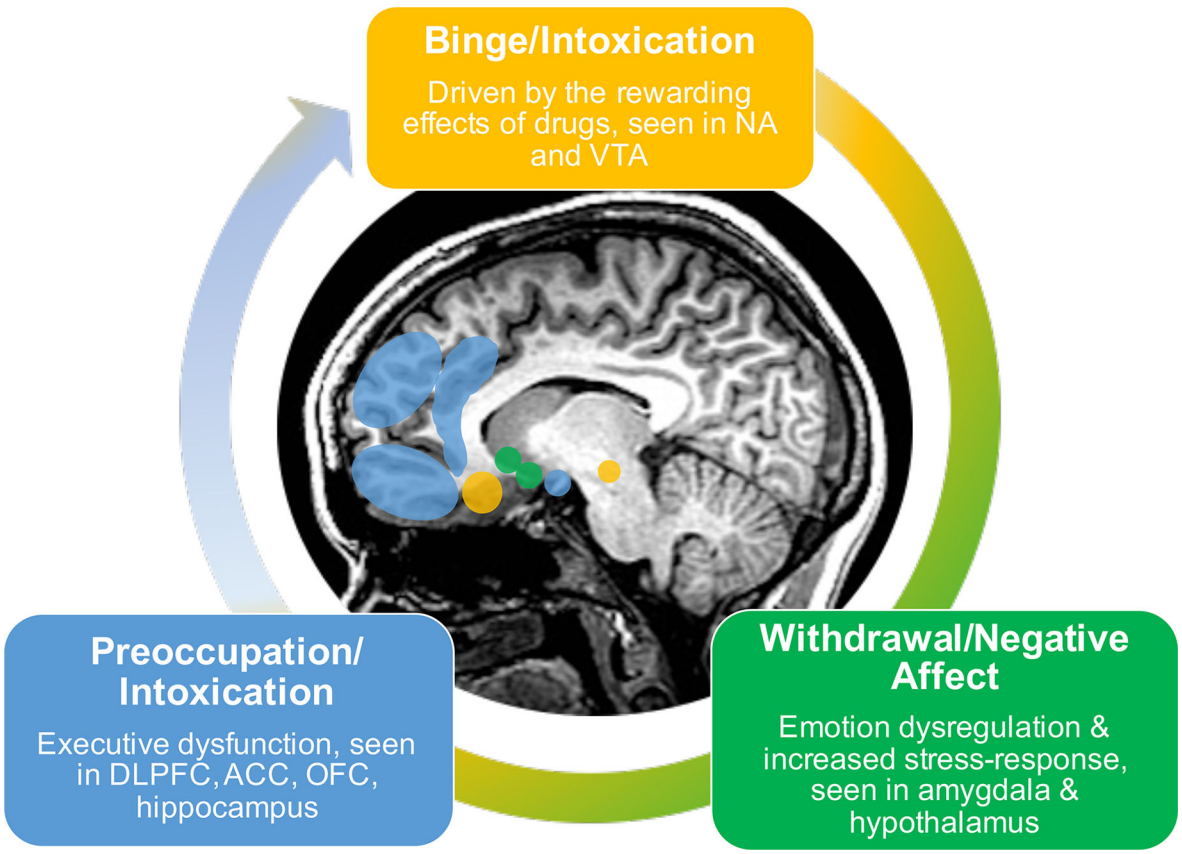

FIGURE 1 | Three-stage model of addiction.

context of other drugs of abuse [e.g., opioids; Koob, (21)] but less work has been done to examine these processes in relation to methamphetamine use. Therefore, while the results reported in this review reflect the role of negative reinforcement in methamphetamine specifically, these findings may be used as a framework for understanding its role in substance use at large.

A literature search was conducted in the PubMed database using the search terms listed in **Table 1**. The same search was then conducted using Google Scholar. Any additional articles identified through Google Scholar were then accessed via PubMed to ensure they met eligibility criteria. To be included, studies were required to examine some component of negative reinforcement among adult methamphetamine users. Samples were required to consist of individuals with either a primary diagnosis of methamphetamine use disorder (MUD) as defined by endorsement of 2+ diagnostic criteria (22), methamphetamine dependence based on endorsement of 3+ diagnostic criteria (23), or methamphetamine abuse (MA) associated with endorsement of 1 symptom (23). Negative reinforcement could be examined within the context of negative emotions/affect, withdrawal, craving, losses, pain, rejection, and/or stress. The article selection process is detailed in **Table 1**.

In the sections below, we review the evidence on the role of negative reinforcement in methamphetamine addiction based on self-report and behavioral data. We then describe functional and structural magnetic resonance imaging (fMRI; sMRI), event-related potential (ERP), and positron emission tomography (PET) studies

TABLE 1 | Search terms and article selection.

	Key words
Drugs	Methamphetamine, amphetamine, stimulant, dependence, use disorder, addiction, craving, withdrawal
Brain	Magnetic resonance imaging, fMRI, MRI, brain stimulation, repetitive, magnetic, event-related potential, positron emission tomography
Negative reinforcement	Depression, anxiety, (negative) affect, loss/es, (negative) emotion, stress, sad, angry, fearful, distress, pain, nociception, rejection
Modality	Human
	Journal articles
# Evaluated	190
# Included	Self-report/behavioral = 21; fMRI = 10; sMRI = 1; ERP = 1; PET = 6; treatment = 25
Reasons for exclusion	Review papers (n = 23); did not examine negative reinforcement variables (n = 67); not MUD focused (n = 25); case study (n = 3); acceptability/feasibility study (n = 4); adolescents (n = 2); rats (n = 2)

fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; ERP, event-related potential; PET, positron emission tomography; MUD, methamphetamine use disorder.

aiming to provide insight into the neural mechanisms related to negative reinforcement in methamphetamine addiction. The details of the studies reviewed in these sections can be found in **Table 2**. Lastly, treatments for MUD that specifically address negative reinforcement mechanisms are evaluated (see **Table 3**), and implications for future interventions and research avenues are discussed.

SUBJECTIVE, BEHAVIORAL, AND PHYSIOLOGICAL EVIDENCE FOR NEGATIVE REINFORCEMENT

Depression and anxiety are two common negative affective states that have been found to have strong associations with MUD. Major Depressive Disorder (MDD) is characterized by depressed mood, anhedonia, sleep, and appetite disturbance, suicidal ideation/intent, extreme guilt, and difficulties in concentration and attention (22). Anxiety disorders are characterized by exaggerated worry and/or panic symptoms that are linked to distress and impairments in social, occupational, or other functioning (22). Initial or maintained use of methamphetamine may be motivated in part by the alleviation of symptoms related to depression or anxiety.

It is unclear whether symptoms associated with negative emotional states characteristic of MDD and anxiety disorders exist prior to methamphetamine use or develop only as a consequence of use. Pre-existing negative emotional states may initially motivate substance use only to be exacerbated by further use, or these emotional states may develop as a symptom of persistent methamphetamine consumption, tolerance, and withdrawal. It has been reported that 39% of methamphetamine patients have a history of anxiety disorders prior to methamphetamine initiation, while 76% of patients report anxiety symptoms after initiating use (2). A dose-dependent response has also been observed, with each additional day of methamphetamine use in the past 6 months corresponding to an increase in anxiety over that time window (74). MDD is also highly prevalent in methamphetamine users; for instance, approximately 40% of a sample of 400 current MUD entering treatment met diagnostic criteria for MDD. An additional 44% met symptom criteria for MDD, although the symptoms users were experiencing were better explained by consequences of psychoactive substance use (75). These findings clearly demonstrate the high prevalence of anxiety and depressive symptoms evident in MUD and demonstrate that these symptoms are often present prior to substance use initiation but can also be a consequence of use. These results are particularly concerning in light of research suggesting that among MUD, ineffective emotion regulation and coping strategies result in negative emotions and stress, which in turn are associated with drug use disorders, increased likelihood of relapse, and extended length of relapse periods (33).

Negative emotional symptoms are also a well-documented manifestation of methamphetamine withdrawal; after 1-7 days of abstinence, 34% of 210 MUD individuals report some symptoms of anxiety disorders ranging from mild to moderate (73). But with continued abstinence from methamphetamine (ranging from 6 days to 1 year), self-reported emotional symptoms of depression and anxiety appear to decrease among a cross-sectional sample of MUD (76). However, in a cohort of incarcerated women, lifetime MUD predicted current and past psychological symptoms, but lifetime psychological diagnoses did not predict lifetime drug use disorder or increased risk of use prior to incarceration (77). Taken together, these findings suggest that while depression and anxiety may predate MUD or remain persistent during abstinence for some individuals, for others these symptoms may be brought about or exacerbated by methamphetamine use and MUD. However, these studies rely solely on cross-sectional samples, and longitudinal studies are needed to determine the exact temporal relation between psychological symptoms and methamphetamine use.

Subjective Evidence

The presence of negative emotional states such as depression and anxiety among MUD is hypothesized to be the manifestation of emotional dysregulation (26). It is thought that, in the absence of effective emotion regulation strategies, individuals with MUD may resume methamphetamine use to cope with life events, stress, or withdrawal and relieve negative affect (78–81). Based on self-report, MUD endorsed lower self-regulation and affective control compared to healthy comparison subjects (CTL) as well as individuals with problematic narcotic use (NA), although detailed characteristics were not provided about the substance using groups (25). Specifically, on a questionnaire developed to measure one's ability to conceptualize and flexibly implement goal-directed behaviors, MUD reported lower levels on the subscales of receiving, triggering, searching, and formulating (4 out of 7 subscales) than both NA and CTL. MUD also reported lower affective control over angry, depressed, anxious, and positive emotions compared to NA and CTL (25). These findings suggest that affective regulation deficits may be unique to methamphetamine or stimulant users.

The role of negative reinforcement in perpetuating methamphetamine use was also explored by Newton and colleagues (24). Seventy-three non-treatment seeking MUD were surveyed to examine their reasons for continued substance use, which were categorized as positive reinforcement, negative reinforcement, or inhibitory control dysfunction (i.e., impulsivity). While questions pertaining to positive reinforcement or "pleasure seeking" (i.e., to experience a high) as an important motivator for continued use were endorsed more frequently, a significant proportion of the sample endorsed questions pertaining to negative reinforcement or "pain avoidance" (i.e., to reduce bad feelings or withdrawal symptoms; (24). Importantly, the majority of the sample endorsing negative reinforcement items perpetuating their drug use did not endorse questions related to positive reinforcement. This suggests that while positive reinforcement is commonly thought to play a larger role in maintaining substance use than negative reinforcement, there may be a unique subsample of substance users whose drug consumption is predominantly maintained by negative reinforcement processes.

TABLE 2 | Subjective, behavioral, physiological, and brain-based findings of negative reinforcement in methamphetamine users.

Author (first author, year)	Meth Group (N)	Comparison Group (N)	Abstinence Duration (Days)	Meth Chronicity [M(SD)]	Comorbid Diagnoses	Gender Examined?	Methods	NR Variables	Results ↑↓
Self-Report findings									
Newton et al. (24)	73 non-treatment seeking, current users	None	N/A	10.6(8.2) yrs	No Axis I psychiatric disorders, no dependence on drugs other than MA or nicotine	No	Self-report questionnaires	Reasons for taking drugs	23% of respondents reported negative reinforcement reasons for substance use
Tayyebi et al. (25)	40	40 narcotics users, 40 CTL	N/R	N/R	N/R	No	Self-report questionnaires	Self-regulation, affective control	MA< narcotics users & CTL: self-regulation and affective control
Behavioral and Physiological Findings									
Chen et al. (26)	60	30	4.85(1.12) months	33.12(24.99) months	N/R	Yes; no sig. diff. found	Startle response measured by skin conductance	Self-report emotional response, startle response, skin conductance	MA: ↑ emotional response to anger-eliciting videos, ↓ emotional response to joy-eliciting videos
Henry et al. (27)	12	12	5.9(1.41) months	3.9(2.16) yrs	N/R	No	Facial affect recognition task	Ability to identify emotions	MA: ↓ facial affect recognition
Kim et al. (28)	28	27	19.46(7.86) days	13.93(7.76) yrs	N/R	No	Facial affect recognition task	Ability to identify emotions	MA: ↓ facial affect recognition
Zhong et al. (29)	54	58	44.85(20.65) days	4.14(3.42) yrs	75.9% of MA reported history of psychiatric symptoms	No	Baseline, 3-and 6-months abstinent	Ability to identify emotions	MA: ↓ social emotional cognition at baseline but improvement after 6-months abstinence
Sex-Specific Findings									
Chen et al. (30)	30 females	30 females	8.68(3.64) months	35.23(22.41) months	N/R	No; females only	Cross-sectional	Startle response & self-reported arousal & valence of emotional music stimuli;	Startle, MA<CTL for fearful stimuli; Self-report arousal: MA<CTL for fearful and happy stimuli; Self-report valence: MA>CTL for fearful stimuli
Hartwell et al. (31)	203	None	1.6(3.6) days	N/R	5.4% current MDD	Yes	One-time self-report assessment	Dep. & Anx. symptoms, craving	Within males only: Positive corr. b/w Dep. symptoms & craving, Positive corr. b/w Anx. symptoms and craving
Maxwell et al. (32)	222	None	N/R	N/R	N/R	Yes	One-time self-report assessment	Motivations for MA use	Female > male: using MA to "not feel depressed"
Mehrjerdi et al. (33)	80	80	N/R	5(6.1) yrs of dependence, years of use not reported	N/R	No; females only	Cross-sectional	Coping strategies	MA<CTL: seeking social support, cognitive evaluation, problem-solving; MA>CTL: emotion control, physical control
Shen et al. (34)	113 females	None	8.7(4.8) months of detoxification	2.0(1.4) years	Dep. & Anx. symptoms	Yes; females only	Self-reports every 3 months for 1-3 yrs while undergoing detoxification program	Mood symptoms, craving	Positive correlation between craving and 5 aspects of negative mood disturbance (fatigue, bewilderment, anxiety, depression, and hostility)
Simpson et al. (35)	124	None	N/R	N/R	Current psychiatric disorder in 53.2% females and 27.4% males	Yes	One-time self-report assessment	Psychiatric symptoms, perceived stress, coping strategies,	Female > male, childhood emotional and sexual trauma, psychiatric and drug problems, poorer treatment outcomes, current psychiatric disorder

(Continued)

TABLE 2 | Continued

Author (first author, year)	Meth Group (N)	Comparison Group (N)	Abstinence Duration (Days)	Meth Chronicity [M(SD)]	Comorbid Diagnoses	Gender Examined?	Methods	NR Variables	Results ↑↓
Brain-Based Findings									
Berman et al. (36)	10	12	T1: 6.7(1.6) days T2: 27.6(.96) days	8.89(4.2) years	Dep. symptoms	No	PET, glucose metabolism	Dep. symptoms	MA>CTL: change in global GM; Within MA: ↑ GM in parietal regions, dep. symptoms neg. corr. w/ parietal GM
Bischoff-Grethe et al. (37)	17	23	173(160) days	N/R	No other substance abuse/dependence besides meth, nicotine, cannabis, alcohol	No	Cross-sectional, fMRI	Monetary loss	Loss anticipation – MA<CTL: VS, posterior caudate; MA only: loss>gains in anterior & posterior caudate
Dean et al. (38)	15	None	7.5(2.6) days	7.80(4.89) years	No Axis I diagnoses other than MA and nicotine dependence	No	RSFMRI within MA only	Dep. & anx. symptoms, ER	Within MA: amygdala-hippocampus RSFC pos. corr. w/ childhood maltreatment, dep., anx., ER & neg. correlated with self-compassion, mindfulness
Kim et al. (39)	19	19	20.5(8.3) days	13.6(7.3) years	None	No; males only	Cross-sectional, fMRI	Empathy task	MA<CTL: OFC, hippocampus, mean % correct answers on empathy task; MA>CTL: DLPFC
Kim et al. (40)	19	19	20.5(8.3) days	13.6(7.3) years	None	No; males only	Cross-sectional, fMRI	Emotion-matching task	MA<CTL: DLPFC, Insula; MA>CTL: fusiform gyrus, hippocampus, parahippocampal gyrus, posterior cingulate cortex
London et al. (41)	17	18	4-7 days	10.1(1.3) years	Dep. symptoms	No	PET, glucose metabolism	Dep. & anx. symptoms	MA>CTL: Dep. & anx. symptoms, GM in OFC, posterior cingulate, amygdala, ventral striatum, cerebellum; MA<CTL: GM in ACC, insula; Within MA only: Dep. symptoms pos. corr. w/ GM in amygdala & anterior cingulate gyrus, State/trait anx. neg. corr. w/ GM in ACC & Insula
Okita et al. (42)	94 (27 PET)	102 (20 PET)	Among PET: 4.0(2.59) days	N/R	N/R	No	PET, dopamine	Emotion Regulation	MA>CTL: DERS total score; Across groups: DERS total score pos. corr. w/ amygdala D2-type receptor availability; MA only: DERS + corr. w/addiction severity
Okita et al. (43)	23	17	≥7.2(3.11) days	10.4(7.33) years	N/R	No	PET, dopamine	Alexithymia	MA>CTL: alexithymia; Within CTL: alexithymia; pos. corr. w/ D2-type receptor availability in ACC, Insula
Payer et al. (44)	25	23	9.91(4.57) days	11.4(7.8)	N/R	No	Cross-sectional, fMRI	Affect processing	MA<CTL: IFG during affect matching, Affect labeling – no group diff.
Payer et al. (45)	12	12	8.6(3.5) days	N/R	N/R	No	Cross-sectional, fMRI	Affect matching task	MA<CTL: VLPFC, fusiform gyrus; MA>CTL: dACC; Contrast: emotion match>shape match

(Continued)

TABLE 2 | Continued

Author (first author, year)	Meth Group (N)	Comparison Group (N)	Abstinence Duration (Days)	Meth Chronicity [M(SD)]	Comorbid Diagnoses	Gender Examined?	Methods	NR Variables	Results ↑↓
Payer et al. (46)	53	47	N/R	11.0(7.7)	None	No	Cross-sectional, fMRI	Emotional faces viewing task	MA<CTL: VLPFC, DLPFC; MA>CTL: self-reported aggression
Sekine et al. (47)	11	9	7 days-1.5 years	1 month-15 years	Anxiety, depression, hallucinations	No, males only	PET, dopamine	Psychiatric symptoms	MA<CTL: DTD in nACC, PFC, caudate; MA only: severity of psych. symptoms pos. corr. w/ duration of use, ↓DTD in caudate/ nACC, neg. corr. w/ duration of MA use
Sekine et al. (48)	11	9	7 days-1.5 years	1 month-15 years	Anxiety, depression, hallucinations	No, males only	PET, dopamine	Psychiatric symptoms	MA<CTL: DTD in OFC, DLPFC, amygdala; Within MA: DTD in OFC, DLPFC neg. corr. w/ duration meth use & severity of psych symptoms
Stewart et al. (49)	20	22	45.47(19.76)	N/R	Comorbid alcohol (n=8), cocaine (n=2), cannabis (n=2), opiate (n=2) use disorders	No	Cross-sectional, fMRI	Loss and aversive interoceptive stimuli	MA>CTL: trait anxiety; MA<CTL; AI, IFG across trials, PI, ACC during aversive stimuli, ACC to punishment/loss & aversive stimuli
Stewart et al. (50)	18 relapsed MA	42 abstinent MA	33.9 ± 20.1 days	Relapsed: 13.3(8.9): Abstinent: 13.7(10.0)	Comorbid alcohol, cocaine, marijuana, nicotine use	No	Cross-sectional fMRI & longitudinal SU data	Loss	Relapsed<Abstinent – across win, loss, tie: insula, striatum, thalamus, posterior cingulate, precuneus; across loss and tie: AI
Uhlmann et al. (51)	21	19 MA-associated psychosis, 19 CTL	Median = 21 days, range 1-240 days	5.6(2.3) years	No other lifetime or current dx of psychiatric disorder	Yes; within MA insula cortical thickness M>F	Cross-sectional, structural MRI	ER self-report	MA>CTL: entorhinal cortex, insula cortical thickness; MA<CTL: overall ER skills
Wei et al. (52)	21	22	9.71(8.19) months	27.14(13.79) months	N/R	No, females only	ERP	Monetary loss	MA>CTL: FRN for loss vs. gain
Yin et al. (53)	26	26	≥ 24 h	Median=2.8 yrs	N/R	No	Cross-sectional, fMRI	Emotional faces vs. MA cue viewing task	MA cue images – MA>CTL: ACC; Emotional faces – MA<CTL: frontal lobe

ACC, anterior cingulate cortex; AI, anterior insula; CTL, control; dACC, dorsal anterior cingulate cortex; DERS, Difficulties in Emotion Regulation Scale; DLPFC, dorsolateral prefrontal cortex; DTD, dopamine transporter density; ER, emotion regulation; FRN, feedback-related negativity; F, female; fMRI, functional magnetic resonance imaging; f/u, follow-up; GM, glucose metabolism; IFG, inferior frontal gyrus; M, male; MA, methamphetamine; MDD, major depressive disorder; nACC, nucleus accumbens; N/R, not reported; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; PI, posterior insula; RSFC, resting state functional connectivity; SU, substance; T1, time 1; T2, time 2; VLPFC, ventral lateral prefrontal cortex; VS, ventral striatum.

TABLE 3 | Treatment studies involving negative reinforcement processes in methamphetamine users.

Author *(first author, year)*	Meth Group *(N)*	Comparison Group *(N)*	Meth Chronicity [*M*(*SD*)]	Comorbid Diagnoses	Gender Examined?	Study Design	Intervention	NR Variables	Results
Psychotherapy Interventions									
Carrico et al. (54)	55 HIV+ MSM randomly assigned to positive affect intervention	55 HIV+ MSM randomly assigned to attention-control	N/R	N/R	N/A	Pre- and post-intervention, 3-month f/u	Positive affect intervention vs. attention control delivered during CM	Negative and positive affect	PA intervention ↑ positive affect, mindfulness, ↓ craving, stimulant use
Glasner-Edwards et al. (55)	526	None	N/R	Depression	No	Longitudinal, 3 yr f/u	16-week Matrix Model: CBT, family edu. groups, support groups, individual sessions	Depression symptoms	Dep. severity ↓ treatment adherence Dep. at f/u ↑MA use outcomes MA abstinence ↓ depressive symptoms Dep. ↑ overall impairment
Glasner-Edwards et al. (4)	526	None	N/R	Anxiety	No	Longitudinal, 3 yr f/u	16-week Matrix Model: CBT, family edu. groups, support groups, individual sessions	Anxiety symptoms	Anx. ↓ treatment adherence, ↑ family, medical, drug, psychiatric problems
Glasner-Edwards et al. (56)	526	None	N/R	34% with current dx of mood, anxiety, or antisocial personality disorders	Yes	Longitudinal, 3 yr f/u	16-week Matrix Model: CBT, family edu groups, support groups, individual sessions	Depression & anxiety symptoms	Anx. ↓ substance use outcomes, ↑ utilization of health services, ↑ psychiatric symptoms 3-years post-treatment
Glasner-Edwards et al. (57)	9 stimulant users assigned to MBRP intervention	13 stimulant users assigned to health education	N/R	N/R	No	Longitudinal, baseline and treatment end	8-week MBRP	Salivary cortisol stress response, subjective stress, anxiety, craving	MBRP ↓ salivary cortisol, subjective stress, anxiety, & craving in response to post-tx stress-test
Hopwood et al. (58)	94 tx completers	21 d/c tx	N/R	21% Dep., 17% phobias, 16% PTSD, 20% Borderline PD, 28% ASPD	No	Longitudinal, 30-180 days	Group therapy focused on functional analysis and relapse prevention + NA/AA techniques	Emotion regulation, negative emotionality	↑ ability to regulate negative emotions ↑ tx persistence -↓ negative emotionality ↑ tx outcomes
Kay-Lambkin et al. (59)	135 MA + comorbid depression	52 MA without depression	N/R	N/A	No	Baseline, 5 weeks, 6 months	Self-help book vs. 2 sessions CBT/MI vs. 4 sessions CBT/MI	Depression symptoms	DEP+>DEP: severity of MA use, change in MA use from baseline to 5 weeks DEP+ only: ↓ dep. at 5 weeks w/ 3-4 sessions
Peck et al. (60)	162 gay and bisexual men	None	8.34(5.9) years	73.2% mild or higher severity depression	N/A	16-week randomized clinical trial, 26- and 52-week f/u	Random assignment to: CBT, CM, CBT +CM, Gay-specific CBT	Depression symptoms	All participants reported ↓ MA use and dep. symptoms up to 1-yr post-tx, MA use in past 5 days predicted Dep. symptoms, Dep. symptoms did not predict MA use
Polcin et al. (61)	111	106	N/R	N/R	No	Baseline, 2-, 4-, 6-month follow-up	9-session Intensive MI vs. 1-session standard MI + 8	Psychiatric problems and	Intensive MI only: psych. prob. ↓ days, ↓ psych. prob. Severity from baseline to 2-month

(Continued)

TABLE 3 | Continued

Author *(first author, year)*	Meth Group *(N)*	Comparison Group *(N)*	Meth Chronicity [*M*(*SD*)]	Comorbid Diagnoses	Gender Examined?	Study Design	Intervention	NR Variables	Results
							nutrition edu. sessions	problem severity	
Polcin et al. (62)	111	106	N/R	N/R	No	Baseline, 2-, 4-, 6-month follow-up	9-session Intensive MI vs. 1-session standard MI + 8 nutrition edu. sessions	Depression symptoms	Across interventions: ↓ psych. prob. severity from BL to 2-month predicted ↓ use prob. severity
Exercise Interventions									
Rawson et al. (63)	69	66	N/R	N/R	No	Pre- and post-intervention	8-week structured exercise program vs. health education sessions	Depression & anxiety symptoms	Exercise intervention: ↓ Dep. & Anx. symptoms overall; Dose effect: ↑exercise sessions ↓ Dep. & Anx. symptoms
Wang et al. (64)	24	N/A	83.92(56.04) months	N/R	No	counterbalanced	Acute exercise session vs. active reading session	Craving	Acute exercise session ↓ craving
Wang et al. (65)	25	25	Exer.: 83.32(53.71) months Att. CTL: 83.92 (58.32)	N/R	No	Baseline, 6-week, post-tx	12-week RCT of aerobic exercise vs. attentional control	Craving	Exercise intervention ↓ craving
Pharmacotherapy Interventions									
Cruickshank et al. (66)	13	18	N/R	Elevated Dep. & Anx. Symptoms but specifics N/R	No	2 week randomized placebo-controlled, double-blind, trial of mirtazapine	Narrative therapy counseling + mirtazapine or placebo	Depression & anxiety symptoms, stress	No sig. group diff. for any symptom measure
Elkashef et al. (67)	79	72	Bupropion: 10.42(7.59) yrs Placebo: 9.97(6.10)	Dep. symptoms on HAM-D Bupropion: 19% Placebo: 21%	Yes	Randomized, placebo-controlled, double-blind trial of bupropion	Bupropion + group CBT vs. placebo + group CBT	Depression symptoms	No group differences in dep. symptoms or craving
Heinzerling et al. (68)	Baclofen: 25, Gabapentin: 26	Placebo: 37	Baclofen: 8.8(7.43) yrs Gabapentin: 10.12(6.28) yrs Placebo: 9.59(5.92) yrs	Dep. symptoms on BDI	No	16-week, randomized, placebo-controlled, double-blind trial of two GABAergic medications: baclofen & gabapentin	Relapse prevention groups + baclofen, gabapentin, or placebo	Depression symptoms	No sig. group diff. in craving, retention, or depression
Shoptaw et al. (69)	Sertraline + CM: 61, Sertraline only: 59	Placebo + CM: 54, Placebo only: 55	Sertraline + CM: 10.1 (6.0) yrs sertraline only: 9.9(6.1) yrs placebo + CM: 8.7(5.4) yrs placebo only: 8.5(4.8) yrs	Depression symptoms on BDI	No	Randomized, placebo-controlled, double-blind trial	12-weeks: sertraline +CM vs. sertraline only vs. placebo +CM vs. placebo only	Depression symptoms, craving	No sig. effects of sertraline; sertraline contraindicated for MA dependence; CM: higher proportion of 3-weeks abstinence
Shoptaw et al. (70)	36	37	Buproprion: 11(9.6) yrs Placebo: 8.3(5.8) yrs	Depression symptoms on BDI	No	12-weeks longitudinal	Buproprion vs. placebo, in addition to CM+CBT	Depression symptoms, craving	No sig. diff. between bupropion and placebo on reducing dep. symptoms or craving
Brain Stimulation Interventions									
Liang et al. (71)	24 rTMS	24 sham rTMS	Real: 6.5(4.4) Sham: 8.5 (4.2) days	Real: 4.6(3.0) Sham: 5.6(3.3) yrs	No, males only	10-sessions randomized, double-blind, controlled trial	10 Hz rTMS to left DLPFC	Depression & anxiety symptoms	Real rTMS: ↓ Dep. & Anx. symptoms, craving; Both groups: ↓ withdrawal symptoms → ↓ craving and ↓ anx. but not dep.

(Continued)

TABLE 3 | Continued

Author *(first author, year)*	Meth Group *(N)*	Comparison Group *(N)*	Meth Chronicity *[M(SD)]*	Comorbid Diagnoses	Gender Examined?	Study Design	Intervention	NR Variables	Results
Lin et al. (72)	40 rTMS	40 sham rTMS, 25 waitlist/no treatment	Real: 197.10(16.87); Sham: 189.23(14.31); Wait-list: 190.08(15.17) days	Real: 8.30(.81); Sham: 7.15(.73); Wait-list: 8.92 (1.22) yrs	No, males only	5 sessions/week for 6-weeks, randomized, double-blind, controlled trial	10 Hz rTMS to left DLPFC	Depression & anxiety symptoms	Real rTMS: ↓ dep. & anx. symptoms; Sham & CTL: ↑ dep. symptoms
Su et al. (73)	15 rTMS	15 sham rTMS	Real: 3.00(1.56); Sham: 2.80(1.70) months	Real: 40.33 (32.04); Sham: 60.80(41.40) months	No, males only	5-session, randomized, double-blind, controlled trial	10 Hz rTMS to left DLPFC	Depression & anxiety symptoms	Real TMS: ↓ craving; Both groups: ↓ dep. symptoms, no change in anx. symptoms

ASPD, antisocial personality disorder; BDI, Beck depression inventory; CBT, cognitive behavior therapy; CM, contingency management; DLPFC, dorsolateral prefrontal cortex; f/u, follow-up; HIV, human immunodeficiency virus; MA, methamphetamine; MBRP, mindfulness-based relapse prevention; MI, Motivational interviewing; MSM, men who have sex with men; N/R, Not reported; PA, positive affect; PD, personality disorder; PTSD, posttraumatic stress disorder; rTMS, repetitive transcranial magnetic stimulation.

Behavioral and Physiological Evidence

Using behavioral measures, Chen and colleagues (26) examined the emotional response of 60 MUD, currently receiving treatment (abstinent 4.85 ± 1.12 months), and 30 CTL while viewing videos selected to elicit fear, anger, amusement, and joy. Self-reported emotional ratings were collected in conjunction with objective physiological measures of startle response and skin conductance. Skin conductance levels have been shown to reflect the arousal level of a stimulus, with an increase reflecting stress and excitement and a decrease reflecting relaxation (82). Startle response provides a measure of emotional valence, whereby negative emotional experiences exacerbate the startle response and positive emotional experiences reduce it (83). Overall, MUD compared to CTL reported lower levels of subjective arousal in response to fear videos but demonstrated higher levels of physiological arousal (startle response and skin conductance) to anger videos when compared to neutral videos (26). MUD also showed a greater level of skin conductance and lower level of startle response than CTL while viewing joy versus neutral videos. The higher objective response to anger videos demonstrated by MUD may be reflective of an increased negative emotional state and overall increased stress-response. The self-reported lower arousal levels in response to fearful stimuli among MUD may reflect an inability to accurately recognize and regulate withdrawal-related negative emotions, resulting in real-life difficulties in avoiding such stimuli and the continuation of drug-seeking behavior. MUD also differed from CTL in their physiological response to joyful videos. The increased level of skin conductance to joyful videos suggest that MUD find joyful stimuli more arousing than CTL, while the dampened startle response to joyful stimuli in MUD compared to CTL suggests that their evaluation of positive emotional stimuli is blunted. This finding is contrary to expectations, given that MUD is conceptualized as involving a blunted response to non-drug related positive stimuli. However, this may reflect a cognitive bias towards negative stimuli within MUD wherein positive stimuli evoked a greater response from MUD than CTL on a measure of arousal, but the reduced startle response among MUD compared to CTL may suggest an inability to assess the positive value of natural rewards. Again, the cross-sectional nature of this study limits the conclusions that can be drawn about the temporal relationship between substance use and emotion dysregulation; however, the results clearly demonstrate altered emotional processing in MUD relative to CTL.

Deficits in emotional processing are also thought to relate to impaired social cognition among MUD. A facial affect recognition task has been used to demonstrate this deficit in MUD abstinent for an average of 6 months (27) as well as MA/MUD abstinent an average of 20 days (28). In both of these studies, individuals who used methamphetamine demonstrated a decreased ability to correctly match faces based on the expressed emotion. Similar results were found among MUD in relation to social emotional cognition and problem solving; at enrollment, MUD (abstinent from MA < 3 months) performed worse than CTL on a task requiring individuals to identify different facial

expressions, as well as on a maze learning task assessing problem-solving skills (29). However, this same study reported that, at re-test 6 months later, MUD demonstrated improved social emotional cognition and problem solving compared to CTL using the same tasks. These results suggest that methamphetamine users may experience difficulties and be uncomfortable in social interactions because they cannot accurately read and respond to a speaker's emotional state (27, 28) and lack the skills needed to resolve these issues (29). These social deficits may be a risk factor for additional use, as methamphetamine can acutely lessen social anxiety and irritability (28, 32). However, continued abuse may cause interpersonal problems due to misunderstandings, resulting in stress and negative mood states (84). This then leads individuals to use methamphetamine again to alleviate this discomfort, ultimately resulting in a negatively reinforcing cycle of use and uncomfortable sensations.

Sex-Specific Findings

A number of studies have specifically focused on examining methamphetamine use among females, providing evidence for gender-based differences. Such studies have shown strong relationships between negative emotions and drug craving among female users, as well as deficits in coping. Among 113 female methamphetamine users participating in a compulsory detoxification program (average detoxification duration of 8.7 ± 4.8 months), craving level positively correlated with negative mood disturbances including fatigue, bewilderment, anxiety, depression, and hostility after controlling for each user's weekly dose of methamphetamine (34). Alternatively, among a sample of 203 non-treatment seeking methamphetamine users, the opposite pattern was observed, wherein depression and anxiety symptoms positively correlated with methamphetamine craving among men, but not women (31). This difference in findings may be related to use status at the time data were collected, given that two studies reported on abstinent users (34, 73) and one examined current users (31).

Gender differences have also been observed among self-reported reasons for use. Maxwell and colleagues (32) conducted a large survey with 222 methamphetamine users to better understand motivations for drug consumption. According to this survey, in addition to accomplishing tasks and losing weight, women also reported using methamphetamine to feel less depressed, suggesting they may have difficulty regulating their emotions in other ways even prior to initiation of methamphetamine use. This potential deficit in emotion regulation was examined behaviorally among 30 females with MUD (abstinent an average of 8.68 ± 3.64 months) and 30 CTL females using musical stimuli (30). In comparison to CTL, female MUD reported lower arousal ratings and showed an inhibited startle response to fearful music. Female MUD also reported lower arousal than CTL in response to happy music. These findings demonstrate that, within a sample of female patients, MUD have an altered perception of emotional stimuli regardless of valence relative to CTL. Additionally, female methamphetamine users endorse higher emotional and sexual childhood trauma than male users (35), and it has been hypothesized that women may use substances as a method of coping with these past traumas. In line with this hypothesis, women with MUD reported higher-levels of emotion-focused coping, including substance use, than both women CTL (33) and men with MUD (35), while men and women with MUD report comparable low levels of problem-focused coping (35). However, neither of these studies reported important use characteristics (i.e., chronicity of use, duration of abstinence) that may influence one's ability to cope. Despite this limitation, these findings strengthen the hypothesis that MUD may administer methamphetamine as a form of self-medication to relieve uncomfortable mood and body-relevant sensations, thereby negatively reinforcing methamphetamine use; this relationship may be stronger in female than male patients. Therefore, female methamphetamine users may be more prone than male users to turn to substance use to cope with uncomfortable emotional distress.

Conclusions

The literature demonstrates that emotional processing is dysfunctional among MUD and supports the hypothesis that methamphetamine use is not only reinforced by its rewarding euphoric effects but also by its relief of negative and uncomfortable effects. Specifically, methamphetamine use appears to relieve symptoms of anxiety and depression that may or may not be pre-existing. These psychiatric symptoms are often worsened when individuals try to reduce or abstain from use, leading individuals to crave methamphetamine to alleviate these uncomfortable feelings. MUD is also associated with deficits in emotional processing. These deficits relate to the processing of positive and negative stimuli and methamphetamine use may help to reduce the exaggerated response to negative stimuli and alter the lack of response to natural rewards. Overall, the data support the conclusion that negative reinforcement, not just positive reinforcement, is an important factor in the perpetuation of substance use and suggests that learning to use healthy coping skills to address these symptoms in lieu of substance use may improve treatment outcomes. However, the extent to which negative reinforcement contributes MUD over positive reinforcement remains unclear.

BRAIN-BASED EVIDENCE FOR NEGATIVE REINFORCEMENT MECHANISMS

The three-stage model of addiction coincides with dysfunction in brain systems implicated in reward, stress, and executive function (9). The initial stage of binge/intoxication is driven by the acute reinforcing effects of stimulant use, which activate and alter dopamine transmission in brain regions associated with reward including the ventral tegmental area and nucleus accumbens (7). With prolonged use, these changes in neurocircuitry are thought to interact and alter other brain networks implicated in executive functioning (frontal regions), emotion regulation and stress responsivity (amygdala and hypothalamus), and interoception (insula and ACC). Prolonged use also results in the attribution of incentive salience to previously neutral cues that have become paired with drug use, and a conditioned response to continue seeking drugs of abuse. This neural change involves striatal regions and ultimately

effects synaptic changes in glutamate transmission within PFC and amygdala (9). This in turn results in reduced executive functioning and increased drug-seeking behavior.

The binge/intoxication stage is followed by a stage of withdrawal/negative affect characterized by irritability, emotional discomfort, stress, and alexithymia (9). With prolonged exposure, the rewarding effects of the drug decrease as reflected by hypoactivation within reward regions (e.g., ventral striatum) and over-active stress-systems reflected by amygdala hyperactivation (8). This evolves into the third stage of preoccupation/anticipation, a key contributor to relapse. Altered functioning within frontal regions results in executive dysfunction when presented with a salient cue signaling substance use. Such cue-induced craving has been observed to activate regions including dorsolateral PFC (DLPFC), ACC, OFC, and hippocampus. These deficits in executive function impact decision making, self-regulation, and inhibitory control, resulting in an inability to inhibit maladaptive behaviors and continued drug-seeking behaviors despite negative consequences.

Overall, the three-stage model of addiction describes a cycle wherein initial positive reinforcement of substance use evolves to include negative reinforcement as the rewarding effects of the drug decrease and uncomfortable emotional and stress responses emerge. The decreases in prefrontal executive function may exacerbate these effects by reducing one's ability to control responses to negative reinforcement mechanisms. This cycle is reflected by alterations in brain functioning within regions involved in reward (striatum), regulation of emotions and stress (amygdala and hypothalamus), interoception (insula and ACC), and executive functioning [various frontocingulate regions; Koob (7), Koob and Volkow (9), Volkow et al. (8)] . By examining the existing brain-based literature on negative reinforcement, the goal is to determine the state of the evidence supporting the three-stage model of addiction and to highlight regions that can possibly be targeted by intervention to improve substance use outcomes. Details of the studies outlined below can be found in **Table 2**.

Task-based fMRI

Given the relationship between substance use and emotional processing deficits, fMRI studies focused on the experience and processing of emotion in MUD allow for the examination of negative reinforcement mechanisms. Such paradigms include facial affect tasks, which require individuals to match, label, or view emotional stimuli. Other tasks involve performance errors, loss of reward, or perturbations in interoception, defined as the sensing and processing of information signaling the internal state of the body (85). These types of tasks elicit negative and uncomfortable states and sensations and allow for the comparison of CTL and MUD during these experiences in order to draw conclusions about negative reinforcement. Additionally, these types of paradigms have been demonstrated to activate brain regions thought to be implicated in the three-stage model of addiction (7, 9).

Emotion processing among abstinent MUD has been evaluated using an empathy task (39) and emotion matching tasks (40, 43, 44). In response to viewing scenarios designed to evoke an empathetic response, CTL showed greater activation than MUD (abstinent 20.5 ± 8.3 days) in OFC and hippocampus (39), in line with previous findings of abnormal brain functioning among methamphetamine users within OFC, a region associated with social cognition (86, 87). However, MUD showed greater activation than CTL in DLPFC to these empathic scenarios (39), a region previously shown to be underactive in MUD during a two-choice response task involving varying levels of error feedback (87). Coupled with the lower mean percentage of correct answers on the empathy task among MA compared to CTL, this increased DLPFC activity in MA may be reflective of greater cognitive effort in light of inefficient processing of empathy.

Contradictory findings have been found using paradigms requiring individuals to match facial expressions varying on positive and negative valence. While performing an emotion matching task utilizing fearful and threatening images, MUD (abstinent 20.5 ± 8.3 days) demonstrated reduced activation in DLPFC and insula, as well as increased activation in fusiform gyrus (facial processing) and hippocampus relative to CTL (40). Alternatively, using a similar emotion matching task, MUD (abstinent 8.6 ± 3.5 days) showed reduced activation in the inferior frontal gyrus [IFG; Payer et al. (44)] and ventrolateral prefrontal cortex (VLPFC), regions implicated in affect processing, as well as fusiform gyrus (45). Compared to CTL, MUD also demonstrated greater activation in dorsal ACC, a region implicated in social distress, which was associated with increased hostility and interpersonal sensitivity amongst MUD (45). This finding may suggest that individuals with MUD are more susceptible to socially threatening cues. An attenuated response in VLPFC/DLPFC and other frontal regions in MUD compared to CTL has also been observed as a result of simply viewing emotional images [Payer et al., (46), Yin et al., (53)]; however, one of these studies did not report duration of abstinence (46), while the other only required a minimum of 24 h abstinent for inclusion and did not report specific abstinence/illness duration details [Yin et al. (53)], weakening the strength of the conclusions that can be drawn from these results.

These studies all demonstrate altered functioning in various frontal regions (DLPFC, VLPFC, OFC) and hippocampus in MUD compared to CTL, however, the activity patterns are in varying directions. These contradictory findings may be related to the type of emotional task used, as one requires individuals to identify empathetic responses while the other may elicit fear. In relation to negative reinforcement, these findings do suggest that MUD have disrupted processing of socio-emotional information, a pattern which could potentially contribute to their experience of negative mood states and inability to engage in adaptive behaviors. Future research that ties brain activation patterns to real-life function (i.e., neuropsychological functioning, theory of mind tasks, or other performance measures) would be helpful to provide insight into the exact functional role of various brain regions.

Tasks involving loss can also be used to examine negative reinforcement processes among methamphetamine users. Differential response to loss in MUD compared to CTL could

suggest that methamphetamine users experience aversive outcomes differently, which could contribute to relapse. For instance, a stronger (more exaggerated) brain and/or behavioral response to loss among methamphetamine users may negatively reinforce the decision to continue to use stimulants in order to relieve uncomfortable sensations associated with this loss. Bischoff-Grethe and colleagues (37) demonstrated this relationship using a probabilistic feedback expectancy task that allowed for the examination of anticipation and receipt of monetary gains and losses. MUD (abstinent 173 ± 160 days) showed lower ventral striatum signal than CTL when anticipating loss but greater signal in the caudate in response to the experience of loss compared to reward, while CTL did not show a differential response based on outcome (37). Ventral striatum is implicated in anticipating potential reward and loss (88, 89) and the caudate is involved in goal-oriented behavior as it receives projections from the frontal cortex (90). Together, this blunted response to the anticipation and experience of loss in MUD may contribute to the poor decision-making that is characteristic of this population, and continued drug-use despite negative consequences (37).

Loss has also been shown to elicit reduced activation in regions implicated in processing reward and interoceptive signals among a sample of relapsed MUD. Sixty MUD (abstinent 33.9 ± 20.1 days) enrolled in a treatment program completed a rock-paper-scissors task during a baseline fMRI session (50). One year later, MUD were categorized as abstinent (n = 42) or relapsed (n = 18). Examination of the baseline fMRI data revealed that those who relapsed over the follow-up period, compared to those who remained abstinent, had initially exhibited decreased activation in insula and striatum across winning, tying, and losing outcomes. Relapsed MUD also showed significantly lower anterior insula activation specifically to ties and losses than abstinent MUD. These findings suggest that altered activity in brain regions known to be dysfunctional in MUD may be able to be examined prospectively as a potential marker of poor treatment outcomes, such as relapse. These findings are somewhat contradictory to previously reported findings as the altered brain functioning was found across all outcomes (i.e., win, loss, tie). Regardless, these results suggest there may be underlying differences in the neural processing of situational outcomes that put an individual at greater risk for continued substance use problems.

This altered response to loss has also been demonstrated among MUD while simultaneously experiencing an aversive interoceptive manipulation. Interoceptive processing is the ability to sense the internal state of the body and engage in goal-directed behaviors to maintain equilibrium (91). Researchers have suggested that this interoceptive system is altered in addiction, resulting in a bodily prediction error, whereby a discrepancy between one's predicted internal state and the actual internal state experienced may result in an increased propensity towards substance use in an attempt to regain balance of the internal state (49, 92). Among CTL, ACC is implicated in this process of registering and initiating motivated actions to restore balance, while cognitive control frontal regions, including IFG, contribute to decision-making processes. However, in MUD ACC and IFG have been shown to be underrecruited, likely resulting in an inaccurate representation and limited adaptive behaviors to address potential prediction errors. Using a two-choice prediction task with fixed error rates, Stewart and colleagues (49) demonstrated that the experience of loss paired with an aversive interoceptive manipulation (anticipation and experience of loaded breathing) elicited greater ACC response in CTL than MUD (abstinent 45.47 ± 19.76 days), suggesting MUD may be underrecruiting this brain region to help manage this uncomfortable experience and adjust behavior accordingly (49). In comparison to CTL, MUD also exhibited reduced anterior insula and IFG activity across all trials and reduced posterior insula and ACC during breathing load trials regardless of outcome. Anterior and posterior insula differ functionally; posterior insula receives input about the physiological state of the body from other brain regions, such as the thalamus, and then passes this information on to the anterior insula to be further integrated with additional information and motivate the initiation of goal-oriented behaviors to regain homeostasis. Together, these results suggest that MUD have an altered response to unpleasant outcomes and physical stimuli compared to CTL and that they may lack the executive functioning resources needed to engage in goal-directed behaviors to help regulate the effect of unpleasant outcomes. Therefore, drug use may be negatively reinforced because of its ability to alleviate discomfort associated with unpleasant outcomes in the face of limited resources which hinder one's ability to engage in alternative healthy forms of coping.

Overall, the fMRI literature reveals altered neural function in brain regions associated with emotion-processing, loss of reward, and interoception, including frontal regions, insula, ACC, and striatum. Interestingly, there is a lack of fMRI findings linking amygdala impairments to MUD/MA. Given amygdala's role in emotion processing, it would be expected to play a crucial role in negative reinforcement processes. However, no identified study reported functional deficits in this region despite the use of emotion-matching tasks. Future research using tasks that elicit stress or fear responses, may help elucidate amygdala's role in perpetuating methamphetamine use. While the direction of current findings is somewhat mixed between studies, interventions that aim to modify activity in the identified regions, and the behaviors associated with those regions, may hold promise for improving substance use outcomes.

Resting-State fMRI

Differences between MUD and CTL have also been found using resting state fMRI. While task-based fMRI examines changes in blood flow within specific brain regions while an individual completes a task, resting state functional connectivity (RSFC) examines the temporal dependence of neuronal activity patterns between brain regions while at rest (93). In other words, while undergoing a resting state scan, individuals are not performing a task but instead are typically asked to relax and not think of anything in particular. Analyses then indicate the amount of correlation between activation within various regions to yield a measure of functional connectivity, suggesting the degree of communication and information processing between these

regions. Within MUD, RSFC has revealed altered functional patterns compared to CTL. For instance, RSFC between amygdala and hippocampus was found to positively correlate with self-reported depression, trait anxiety, and emotion dysregulation within 15 abstinent (7.5 ± 2.6 days) MUD enrolled in a pilot study (38). Amygdala-hippocampus RSFC was also positively associated with self-reported childhood maltreatment. Together, results may indicate that traumatic experiences in childhood contribute to differences in brain functioning that are in turn associated with negative emotional states and dysfunctional emotional processing in adulthood. Longitudinal research is needed to test the hypothesis that childhood maltreatment as well as other negative or traumatic childhood experiences may foster the development of MUD as a form of emotion-regulation. Negative reinforcement may play a critical role in the development and maintenance of MUD among individuals who may be experiencing negative emotionality prior to substance use initiation as well as those who experience it as a consequence of use.

Structural MRI

Structural brain differences among MUD have also been examined in relation to emotion processing. Cortical thickness was examined in relation to affect regulation abilities among 21 MUD abstinent for 1-240 days (median = 21 days) and 19 CTL, as well as 19 patients with methamphetamine-associated psychosis (51). When comparing MUD and CTL only, MUD were found to have higher cerebral thickness than CTL within insula and entorhinal cortex, a region involved in translating exteroceptive information. Self-report data on emotion regulation capabilities were also gathered using the *Emotion Reactivity Scale* (ERS) and *Difficulties in Emotion Regulation Scale* (DERS). These data revealed that MUD, relative to CTL, reported significantly greater difficulties with emotion regulation based on the ERS total scale and all subscales (d = 0.77-0.87), as well as difficulties with understanding emotions (d = 0.70) and impulse control (d = 0.81) on the DERS scale. However, none of the self-reported differences in emotion regulation reported by MUD correlated with the observed differences in cortical thickness (51). These findings demonstrate the presence of emotional dysregulation in MUD but do not suggest a link with brain structural abnormalities, thereby limiting the conclusions that can be drawn regarding the role of greater insula cortical thickness in methamphetamine addiction.

Conclusions for MRI Findings

Brain regions that are repeatedly represented in the literature on MUD include various frontal regions (VLPFC, DMPFC, IFG, OFC), insula, hippocampus, and ACC (see **Table 2**). Taken together, differing patterns of brain activation in these regions compared to CTL suggest an altered experience of negative outcomes and an inability to regulate or respond in effective ways. Specifically, fMRI data demonstrates that MUD experience negative outcomes more intensely as reflected by an exaggerated response compared to CTL in reward-relevant brain regions [caudate; Bischoff-Grethe et al. (37)] and that they are unable to activate regions (ACC) necessary for regulating their response to negative outcomes (49). MUD show deficits in various frontal regions which are implicated in the ability to recognize and comprehend emotionally salient information and to produce mental representations regarding the internal states of others, suggesting that MUD lack emotional insight (44). Deficits in frontal regions may also contribute to one's ability to integrate socio-emotional information and in turn regulate behavioral responses by inhibiting behaviors that are no longer useful [Payer et al. (44), Yin et al. (53)]. Hippocampus and ACC also play a crucial role in one's ability to incorporate information and regulate a response. ACC monitors conflict and is overactive in MUD compared to CTL while viewing images of substance [Yin et al. (53)] and socially threatening situations (45). Taken together, these findings suggest that MUD are hyper-sensitive to these types of cues, which may stem from an inability to respond appropriately given altered hippocampal functioning which aids in the ability to incorporate previous experience and update response patterns accordingly (39, 40).

General findings on structural differences in MUD have been mixed, reporting both higher and lower cortical thickness in MUD than CTL (51). In relation to negative reinforcement, structural differences within insula and entorhinal cortex did not correlate with any measure of emotional regulation. Alternatively, results from a pilot study utilizing RSFC show more promise for identifying potential treatment targets to decrease psychological difficulties. Connectivity between amygdala and hippocampus appears to correlate with depression, anxiety, and emotion dysregulation, symptoms commonly reported among MUD (38). This suggests that amygdala-hippocampus connectivity may contribute to emotional regulation, and interventions that aim to strengthen the connection between these regions may be effective at breaking the cycle between experiencing negative affect and using methamphetamine to alleviate those symptoms.

A few limitations must be considered when interpreting data from MRI studies. First, the studies reported here predominantly consist of sample sizes with less than 25 per group (MUD vs. CTL), with the exception of three over 30 (44, 46, 50). Additionally, these studies were cross-sectional in nature and do not allow for the examination of the temporal relationship between brain functioning and methamphetamine use. Similarly, there is wide variation between and within studies with regards to duration of methamphetamine use and abstinence (see **Table 2** for abstinence/chronicity details). Reported abstinence ranged from 24 h [Yin et al. (53)] to 330 days (37) across studies, with one study reporting a range of 1-240 days (51). Duration of use was also quite varied, ranging from 3.3 to 20.9 years (see **Table 2**). Duration of abstinence and regular use are important variables in the substance use literature as they can have profound effects on the deficits observed. Without some consistency in these variables, at least within study, it is difficult to draw strong conclusions about the role of negative reinforcement in MUD. Further, only one of the studies presented here examines whether the observed deficits predict relapse or other treatment-related outcomes (50). Lastly, studies eliciting an emotional response were conducted within an experimental setting, suggesting the MUD could possibly respond differently in real-life personal

situations. Overall, fMRI studies support the conclusion that MUD have an altered experience of emotional stimuli relative to CTL based on self-report and behavioral data. This deficit may make it difficult for MUD to understand their own bodily sensations and emotional responses as well as those of others. This may result in increased negative mood and stress, and ultimately reinforce the decision to use methamphetamine given its attenuation of these symptoms.

Event-Related Potentials

Analysis of EEG data in the time domain yields an event related potential (ERP), a time-locked, electrophysiological response of the brain to a stimulus (94, 95). There are various ERP components, each with a unique electrophysiological profile and originating brain region. The feedback-related negativity (FRN) component is thought to originate within ACC and is described as a negative deflection in response to feedback onset. The reinforcement learning-error related negativity theory posits that the FRN is a reflection of a discrepancy between current outcomes and the expected result; in other words, this component peaks when outcomes are contrary to expectations. Compared to CTL (n = 22), individuals with MUD (n = 21; abstinent 9.7 ± 8.19 months) demonstrated an enhanced FRN in response to monetary loss versus gain during a gambling task (52), suggesting MUD have a stronger response to unanticipated loss. This was the only ERP study identified that examined negative reinforcement principles among MUD, and the results are difficult to reconcile with the previously discussed fMRI findings. Stewart and colleagues (49), showed MUD compared to CTL to have a reduced ACC response to punishment paired with an aversive interoceptive stimulus, while Bischoff-Grethe and colleagues (37) reported an exaggerated response within caudate to loss versus reward. These findings all suggest that MUD respond to loss/punishment differently than CTL but our understanding of exactly how they differ remains unclear. In relation to negative reinforcement, one factor that may contribute to these altered brain response patterns is depressive symptoms. Depressive symptoms were not reported in relation to ERP results (52) but MUD reported significantly greater depressive symptoms than CTL in the fMRI studies (37, 49). Future research, utilizing ERP and fMRI, should examine whether depressive symptoms contribute to an exaggerated response to loss/punishment among MUD. Overall, this altered response to negative outcomes and inability to modify behaviors accordingly may contribute to relapse.

Positron Emission Tomography

As described above, the initial binge/intoxication stage of addiction alters neurotransmission in brain regions implicated in executive functioning (frontal regions), emotion regulation and stress responsivity (amygdala and hypothalamus), and interoception (insula and ACC). Dopamine plays a central role in the development and maintenance of substance use disorders. Even with initial use, methamphetamine alters neurotransmission of dopamine in reward areas [i.e., nucleus accumbens; Koob (7)], and with sustained use, these alterations can extend to regions of executive functioning (i.e., PFC) and emotion regulation (i.e., amygdala). PET allows for the examination of neurotransmission and has been employed in conjunction with measurement of emotional and psychiatric functioning within MUD.

Using PET techniques, widespread dopaminergic dysfunction has been demonstrated during periods of substance use and abstinence. Specifically, during early abstinence (4 ± 2.59 days), greater difficulties with emotion regulation reported by MUD than CTL was found to positively correlate with D2-type dopamine receptor availability within amygdala (42). This finding is in line with previous evidence suggesting that D2-type receptors in amygdala are thought to contribute to enhanced neural activity associated with a negative emotional state (96). Emotional dysregulation also positively correlated with severity of drug use as measured by the *Addiction Severity Index*, highlighting the role of negative affect in MUD. MUD (abstinent ≥7.2 ± 3.11 days) also reported greater alexithymia than CTL, but this did not relate to dopamine transmission in MUD. Instead, self-reported alexithymia positively correlated with higher D2-type receptor availability in ACC and insula, regions implicated in emotion processing and awareness of internal states, within CTL only (43). Taken together, these findings may indicate that altered dopamine transmission is associated with MUD's difficulties regulating emotions but does not contribute to other difficulties observed in MUD.

MUD also showed reduced dopamine transmission within brain regions implicated in reward (i.e., nACC, caudate) and cognitive control (i.e., PFC, OFC, DLPFC). Specifically, among MUD (abstinent 7 days to 1.5 years), dopamine transporter binding potential in caudate and nACC negatively correlated with duration of methamphetamine use and overall psychiatric difficulties as measured by the *Brief Psychiatric Rating Scale* (47). Further, reduced dopamine transporter density in OFC and DLPFC negatively correlated with duration of methamphetamine use as well as severity of psychiatric symptoms (48). Although the results regarding regions of reward and cognitive control appear consistent, they were found within the same, relatively small, sample of 11 MUD and 9 CTL (47, 48). The conclusions that can be drawn regarding these findings are severely limited by the characteristics of the sample. MUD ranged in duration of use from 1 month to 15 years and duration of abstinence from 7 days to 1.5 years (see **Table 2**). Given that cessation of methamphetamine use is known to result in acute withdrawal during the first 24 h and subacute withdrawal for the first two weeks, the participants in this study were in varying stages of recovery. Similarly, 2 of the 11 MUD patients reported using methamphetamine for 6 months or less; it is highly likely that these individuals differ in important ways from the individuals reporting 12-15 years of regular use.

PET also allows for the examination of glucose metabolism, which is necessary for the process of neurotransmission (97). Given the importance of the first week of abstinence, two studies have employed PET to examine glucose metabolism in relation to psychiatric symptoms among MUD during this crucial time period. Both of these studies found altered glucose metabolism in MUD within reward, executive function, and emotion-processing regions. Importantly, these changes were found to correlate with self-reported mood symptoms, wherein depressive symptoms positively correlated with glucose metabolism within

amygdala and ACC (41) but negatively correlated with glucose metabolism within left parietal lobe, a region which has previously been shown to have functional abnormalities among MUD (36). Anxiety on the other hand, was found to negatively correlate with glucose metabolism within insula and ACC (41). These findings highlight the altered brain function present among MUD in regions of emotion regulation and how this dysfunction correlates with the actual experience of altered mood. Emotion regulation interventions may help prevent newly abstinent individuals from relapsing and thereby negatively reinforcing their use by alleviating the uncomfortable sensations associated with emotional dysregulation and heightened negative affect.

Overall, the findings from PET studies point towards the importance of targeting emotion regulation skills during early abstinence. In line with negative reinforcement principles, the first week of abstinence is an important determinant of treatment engagement, retention, and outcomes, as MUD patients typically experience physical discomfort, depression, anxiety, and craving, often resulting in relapse as an attempt to reduce these uncomfortable sensations (36). Alterations in dopaminergic transmission and glucose metabolism in MUD appear to contribute to the presence and severity of symptoms related to emotional dysfunction, substance use, and psychiatric distress. These studies lend further evidence to suggest that altering amygdala activity or enhancing emotion regulation strategies may improve MUD treatment outcomes.

IMPLICATIONS FOR THE TREATMENT OF METHAMPHETAMINE ADDICTION

Various treatments for problematic methamphetamine use exist, with varying effects on treatment outcomes of interest, including reductions in amount or frequency of substance use, duration of abstinence post-treatment, and alleviation of psychological symptomology (98). Based on the evidence outlined above, the experience of negative or uncomfortable sensations and emotions often contributes to methamphetamine use and maintenance; leaving these symptoms untreated may place individuals at greater risk for relapse (98). Therefore, interventions aimed at alleviating these symptoms may improve treatment retention and outcomes and prevent relapse (see **Table 3** for further details of studies outlined below).

Psychotherapy Interventions

The primary psychotherapy interventions that have been examined for MUD patients include cognitive behavioral therapy (CBT), contingency management (CM), motivational interviewing (MI), and mindfulness-based relapse prevention [MBRP; Lee and Rawson, (98)]. Treatment can be provided on an outpatient basis or through a more intensive inpatient program. Programs vary in terms of duration, number of sessions, and required activities. Regardless, overall treatment outcome is typically measured in terms of abstinence rather than improvement of psychological symptoms, emotion regulation, or coping strategies. However, the role of these psychological and emotional factors in reinforcing methamphetamine use suggests that interventions targeting these symptoms could help improve substance use outcomes.

CBT, CM, MI, and MBRP are evidence-based psychotherapies that have been examined for the treatment of substance use disorders. CM is a form of operant conditioning wherein reductions in use or abstinence are reinforced by the delivery of some type of incentive (99). This approach utilizes positive reinforcement and can effect change by teaching patients new patterns and replacing previously reinforced patterns of substance use with new healthy patterns of behavior (99). CBT on the other hand, focuses more on helping patients better cope and respond to uncomfortable thoughts or emotions they may experience (100). Similarly, this helps patients learn new, healthy ways of coping to replace their previously patterns of using substances to cope with uncomfortable thoughts, emotions, or sensations. MI focuses on increasing a patient's readiness for change by eliciting their own motivation for enacting change and by exploring any ambivalence they may have (101). It is often conducted over 1-2 sessions in preparation for more intensive treatment but can also be used as a stand-alone treatment for substance use reduction. Lastly, MBRP focuses on stress reactivity and negative affect in relation to drug craving. By using mindfulness techniques, patients learn to focus on the present and cope with discomfort without the use of substances (57). All four of these interventions have been examined within substance using populations and the following studies demonstrate the importance of treating co-occurring psychological symptoms in conjunction with substance use treatment.

Based on the hypothesis that methamphetamine use is reinforced by the relief of negative emotional symptoms, it is logical that interventions should aim to alleviate these emotional symptoms to promote substance use reduction or abstinence. This is supported by the finding that depression severity predicted poorer treatment adherence in a study of 526 MUD patients undergoing psychosocial treatment [β = -0.18, SE = 0.07; p = 0.01; Glasner-Edwards et al. (55)] . Similarly, among the same cohort, anxiety disorders predicted poorer substance use outcomes, increased utilization of health services, and greater levels of psychiatric symptoms 3-years post-treatment (4, 56). Taken together, these data highlight the effect of negative emotional symptoms on substance use and emphasize the need for psychiatric intervention in substance treatment programs.

Polcin and colleagues (61, 62) examined the relationship between psychiatric symptoms and substance use problems among 217 MUD patients randomized to receive either an intensive nine-session MI intervention or a single session of standard MI paired with eight nutrition education classes. Overall, both interventions resulted in reduced methamphetamine use and severity of use-related problems. However, only patients in the intensive MI group reported fewer days with psychiatric problems (other than depression and anxiety) and reduced severity of these problems (61). With further examination, across both interventions, changes in psychiatric problem severity from baseline to 2-month follow-up were found to predict changes in the severity of methamphetamine use-related problems, but not in the

number of days individuals used substances (62). This relationship persisted through 6-month follow-up. Depression specifically has also been examined in the context of treatment for methamphetamine use. Methamphetamine users (MA and MUD; $n = 214$) with and without depressive symptoms were randomized to receive either a self-help book, or two or four therapy sessions consisting of MI and CBT (59). At baseline, individuals reporting depressive symptoms endorsed more severe methamphetamine use and drug-related problems than those who were not depressed. These depressed individuals also had greater change in methamphetamine use and depressive symptoms at 5-week follow-up, but unfortunately improvements were not sustained through 6-month follow-up. Importantly, these results suggest that methamphetamine use and depression are highly intertwined, and that methamphetamine-focused treatment may not be sufficient for long-term reduction of depressive symptoms, putting these individuals at increased risk for relapse. Overall, these results highlight the complex negatively reinforcing relationship between psychiatric problems and methamphetamine use. Additionally, MI appears to be an effective treatment for psychiatric symptoms and methamphetamine use but these effects may not be long-lasting.

Emotion regulation capacity has also been shown to predict treatment adherence. One hundred fifteen MUD patients enrolled in a residential substance use treatment program were followed from treatment entry and classified on the basis of whether or not they discontinued treatment early (58). Measures related to emotion regulation were collected including the DERS [Gratz and Roemer, (102)] and *The Multidimensional Personality Questionnaire Negative Emotionality Scale* [MPQ-NEM; Tellegen and Waller, (103)] . Overall, greater emotion regulation capacity at the time of treatment entry was associated with persistence through treatment (MPQ-NEM: $d = .70$; DERS: moderate to strong effect, $d \leq .70$). MUD who discontinued treatment early reported lower emotional clarity, decreased ability to engage in goal-directed behavior despite emotional distress, and higher trait negative emotionality than those who completed treatment (58). Contrary to previous research showing motivation to be a predictor of treatment persistence (104), level of motivation as assessed by *The Stages of Change Readiness and Treatment Eagerness Scale* [SOCRATES; Miller and Tonigan, (105)] was unrelated to whether or not MUD discontinued treatment. Therefore, emotional regulation capacity may be a more important contributing factor to treatment success than motivation for treatment alone. This demonstrates the importance of addressing emotion regulation skills to help substance use patients better cope with negative emotion symptomatology they may experience while going through treatment that could put them at greater risk for relapse.

Peck and colleagues (60) examined the temporal relationship between depressive symptoms and methamphetamine use among a sample of MUD gay and bisexual men undergoing 16 weeks of behavioral therapy. Patients were randomly assigned to one of four behavioral treatments: CBT, CM, CBT + CM, or gay-specific CBT. Approximately 28.5% of participants reported moderate to severe depression at the start of treatment, and all participants reported a decrease in depression by the end of treatment, regardless of condition. Additionally, patients reported reduced methamphetamine use up to one-year post-treatment. This suggests a strong connection between methamphetamine use and co-occurring depressive symptoms. However, methamphetamine use up to 5 days prior was found to predict depression ratings, but depressive symptoms were not found to predict methamphetamine use. This finding is interesting because it strengthens the hypothesis that depression may be a result of methamphetamine use rather than a motivating factor. The authors conclude that extended abstinence results in reduced depressive symptoms. However, methamphetamine use is likely reinforced by immediate relief of depressive and withdrawal symptoms, despite its long-term perpetuation of depressive symptoms (60).

Long-term stimulant use has been shown to modify how stress is processed, which can be detrimental to recovery from addiction (57). A pilot study investigated the use of MBRP in reducing stress-response among 22 adults with a stimulant use disorder. Patients were randomized to an 8-week intervention consisting of either MBRP or a health education program. Patients completed the Trier Social Stress Task pre- and post-intervention and provided self-report ratings of stress, anxiety, mood disturbance, and craving. Saliva samples were collected immediately following the stress task as well as 15, 30, and 60 min post-task as a measure of cortisol levels. Individuals in the MBRP group had significantly lower salivary cortisol levels 15 and 60 min after the stress task (29% and 24% variance explained, respectively). Additionally, MBRP patients had lower levels of subjective stress, anxiety, mood disturbance, and craving after the stress test administered post-treatment. This study shows promise for the use of MBRP to modify the way stimulant addicted individuals respond to stress; however, this study did not report on any substance use outcomes, so no conclusions can be drawn about whether MBRP is effective at reducing substance use. This study also did not differentiate between individuals addicted to cocaine versus methamphetamine. Although these drugs are both stimulants, they have different chemical properties, which research suggests may have differential effects (106). Regardless, this study suggests promise for the use of MBRP for treating substance use disorders by reducing stress, anxiety, and craving.

As demonstrated above, poor emotion/affect regulation can contribute to continued substance use. In addition to interventions attempting to decrease negative affect, there is also some promise for interventions attempting to enhance non-drug related positive affect. This was demonstrated in a sample of 110 MA sexual minority men positive for human immunodeficiency virus (HIV), who were randomly assigned to receive either CM combined with a positive affect (CM+PA) intervention or an attention-control condition (54). Patients in the CM+PA condition reported increases in positive affect ($d = 0.31$) and mindful awareness ($d = 0.36$) 3-months post-intervention, two factors related to emotion regulation. Importantly, these improved psychological processes were found to correspond with decreased craving ($d = -0.51$) and substance use ($d = -0.46$) at the 3-month follow-up (54). This

finding suggests that positive affect interventions have the potential to improve substance use outcomes by: (1) increasing reward responsivity to non-drug related rewards; and (2) increase emotional processing in a way that reduces negative reinforcement. This supports the hypothesis that negative reinforcement plays an important role in the perpetuation of problematic substance use and that psychological interventions seeking to improve emotion regulation and stress response can simultaneously improve psychological factors as well as substance use outcomes.

Exercise Interventions

Exercise has generally been shown to aid in the reduction of anxiety and depression (107), suggesting that it may be useful in reducing these uncomfortable sensations in methamphetamine addiction. A few studies have shown promising results for the use of exercise as either a primary or additive intervention for problematic methamphetamine use. In addition to treatment as usual, MUD newly enrolled in a residential treatment program for problematic methamphetamine use were randomly assigned to receive 8 weeks of either a health education control group or exercise program consisting of a 60-min structured exercise sessions three times per week. Among patients assigned to the exercise program, reductions in depression and anxiety symptoms were reported at the end and a dose effect on mood symptoms was also observed (63). Unfortunately, this study did not examine the relationship between depression and anxiety symptoms and treatment outcome variables related to substance use. However, other researchers have found that exercise, when compared to an attentional control group, reduced drug craving among MUD during and after a 12-week aerobic exercise program [η_p^2 = 0.16; Wang et al. (65)], and up to 50 min after an acute 30-min exercise session [η_p^2 = 0.34; Wang et al. (64)] . Together, these data suggest that reductions in anxiety and depression symptoms may mediate the relationship between exercise and reduced craving. Further studies are warranted to support this conclusion.

Pharmacotherapy Interventions

Various medications have been investigated for the treatment of MUD. In line with the theory of negative reinforcement, it is hypothesized that antidepressant medications may improve substance use outcomes by treating mood symptoms that can precipitate relapse (108). Bupropion, sertraline, and mirtazapine are three antidepressant medications that have been examined within randomized, placebo-controlled trials. Two trials examined CM with either bupropion (70) or sertraline (69) in comparison to placebo. Outcome variables of interest included methamphetamine use, severity of depressive symptoms, and drug craving; however, no significant differences were found between either medication group and the placebo groups. These results suggest that bupropion and sertraline do not effectively reduce depressive symptoms among MUD above and beyond CM alone. Bupropion was also examined in conjunction with CBT. Again, no significant differences in craving or depressive symptoms were found between groups (bupropion vs. placebo), providing further evidence to suggest that bupropion is not effective for the treatment of MUD (67). A lack of group differences in reductions of depressive and anxiety symptoms have also been found following treatment with mirtazapine in conjunction with narrative therapy counseling compared to placebo (66). Overall, these trials imply that antidepressant medications do not reduce negative mood symptoms, and in turn, improve treatment outcomes in MUD beyond the effects of co-occurring interventions including CM, CBT, and narrative therapy. However, this evidence does not suggest that mood symptoms do not play a role in negatively reinforcing methamphetamine use; rather, it leaves the question of whether effectively treating mood symptoms can improve substance use outcomes unanswered.

In addition to antidepressant medications, other classes of drugs have been investigated for the treatment of MUD in conjunction with psychotherapy interventions. Previous research has suggested that GABAergic medications may be effective for the treatment of cocaine use, suggesting it may have similar efficacy for MUD (68). Thus, treatment-seeking MUD were randomized to receive either baclofen, gabapentin, or placebo in addition to attending relapse prevention groups. All three groups showed reductions in outcome measures including craving, retention, and depression scores over time with no significant difference between groups (68). The same research group investigated modafinil compared to placebo in conjunction with CM and CBT for MUD (70). This trial yielded similar results, wherein all patients reported reduced depressive symptoms regardless of medication condition. Additionally, there were no significant group differences for craving, methamphetamine use, or retention. Lastly, aripiprazole, an anti-psychotic, was investigated given its potential to increase dopamine transmission in light of reduced striatal dopamine levels among MUD (109, 110). However, similar to other trials investigating adjunctive medications for the treatment of MUD, aripiprazole did not appear to significantly reduce methamphetamine use, depressive symptoms, or craving beyond placebo (70). Further, individuals who received aripiprazole reported experiencing an increase in the rewarding and stimulatory effects after methamphetamine dosing, suggesting that this medication is unlikely to be efficacious for the treatment of MUD.

Brain Stimulation Interventions

Based on fMRI findings of altered functioning in various frontal regions among MUD, repetitive transcranial magnetic stimulation (rTMS) delivered to these regions has been examined as a potential treatment intervention for addiction. rTMS delivers noninvasive stimulation to specific cortical regions by applying a fluctuating magnetic field between 0-10 Hz [Liang et al. (71)]. As frontal processing deficits may contribute to difficulties with attention and emotion regulation, resulting in an inability to adjust behavioral responses accordingly (44), using rTMS to alter neural activity in frontal regions may result in improved emotional functioning. Although the literature is limited, two studies found that, in comparison to sham control groups, 10 Hz rTMS delivered to left DLPFC decreased depression and anxiety symptoms in men with MUD (71, 72). Observed reductions in symptoms of anxiety also related to reductions in MA craving

(71). An additional study reported that real rTMS reduced craving, but both real and sham rTMS decreased depressive symptoms, while neither condition resulted in any change in anxiety symptoms (111). These contradictory findings may be due to differences in study design as reductions in depressive symptoms were found after 10 or 30 rTMS sessions, but not after five sessions, suggesting that change in mood symptoms may be dose dependent. Currently, there is no research examining rTMS in female MUD patients, nor longitudinally to determine if any effect on mood symptoms is sustained over time. Further research is needed to elucidate the effects of rTMS on mood symptoms.

In line with the theory that methamphetamine use is negatively reinforced by the relief of negative mood states, treating symptoms of anxiety and depression holds promise for improving substance use outcomes. Findings are mixed with regard to efficacy of psychotherapy, exercise, pharmacotherapy interventions, and brain stimulation. Various psychotherapy treatments including CBT, CM, MBRP, MI, and positive affective interventions have shown promise for reducing mood symptoms and thereby improving substance-related treatment outcomes including greater treatment adherence, and reduced craving and methamphetamine use (see **Table 3**). Exercise may also improve treatment outcomes among MUD by reducing anxiety and depressive symptoms as well as craving. rTMS may also hold promise for improving mood symptoms and reducing craving but the research is too limited at this time to draw any strong conclusions. Less compelling evidence has been found for the use of adjunctive medications in the treatment of MUD. Multiple controlled-trials have been unable to demonstrate any significant reductions in outcomes related to mood symptoms or substance use above and beyond placebo. Regardless, some progress has been made in the treatment of MUD, but further research is warranted to improve treatment outcomes. Targeting negative mood symptoms related to anxiety and depression appears to be a promising avenue for effectively improving treatment outcomes among MUD.

LIMITATIONS AND FUTURE DIRECTIONS

The findings related to negative reinforcement in MUD suggest a number of promising avenues for future treatment research. One such avenue is emotion-focused interventions. One study demonstrated a positive affect intervention to be effective at improving emotion regulation processes, thereby reducing drug craving and use among HIV-positive sexual minority men with MUD (54). Given these promising findings within a specific subpopulation of individuals with MUD, additional research is warranted to examine the efficacy of emotion-focused interventions in the general MUD population. Additionally, considerable efforts should be put towards developing emotion-focused interventions that specifically target suicidal ideation given the high rates of suicide among MUD. Based on the findings outlined above, interventions aimed at helping individuals develop efficient emotion regulation and healthy coping skills hold promise to effectively reduce emotional symptoms common among MUD and in turn improve substance use outcomes. Additionally, while some improvement has been found with other interventions (i.e., CBT, CM, MI, and MBRP), features of anxiety and depression, such as severity, have been found to predict poorer adherence to such treatments (55). This further highlights the need for emotion-focused interventions that target negative mood symptoms that maintain and exacerbate substance use disorders. Adjunctive pharmacotherapy may also prove effective in reducing mood symptoms to allow for better treatment adherence, although the evidence is less compelling.

Efforts should be made to develop and test interventions that alter activity in brain regions in which MRI, PET, and ERP research have demonstrated deficits among MUD. Current findings among MUD suggest that brain stimulation may be one intervention effective in modifying brain activity. rTMS of DLPFC has been applied to MUD with mixed results in terms of changes in mood symptoms and drug craving (71, 72, 111). Additional research should examine if these changes in mood and craving coincide with sustained abstinence/reductions in use and whether rTMS can effectively increase executive functioning and enable MUD to choose adaptive behavioral responses despite negative emotional symptoms. rTMS has yet to be applied to brain regions other than DLPFC that exhibit altered functioning among individuals with MUD.

Various other interventions that have been shown to modify brain function in non-substance-using individuals may be potential treatments for targeting brain regions altered in MUD. These include mindfulness meditation [e.g., Taren et al. (112)], behavioral activation therapy [e.g., Dichter et al. (113)], and trauma-focused therapy [e.g., Aupperle et al. (114), Simmons et al. (115)], have been found to impact brain function in circuitry considered important for emotional processing and regulation and have beneficial effects for negative affect related symptoms. Using related strategies with MUD populations (or particularly those with co-occurring depression, anxiety, or PTSD) may therefore be beneficial for interrupting the negative reinforcement cycle. Additionally, other pharmacological interventions may also be useful for altering dysfunctional brain regions in MUD, such as modafinil, which has been shown to increase insula and ACC RSFC with other brain regions (116). By exploring interventions that target dysfunctional brain regions highlighted in the literature on MUD, researchers may be able to develop treatments that break the negatively reinforcing cycle of using methamphetamine to reduce uncomfortable sensations.

Overall, our understanding of negative reinforcement in MUD and its implications for treatment is hindered by limitations in the research. In addition to the potential avenues of treatment research outlined above, future researchers should aim to address the following limitations. First, many findings come from studies of small sample sizes and specific populations (e.g., HIV-positive, sexual minorities) which limits the ability to generalize to the MUD population overall (see **Tables 2** and **3**). Second, the prevalence of cross-sectional studies greatly limits the inferences that can be made regarding causation of observed

individual differences (i.e., emotional processing deficits). Longitudinal studies would allow for examination of the temporal relationship between emotion dysregulation and MUD and the results could potentially inform the development of successful prevention efforts. For example, the Adolescent Brain Cognitive Development (ABCD) study began in 2016 and is the largest long-term study of brain development to date, following a cohort of approximately 11,500 youth for ten years. The data from the ABCD study hold promise for elucidating the relationship between emotion dysregulation and substance use disorders as it will allow for a prospective examination of these problems as they develop. Longitudinal treatment studies would also be useful to determine whether the observed deficits observed in long-term methamphetamine users are predictive of relapse and other treatment-related outcomes. Third, reported data on drug use characteristics such as duration of use, recency of use, duration of abstinence, etc., is varied and lacking. This information is crucial to examine in relation to observed behavior and brain functioning to better understand the interaction between substance use and unfavorable outcomes. This could also aid our understanding of which interventions are most effective and for whom. Lastly, there is a lack of treatment studies coupled with neuroimaging. Pairing these methods together would allow researchers to determine whether an intervention impacts brain networks that are dysfunctional in MUD (e.g., executive function, reward processing, and emotion regulation) and whether it is likely to impart lasting change.

The current body of literature appears to preliminarily support the hypothesis that negative reinforcement is at play in the development and maintenance of MUD. However, the majority of the studies included in this review employed cross-sectional and/or quasi-experimental designs, which do not allow for the precise testing of the longitudinal nature of the three-stage model of addiction (9). There is room for continued research efforts to further clarify the extent to which negative reinforcement contributes to substance use disorders and whether interrupting these processes holds value as a potential treatment option.

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AM contributed to the development of the concept for the review, completed literature search, and wrote the first draft of the manuscript. JS and RA both contributed to the development of the concept for the review, and revised subsequent drafts of the review.

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Memory Retrieval-Extinction Combined With Virtual Reality Reducing Drug Craving for Methamphetamine: Study Protocol for a Randomized Controlled Trial

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Background: Relapse, often precipitated by drug-associated cues that evoke craving, is a key problem in the treatment of methamphetamine use disorder (MUD). Drug-associated memories play a major role in the maintenance of relapse. Extinction training is a common method for decreasing drug craving by suppressing drug-associated memories. However, the effects are often not permanent, which is evident in form of spontaneous recovery or renewal of cue-elicited responses. Based on memory reconsolidation theory, the retrieval-extinction (R-E) paradigm may be more effective in decreasing spontaneous recovery or renewal responses than extinction. After the original memory reactivated to a labile state, extinction will be introduced within the reconsolidation window, thereby updating drug-associated memories. However, there are still some controversial results, which suggest that the reactivation of drug-associated memories and the 10 min-6 h of limited time window are two main elements in the R-E protocol. Virtual reality (VR) is supposed to promote memory reactivation by providing vivid drug-related stimuli when compared with movies.

Objective: The aim of this study is to examine the effectiveness of R-E training combined with VR on reducing spontaneous recovery or renewal of cue-elicited responses, in comparison to extinction, R-E training provided outside the time window of 6 h and R-E training retrieved using videos, in methamphetamine abusers.

Methods: The study is a parallel matched controlled study including 95 participants with MUD. Participants will be randomly assigned to either a R-10 min-E group (methamphetamine-related cues retrieval in VR followed by extinction after 10 min) or a NR-10 min-E group (neutral cues retrieval in VR followed by extinction after 10 min) or a R-6 h-E group (methamphetamine-related cues retrieval in VR followed by extinction after 6 h) or a RV-10 min-E group (methamphetamine-related cues retrieval in videos followed

by extinction after 10 min). Cue-evoked craving and reactivity will be assessed at pre-test and at 1 day, 1 week, 1 month, and 6-month post-tests.

Discussion: To our knowledge, this study will probably be the first study to examine the efficacy of R-E training combined with VR to reduce cue-evoked responses in people with MUD. This innovative non-pharmacological intervention targeting drug-associated memories may provide significant clinical implications for reducing relapse, providing the study confirms its efficacy.

Clinical Trial Registration: The trial is registered with Chinese Clinical Trial Registry at 17 October 2018, number: ChiCTR1800018899, URL: http://www.chictr.org.cn/showproj.aspx?proj=30854

Keywords: memory reconsolidation, retrieval-extinction, extinction, drug-associated memories, virtual reality, methamphetamine

INTRODUCTION

Methamphetamine is the commonly abused illegal drug recent years in China and entails great personal and societal costs (1, 2). Even after long periods of abstinence from drugs, the risk of relapse remains high in people with methamphetamine use disorder (MUD) (3, 4). Relapse is a core characteristic of substance use disorders (SUDs) and a major obstacle to successful treatment. Craving or cue reactivity elicited by drug-associated stimuli is invoked as a main motivating force behind relapse (5, 6). As drug-paired stimuli (cues, contexts, and behaviors) that are repeatedly associated with the reinforcing properties of drugs over the course of drug use, when subsequently encountered, are known to evoke craving or cue reactivity and then result in compulsive drug taking (5–7). Drug-associated memories supposed to be a primary trigger of drug craving and relapse. This suggests that effective treatments focused on the manipulations of the cue-drug memory to reduce cue-elicited craving or reactivity are needed for relapse prevention of MUD.

Extinction training is a common method used to decrease craving and reactivity evoked by drug-associated stimuli in an effort to reduce relapse propensity through suppressing the cue-drug memory (8). Initially, it had been assumed that repeated, unreinforced presentation of drug-associated stimuli (without drug administration), would "extinguish" cue-elicited craving and reactivity. Extinction training has been applied in a variety of forms to treat SUDs in clinical studies with varying levels of success (9). However, these cue-evoked responses frequently reemerge after the passage of time (spontaneous recovery) or in the presence of drug-associated stimuli different from the ones used in extinction training (renewal) (10, 11). This suggests that extinction might involve a new "cue-no drug" learning to inhibit or interfere with the initial "cue-drug" association instead of erasing the original memory trace (12, 13).

Recent studies have proposed that retrieval-extinction (R-E) training, based on the theory of memory reconsolidation, may be more effective in reducing spontaneous recovery or renewal of cue-elicited responses than extinction through modifying drug-associated memories (14, 15). Memory reconsolidation is a process to maintain and strengthen consolidated memories over time, during which previously consolidated memories re-stabilize after it is retrieved or "reactivated" (16). The R-E training follows the rationale to reactivate original drug-associated memories to a labile state by a brief and/or weak exposure to the drug-associated stimuli, and then extinction training will be used to interrupt the reconsolidation process of drug-associated memories within a limited time window by incorporating new information, thereby updating the original drug-associated memories (16). The 10 min-6 h of reconsolidation window has been examined in preclinical studies (17, 18) without enough clinical studies in SUDs. To our knowledge, only two translational studies have used R-E training to treat SUDs, which found that R-E training in 10 min-6 h, had better intervention effects on inhibiting spontaneous recovery (19) or renewal (20) of cue-elicited responses than extinction training. Nonetheless, other studies failed to replicate the results (21, 22). One of the key reasons is that the consolidated memories had not been reactivated to a labile state (23) for memory reconsolidation.

Virtual reality (VR), which has high ecological validity, may improve the effects of R-E training from a methodological perspective. VR can provide a variety of vivid drug-associated cues and contexts for individuals to interact with and the individuals with SUDs will be immersed in customized scenes by putting on a headset. Previous studies found that using VR to present drug-associated stimuli and interact with these stimuli during the retrieval process evoke craving more robustly than using traditional methods, such as pictures (24) and videos (25, 26). It suggests that VR may be a promising way to reactivate drug-associated memories by providing vivid drug-associated stimuli (25). Thus, combined VR with R-E training may be a prospective approach to treat MUD.

The primary objective of the present study is to examine the effectiveness of R-E training combined with VR in decreasing

Abbreviations: MUD, Methamphetamine use disorder; R-E, Retrieval-extinction; SUDs, Substance use disorders; VR, Virtual reality.

cue-elicited craving and reactivity in individuals with MUD, when compared to extinction training or R-E training provided outside the time window of 6 h. The second objective is to examine the effects of VR in promoting the reactivation of drug-associated memories during R-E training. The R-E training combined with VR will be compared with the R-E training combined with videos during the retrieval in decreasing cue-elicited responses. The third objective is to examine the effectiveness of R-E training combined with VR in attenuating spontaneous recovery and renewal of cue-elicited responses when compared to the other three interventions. All the cue-evoked craving and reactivity will be assessed at pre-test and 1 day, 1 week, 1 month, and 6-month posttests after intervention to investigate how long the effectiveness of R-E training will last. A novel methamphetamine-related scene will be added to the follow-up post-tests to assess if the effectiveness can translate to the new drug cue-induced craving and reactivity.

MATERIALS AND METHODS

Design

The study will be a randomized controlled comparative clinical trial with two successive days of therapy and 6 months of follow-up. It will involve four parallel groups, namely a R-10 min-E group (methamphetamine-related cues retrieval in VR group), a NR-10 min-E group (neutral cues retrieval in VR group), a R-6 h-E group (group that will receive extinction training outside the reconsolidation window of 6 h) and a RV-10 min-E group (methamphetamine-related cues retrieval in videos group).

Participants

This study will be conducted at the Changsha drug rehabilitation center, Changsha, Hunan, and Women' drug rehabilitation Center of Guangdong province, Foshan, Guangdong. The inclusion criteria are as follows: 1) age: 18–45 years old; 2) a history of using methamphetamine meets Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for MUD (27); 3) abstinence periods at least 2 weeks without obvious withdrawal symptoms (e.g., drowsiness and dysphoria); 4) able to speak and read Chinese; 5) a signed consent form; and 6) cue-elicited responses including self-report craving, heart rate, skin conductance responses, and electroencephalogram power spectrum are all more obvious in methamphetamine-associated scenes than in neutral scenes in VR during the pre-test (28).

The exclusion criteria are as follows: 1) a history of using illicit drugs other than methamphetamine or methamphetamine tablets (e.g., heroin, cocaine, marijuana); 2) uncontrolled medical illnesses or psychosis; 3) use of any medication or medical condition that may affect cardiovascular function and mental state; 4) some kinds of nervous system diseases may influence performing the experiment (e.g., epilepsy, parkinsonism); 5) a history of head trauma that caused a coma lasting more than 30 min; 6) movement disorders; 7) hearing impairments; 8) color blindness or color amblyopia; 9) a vision or corrected visual acuity less than 1.0. The subjects with psychiatric comorbidities and other kinds of SUDs will be excluded using DSM-5 (27, 29).

Study Procedure

Psychotherapists in the rehabilitation center will make the advertisements and announcement for recruitment. The participants will be screened by a psychologist for eligibility. Then, the researcher will meet the eligible participants, describe the study procedure, discuss with the participants on the questions they concerned, and ask each eligible participant for informed consent.

Firstly, participants will attend a 1 h individual face-to-face interview to collect demographic information, the use history (dosage, duration, frequency) of methamphetamine, cigarettes, and alcohol and the questionnaire on anxiety. The use history of methamphetamine, cigarettes, and alcohol and the anxiety index will be regarded as variables for the data analysis. Then, a VR using practice with a neutral scene lasting 6 min for accommodation will be implemented. Participants will adapt to VR scenes and know how to operate wireless controllers of the VR system. After this, participants will attend a VR cue reactivity assessment as a pre-test, during which participants will engage in two VR sessions (composed of a methamphetamine-VR scene for 3 min and a placebo-VR scene for 3 min) with a real-time recording of psychophysiological reactivity (heart rate, skin conductance reactivity, and electroencephalic response). There will be a 1 min break between the two sessions, and the placebo-VR scene will always be presented before the methamphetamine-VR scene to avoid the disturbance elicited by the methamphetamine-related cues. Self-report craving to methamphetamine-related cues will be rated after exploring both VR scenes. The pre-test will be used not only for measuring the baseline of cue-elicited responses but also for screening the participants who will respond more robustly to methamphetamine-associated cues in VR. According to the inclusion criterion, participants the cue-elicited responses including self-report craving, heart rate, skin conductance responses, and electroencephalogram power spectrum are all more obvious in methamphetamine-associated scenes than in neutral scenes during the pre-test will be included in groups (28).

Thereafter, participants will be randomly assigned to one of four therapeutic groups using a randomization table generated by a sequence generator in a computer for matching. One group (R-10 min-E group) will receive R-E training, namely memory retrieval of methamphetamine-related cues in VR followed by extinction training after 10 min. Another group (NR-10 min-E group) will receive extinction intervention, namely memory retrieval of neutral cues in VR followed by extinction training after 10 min. The other group (R-6 h-E group) will receive R-E training outside the time window of 6 h, namely memory retrieval of methamphetamine-related cues in VR followed by extinction training after 6 h. The RV-10 min-E group will receive memory retrieval of methamphetamine-related cues in videos

followed by extinction training after 10 min. Psychophysiological reactivity will be recorded instantaneously during the two times of intervention. The cue-elicited responses during the retrieval session will be assessed to indicate memory reactivation (28).

With the purpose of examining the effectiveness of R-E training in decreasing the spontaneous recovery of cue evoked responses, self-report craving and the VR cue reactivity assessment will be conducted at five different time points: pre-test, 1 day, 1 week, 1 month, and 6 months after the last intervention session. To measure the renewal effect, a new VR session with novel methamphetamine-related cues will be added to the VR cue reactivity assessment during the four post-tests compared to pre-test. Three psychotherapists with VR operation knowledge will conduct all the procedures for the four groups. The whole procedure of this study is depicted in a flow chart (**Figure 1**).

Intervention

All four groups will receive two intervention sessions over two consecutive days (19, 20). The intervention process will be conducted by one of three psychotherapists including a 3 min memory retrieval session and a 30 min extinction training session. Psychotherapists should have technical ability to operate VR (self-developed through the collaborative work of the psychotherapists and researchers) to ensure the treatment's consistency and fidelity. The content of the extinction training session will be the same for the four groups. However, the intervention processes of four groups will differ in the content of the memory retrieval session and the time point of implementing extinction training.

R-10 min-E Group

Participants will receive two intervention sessions for the same, which both consist of memory retrieval for 3 min and extinction training for 30 min. The extinction training session will be implemented 10 min after the memory retrieval session. During the retrieval session, participants will be guided to explore a VR scene, which is considered as a high-risk situation for relapse, with both distal and proximal methamphetamine-related cues (e.g., a substance that appears to be methamphetamine, the water filter bottle of methamphetamine, straws, foil paper). In this way, the methamphetamine-associated memories of participants may be reactivated to a labile state.

During the extinction training session, six VR scenes with different methamphetamine-related cues in a room will be given to participants in six consecutive sessions. Participants will be asked to sit in front of a table on a sofa (or on a chair) in VR scenes. All the while, they will sit on a real sofa (or on a real chair) in the experimental environment in reality. Each VR session with one VR scene will last for 5 min. Six VR scenes will be presented in a randomized order to regulate individual differences in the relevance of craving-specific among participants. During the first and last minute of each VR session, participants will be instructed to observe the entire VR scene, and in the middle three minutes, a task for fully exposing methamphetamine-related cues will be assigned to the participants. After each session, participants are going to rate their craving to methamphetamine-related cues using a visual analog scale. Throughout the intervention process, psychophysiological cue reactivity will be recorded in real time.

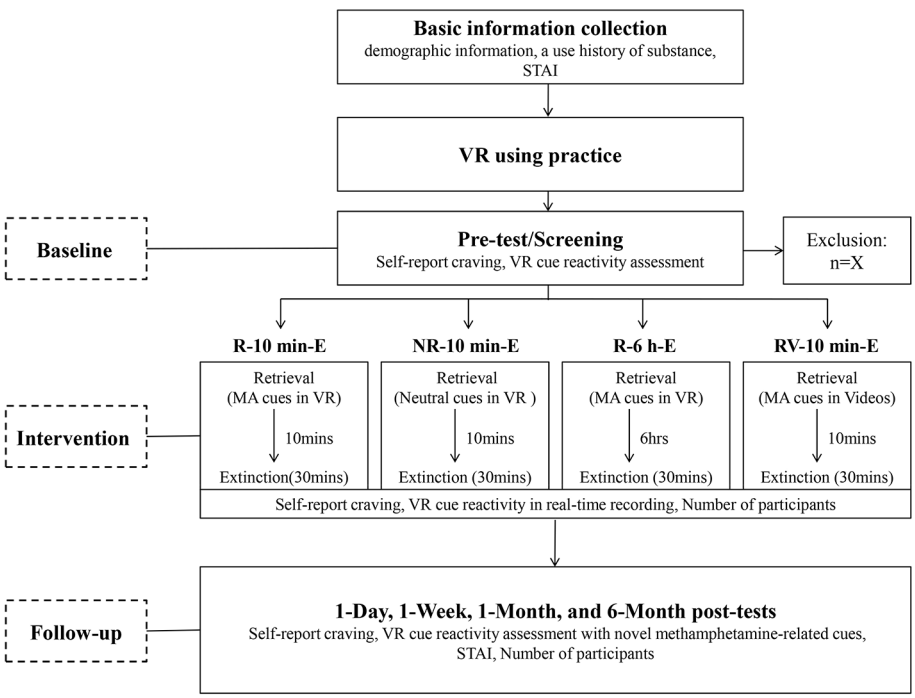

FIGURE 1 | Flow chart of the study. STAI, State and Trait Anxiety Inventory; MA cues, Methamphetamine-related cues.

NR-10 min-E Group

Participants will be provided with two intervention sessions for two days, both including 3 min of neutral cues retrieval followed by 30 min of extinction training 10 min after. The implementation of the retrieval session will guide participants to explore a neutral VR scene without methamphetamine-related cues. To ensure that the methamphetamine-associated memories of the participants will not be reactivated to a labile state, this session should be irrelevant to drug-associated stimuli.

The content of the extinction training session that the NR-10 min-E group will be exposed to is the same as the content that the other three groups will be exposed to.

R-6 h-E Group

Participants will receive two intervention sessions that the content of the retrieval session and the extinction training session will be identical to the R-10 min-E group. The only difference is that extinction training will be conducted 6 h after memory retrieval, when methamphetamine-associated memories are supposed to be reconsolidated again.

RV-10 min-E Group

Participants will receive two intervention sessions for two successive days. The duration and the time interval to implement the intervention sessions of the RV-10 min-E group are the same with the R-10 min-E group and the NR-10 min-E group. However, the method to present methamphetamine-associated cues of the RV-10 min-E group in the retrieval session is different from the other three groups. The participants will watch a video related to methamphetamine lasts 3 min to retrieve drug-associated memories. 10 min after the retrieval session, a same extinction training session will be implemented.

Apparatus

The experiment is going to use HTC VIVE virtual reality system containing a headset (110 degrees, 1080×1200, 90Hz), two wireless controllers, and two base stations. Through the head tracker, participants can visually explore the VR scenes and walk around freely in a 3.0 m× 4.0 m space. The head orientation of participants will define the direction of locomotion. The wireless controllers will be used to interact with VR scenes and to provide their ratings on the visual analog scales. The VR scenes will be generated and run on a desk computer (Alienware 15-R2748, i7-7700HQ 16G 256GSSD+1T GTX1070 8G discrete graphics FHD). The required software is Microsoft Windows 10 (64-bit edition). The heart rate and skin conductance reactivity will be recorded by Biopac 16 Physiological multichannel instrument (BIOPAC MP150) including two transmitters and a signal projector connecting to a laptop. The electro encephalic response monitor has been developed by XinSi company in Beijing, China. The monitor has proven to be effective in recording electroencephalic responses (30).

VR Scenes and Videos

The main software exploited to create the VR scenes is unity 3D. Unity is an ultimate and available game development platform used to build and deploy high-quality 3D games across VR. The neutral scene in the process of VR using practice will be a room with a desk, two spheres, two cubes, and a visual analogue scale. In a previous investigation of 60 people with MUD, four completely different VR scenes were constructed by unity 3D, two of which contexts were related to methamphetamine, while the other two were neutral contexts with neutral goods rather than methamphetamine-related cues. Two methamphetamine-related scenes are a living room and a bedroom with methamphetamine-related cues on a table or desk. To resemble the most familiar methamphetamine-related environment of participants in real life, a suitable VR scene will be chosen for each participant from the two methamphetamine-related rooms to be implemented in the pre-test, the memory retrieval session, and four post-tests (31). The other one of the two methamphetamine-related rooms which has not been chosen in the pre-test will be presented in four post-tests as a novel scene to test the renewal effect. Six methamphetamine-related scenes in the extinction training session are based on these two rooms with a double or a triple number of methamphetamine-related cues in different places of the rooms. One of the two neutral VR scenes has been prepared for the memory retrieval session that the NR-10 min-E group will view. The other one will be implemented in cue reactivity assessments as a baseline for the pre-test and post-tests to compare with methamphetamine-related VR scenes.

The dynamic VR scenes also provide participants with direct, realistic interactions, such as the grabbing of objects and physical or mechanical reactions to the user's presence. The four VR scenes including two methamphetamine-related scenes and two neutral scenes will be validated by a small number of people with MUD (n = 10) using self-report craving. All the VR scenes will be run in the software named Steam, which is a game platform as well.

The methamphetamine-associated video used in the retrieval session of the RV-10 min-E group will include an actress using *in vivo* mock methamphetamine paraphernalia (e.g. glass pipe, mock syringe, medical tubing, and a small plastic bag containing a substance that appears to be methamphetamine) to make a water filter bottle for administrating methamphetamine. The video will be validated by the same group of people with MUD (n = 10) using self-report craving. The video will be run on the desk computer.

OUTCOMES

The experimental design will be double blinded. The craving and VR cue reactivity will be recorded by three psychologists during the pre-test, two intervention sessions, as well as the post-tests at 1 day, 1 week, 1 month, and 6 months after the intervention.

Primary Outcomes

1. Self-report craving for methamphetamine will be measured using a 100-point visual analog scale in VR ranging from 0 (no craving) to 100 (high craving).
2. Psychophysiological recordings (see below for details) will be carried out at every VR cue exposure including two

intervention sessions and VR cue reactivity assessments at the pre-test and the 1 day, 1 week, 1 month, and 6-month follow-ups.

Secondary Outcomes

1. Anxiety will be measured with State-Trait Anxiety Inventory (STAI) (32). STAI is a widely used scale for general anxiety (33, 34). Chronic methamphetamine use may cause emotional dysfunction including anxiety (29). The Chinese version of STAI is a 20-item self-report instrument with a satisfying internal consistency (Cronbach's alpha = 0. 88) (35) and scores from 20 (absence of anxiety) to 80 (high anxiety).
2. Dropout rate will be assessed to indicate the motivation of participants to effectively engage in the treatment program (36, 37). Many methamphetamine users are reluctant to enter treatment and once in treatment there is an unacceptably high early dropout rate (38). Dropout rate is an important indicator may reflect the acceptability of the MUD treatments. The number of participants will be recorded at different time points for calculating the dropout rate.

Psychophysiological Outcomes

1. Heart rate (HR) and heart rate variability (HRV) will be evaluated with the Biopac 16 Physiological multichannel instrument (BIOPAC MP150) during VR cue exposure at pre-test, two intervention sessions and four post-tests. HR reflecting the average heart rate is a kind of automatic response to emotional arousal. HR increases during anxiety states and decreases during relaxed states (39). As one of the main indicators of cue reactivity, the HR in individuals with SUDs may increase when they are exposed to drug-associated cues (5). The HRV indicates the fluctuations in HR around an average HR (30), which decreases during an anxious and exciting state and increases during a relaxed and calm state (39). HRV is also used as an autonomic index of emotion regulation capabilities (40), responding sensitively to drug-associated cues (41). HR and HRV are frequently regarded as objective measurements of anxiety responses and craving reactivity (5).
2. Skin conductance reactivity (SCR) will be recorded at the same time as the HR using BIOPAC MP150. Two Ag/AgCl electrodes of 20 mm×16 mm will be attached to the medial phalanges of the first and third fingers of the non-preferred hand of participants to obtain the signal of SCR. SCR is affected by emotional arousal, finger temperature, and finger activity. For recording SCR stably, participants will be told to keep the non-preferred hand down when they are exploring the VR scenes. SCR is considered to be an important index for cue reactivity evoked by drug-associated cues (30). During the state of craving, the blood vessels and sweat glands may change which will cause changes in the skin resistance, resulting in changes of the skin electricity. The spontaneous changes of SCR may be caused by R-E training, as demonstrated by a previous study (22). SCR has been used to measure craving in a previous methamphetamine study (42).
3. Electroencephalogram (EEG) will be recorded using an application of a mobile EEG equipment at the same time as the HR and the SCR. Four channels (TP9, FP1, FP3, TP10) will be kept to measure brain waves including alpha, beta, delta, and gamma frequencies. Previous studies on SUDs revealed that drug-associated cues evoked pronounced EEG power spectrum (43). The EEG has been used in previous studies as an objective index of cue reactivity to show craving (44).

SAMPLE SIZE

ANOVA was used to calculate the sample size (power = 80%, α = 5%). The calculation was based on the relevant data of a previous study of R-E training for individuals with tobacco use disorder, whose main results related to cue-elicited craving and reactivity (reference point =20%) (20). The result indicated that a minimum of 20 participants per group will be required for subsequent analysis. Taking into consideration that 15% of the participants may potentially drop out from the study, 95 eligible participants are needed for inclusion.

STATISTICAL ANALYSIS

The means, medians, standard deviations, and ranges of the data will be summarized for quantitative data and counts and frequencies for categorical data. Primary outcomes and secondary outcomes will be analyzed separately. ANOVA (quantitative variables), Manna-Whitney-Wilcoxon test (ordinal variables), or Chi-square test (frequencies) will be used to compare outcomes between groups at baseline. Non-parametric tests will be used for data that are not normally distributed. Multiple imputations will be used to address the missing data if necessary. Furthermore, the mixed linear model analysis will be applied to compare outcomes among groups at follow-up assessments. Statistical significance is defined as $p \leq 0.05$. Statistical analyses will be performed using SPSS statistics software, version 19.0 (SPSS Inc., Chicago, IL, USA).

DISCUSSION

To our knowledge, this study is the first intending to evaluate the effects of R-E training combined with VR on reducing methamphetamine-related craving and cue reactivity clinically. The primary findings of the randomized controlled trial may suggest that R-E training delivered by immersive VR may be highly effective for the reduction of craving and reactivity evoked by drug-associated stimuli in comparison to extinction and may ultimately decrease the rate of relapse. Another important point of the proposed study may be that using VR is more effective than using traditional methods to implement the memory

retrieval during the reconsolidation intervention in decreasing cue-induced responses. This may provide the first proof that VR may improve the effects of the reactivation of drug-associated memories during R-E training.

First, this study pays close attention to MUD. In China, MUD constitute the majority of SUDs, especially among the youth (1, 2). Methamphetamine is a highly addictive psychostimulant drug that induces psychological dependence and has serious effects on mental health, posing a treatment challenge (45). Relapse is one of the main clinical problems in the treatment of SUDs (46), especially MUD, suggesting that more effective strategies are needed for relapse prevention in MUD.

Drug-associated memories may be the main factor of relapse in MUD. R-E training is expected to decrease cue-evoked craving and reactivity through a single reminder exposure to reactivate drug-associated memories prior to extinction training. A previous study showed that R-E training decreased conditioned fear response which was stubborn in case of spontaneous recovery, renewal (17). Furthermore, the findings of animal and human laboratory studies on conditioned fear are consistent with the reconsolidation hypothesis (18, 47, 48). As far as we know, the clinical utility of R-E training in SUDs has been examined in only two previously published studies. One study was about heroin use disorder, which found a marked reduction in self-report craving 6 months after R-E training, when compared to extinction or R-E training provided outside the time window of 6 h (19). The other one, which concerned nicotine use disorder, showed that using R-E training reduced drug craving elicited by novel drug-associated cues (20). These studies revealed significant clinical benefits of R-E training for inhibiting spontaneous recovery or renewal of cue-evoked craving and reactivity when compared to control groups. The consistent outcomes support the notion that the reactivation of drug-associated memories may be essential for disrupting the reconsolidation of original drug-associated memories by incorporating new information (extinction training) (16). Thus, the present study shares the same opinion with Xue et al. and Germeroth et al. on R-E training reducing spontaneous recovery and renewal of drug craving in SUDs. The effects of R-10 min-E training, NR-10 min-E training, and R-6 h-E training will be compared at 1 day, 1 week, 1 month, and 6-month follow-ups to test for the spontaneous recovery effect after the two intervention sessions, in the meanwhile, craving and reactivity elicited by novel methamphetamine-related cues will be assessed to test the renewal effect. Translational researches on R-E training may help people better understand the mechanism and process of memory reconsolidation. Also, clinical studies provide a new perspective on the treatment of SUDs (49).

Yet, there are still several inconsistent results about the effects of R-E training in some memory studies on conditioned fear (21, 22, 50, 51) or SUDs (52, 53), that may be due to the methodological differences (54) and inter individual differences between studies (55–57), which may result in limited reactivation of previously consolidated memories. From a theoretical perspective, VR appears to be a more useful method to reactivate drug-associated memories as drug-associated cues in VR elicit more stronger craving than drug-associated cues in pictures (24) or videos (25, 26). Using VR can not only present drug-related paraphernalia in proximal confrontation patterns, but also provide interaction with specific drug-related environment or multi-sensorial stimuli (distal risks), which are known to be the most critical triggers of relapse (58, 59). VR might thus offer high-risk methamphetamine-related environments. Then, the methamphetamine-related memories of participants may be reactivated to a labile, modifiable state more probably. To test this inference, the intervention effectiveness of the R-10 min-E group and the RV-10 min-E group in reducing cue-elicited responses will be compared in the present study. VR may be examined to promote the reactivation of drug-associated memories providing the intervention effectiveness is better through using VR to present drug-associated cues than using videos in the retrieval session. On the other hand, VR combined with extinction training may mitigate methamphetamine-related craving or extinguish cue reactivity. It is consistent with a previous study that VR combined with cue exposure treatment made progress in treating nicotine use disorder (60). Through this novel method, the relapse of people with MUD would be in good control when facing similar environments in reality.

There are several limitations to this study protocol. First, considering the feasibility and applicability of the study, the duration of exploring VR may cause discomfort due to the weight of the headset. Second, although VR scenes have been validated to be almost the same as the environments in which participants usually use methamphetamine, it is possible that a proportion of the participants may be unfamiliar with these situations, and therefore they may respond to new stimuli other than methamphetamine-related cues. Third, social interactions (with avatars in VR) are not included in these VR scenes. Future researches should consider employing more diverse designs involving social and personal drug-associated cues or triggers for dynamic plots (e.g., striking a light for methamphetamine or producing smoke) for VR scenes. In addition, there is no exact index to measure the extent of reactivation for drug-associated memories objectively. In this study or future studies, some psychophysiological measures combined with subjectivity experience may be regarded as a reference for the extent of reactivation. More important, as the participants will maintain the abstinence status in the rehabilitation centers when the study protocol are implemented, they will have no access to using methamphetamine that will make some objective measurements to test relapse rate infeasible, such as the urine test and hair test. These tests may be implemented after the participants get out of the rehabilitation centers to confirm the intervention effectiveness in the future.

The present study may extend the efficacy of R-E training on drug-associated memories by combining VR with R-E training to decrease cue-elicited craving and reactivity in people with MUD. The findings of the study may provide initial, compelling evidence that a brief R-E training in VR can attenuate methamphetamine-related craving and cue reactivity, which will have significant implications for relapse prevention and future studies on memory reconsolidation. VR will potentially become a maneuverable and

low-cost approach for presenting controlled, individualized, and ecologically valid high-risk situations to people with SUDs receiving treatments. Ultimately, R-E training combined with VR may be a promising treatment for people with SUDs to prevent relapse.

ETHICS STATEMENT

The ethics committee of the Institute of Psychology (CAS) has approved this protocol (H17015) and the study will be carried out in accordance with the recommendations of this committee. All participants will sign an informed consent form, providing they wish to do so, in accordance with the Declaration of Helsinki and with national and local regulations. The study is registered in the Chinese Clinical Trial Registry (www.chictr.org.cn) with the international standard randomized controlled trial number (ChiCTR1800018899).

AUTHOR CONTRIBUTIONS

WL designed and performed the experiments, and drafted the manuscript. X-JC and Y-TW prepared the published works and participated in the paper writing. MW and PP reviewed and edited the manuscript. LW, Y-LH and H-XC provided instructions for the study materials, computing resources, and laboratory instrumentation. H-XC helped to perform the experiments and to screen the participants. Y-HL guided the study design and directed the experiment implementation.

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Neurocognitive Dysfunctions and Their Therapeutic Modulation in Patients With Methamphetamine Dependence: A Pilot Study

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Aim: Methamphetamine (MA) abuse and dependence are increasing worldwide and are commonly associated with cognitive deficits. Some studies indicate that such impairments can improve if users become abstinent, but overall results remain inconclusive. Hence, we have performed a longitudinal case-control study investigating key surrogates for attention and impulsive decision-making before and after treatment.

Methods: Thirty patients with MA dependence and 24 non–substance-abusing control participants were recruited. Groups were matched on age, sex and education. All subjects performed a baseline assessment to obtain neurocognitive measures of sustained attention and delay discounting. Patients subsequently participated in an MA-specific relapse prevention program including repeated monitoring of relapse status. After 3 months, participants of both groups were reevaluated for neurocognitive performance.

Results: At baseline, MA patients showed a significantly higher number of omissions compared to controls, indicative of lower sustained attention. Interestingly, we observed a steep decrease of omissions in MA patients to control-group level post treatment. On the other hand, MA patients discounted delayed rewards significantly stronger than controls, indicating a more impulsive choice behavior both before and after treatment.

Limitation: The results should be interpreted with care because of the small sample and short follow-up period.

Conclusion: Our data support earlier findings on partial recovery of cognitive deficits in MA patients. They also strengthen the indication for recently recommended psychotherapeutic interventions and may provide a behavioral monitoring tool to inform treatment progress.

Keywords: methamphetamine, crystal meth, sustained attention, delay discounting, psychotherapy

INTRODUCTION

Methamphetamine (MA) also called "crystal meth" is a psychostimulant, whose use has become increasingly popular in several European countries (1). This development reflects its comparably low costs and highly addictive properties. MA abuse and dependence are associated with numerous adverse consequences, which are of great public concern. For example, MA users are more likely unemployed and experience a number of interpersonal difficulties (2). Furthermore, MA users are at high risk for mental and physical health conditions, including depression, anxiety, psychosis, suicide, sexually transmitted diseases and cardiovascular complications (3–5). Consequently, doctors and staff in hospitals, private practices and addiction treatment centers encounter increasing numbers of subjects who suffer from severe complications of MA use. The growing prevalence of MA dependence in Germany prompted the federal government to initiate the development of MA-specific treatment guidelines (6). The areas that are most affected include parts of Saxony, Thuringia and Bavaria. Pharmacotherapy has shown limited effectiveness, making psychotherapeutic interventions the treatment of choice (7). These include cognitive behavioral therapy, motivational interviewing and contingency management, which aim to reduce drug use, positive urine samples and craving. However, such recommendations vastly rely on the transfer of knowledge from overseas and may not be representative of the specific characteristics that are experienced locally. This is especially relevant when mechanistic aspects are not yet fully clarified, which include above all cognitive dysfunctions in MA users and their course under therapy. As such more research is urgently needed to strengthen the evidence for the recommended psychotherapeutic interventions and optimization of care (8).

Compared with other stimulants, MA has a more lipophilic structure and a very long half-life of 8–13h, causing a fast onset and long duration of action in the brain (9). Besides the resulting highly addictive potential through the acute modulation of the monoaminergic system (10), long-term MA exposure produces persistent damage to dopamine and serotonin release in nerve terminals and triggers gliosis and apoptosis (11). Moreover, chronic MA abuse is associated with abnormalities in brain structure, metabolism and functions, predominantly within the frontostriatal and limbic systems (12). Such changes reflect cognitive impairments (13, 14) with pronounced alterations in multiple aspects of attentional control, working memory and executive functions including decision-making (15–19). Clinically, MA-dependent individuals appear distractible and exhibit difficulties in sustaining attention. The ability to keep one's mind continuously focused is considered a fundamental dimension of attentional control with relevance to higher cognitive processes (20). Chronic MA abusers generally show poorer performance than controls on several attention tasks [(18), e.g. CPT and Stroop tasks (19, 21, 22)], linked to MA-associated neuronal damage and network activity in the cingulate and insular cortices (23). Another cognitive domain altered in MA-dependent individuals is impulsive choice behavior with higher rates of delay discounting relative to controls, i.e., the propensity to select an immediate reward at the expense of a greater future reward (24–28). Overly steep discounting is consistently correlated with a range of conditions, including various drug addictions, obesity and schizophrenia (29–32), and suggested to play a causal role in upholding maladaptive behaviors (continued drug taking despite positive long-term outcome of abstinence, e.g., treatment, health, social). Delay discounting in MA abuse is associated with prefrontal inefficiency, an indication of more automatic and diminished deliberate decision-making processes (e.g. habitual response to a cue signaling drug availability) (24). Such impairments in attention and decision-making may thus critically undermine the individual's efforts to stop or reduce MA use, thereby negatively affecting the outcome of treatment including cognitive behavioral strategies. Indeed, a higher number of omissions of target stimuli in attention tasks has been found to predict relapse among recently abstinent MA-dependent patients (33, 34). While maladaptive decision-making has been shown to predict dropout (34), altered neural activity during decision-making may predict relapse (35).

Despite considerable research on adverse functional consequences of chronic MA use and their importance for successful long-term treatment outcomes, the extent to which these problems persist following periods of abstinence remains controversial. Impairments associated with MA use tend to improve with increasing abstinence duration (36–38). The amelioration of cognitive deficits has been shown for short intervals of several weeks (39–41) including attention (42), while other studies have demonstrated that the reinstatement of especially dopamine signaling and associated cognitive functioning may take months to years (16, 36, 43, 44). Moreover, it is still debated whether some of the MA-induced cognitive deficits may be irreversible [e.g. (45)].

The aim of this study was to examine sustained attention and impulsive decision-making in MA-dependent patients and the changes in these domains following a new standardized psychotherapeutic intervention. In addition, we included a healthy comparison sample to help distinguish actual improvement in neuropsychological functioning over time from practice effects. Consistent with previous evidence for partial neurobiological, neuropsychological and psychiatric recovery following treatment of MA-dependent individuals, we hypothesized that sustained attention would improve over a 3-month period while more temporally stable individual characteristics of impulsive choice (46–48) would remain unaltered.

METHODS

Participants

Patients were recruited at the University Hospital Dresden. Study inclusion criteria for MA patients were 18–65 years of age; meeting the diagnostic criteria for MA abuse or dependence according to the International Classification of Diseases (ICD-

10); abstinence from illicit drug use for at least 2 days, proven with negative urine screening results for MA, amphetamines, MDMA, opioids, and THC. Exclusion criteria were any medical conditions, e.g. schizophrenia, severe depressive episodes or limited physical mobility, interfering with the capability to attend group therapy. The assessment of psychiatric comorbidities was supported by a standardized interview using the M.I.N.I. International Neuropsychiatric Interview (49). In addition, non–substance-abusing control subjects (HC) matched for age, sex, and education were recruited *via* advertisements placed on local community-based websites, which offered employment and volunteer opportunities. HC participants were required to have no lifetime experience with any kind of stimulant (MA, amphetamines, MDMA, methylphenidate, cocaine, etc.) and to have never been diagnosed with drug addiction or suspected of having a substance use disorder. Moreover, the presence or history of any psychiatric disease was excluded by applying a standardized questionnaire (including questions such as, "Have you ever been diagnosed with any mental illness?"). In cases of doubt, a psychiatrist was consulted. The final sample consisted of 30 MA-dependent patients (**Figure 1**) and 24 HC subjects. All participants provided written informed consent and received a compensation between 50 and 90€. The study was approved by the local ethics committee of the Technische Universität Dresden and carried out in accordance with the Declaration of Helsinki.

Study Design

Research staff independent of the relapse prevention program conducted the study recruitment as well as baseline (T1) and follow-up (T2) assessments. Assessments comprised a standardized interview to collect socio-demographic information such as age, sex, partnership, migration status, number of children, school, and vocational qualifications as well as current employment status. Participants of both groups then completed a neuropsychological assessment, which encompassed sustained attention and delay discounting as key surrogates for executive function and impulsive decision-making, respectively. After 3 months, subjects completed a follow-up with the same neuropsychological assessment (**Figure 1A**).

Treatment

In- and outpatients were enrolled in our MA-specific relapse prevention program, which is an adaption of the manual by (50) and has demonstrated good feasibility (51) and effectiveness (52) in daily clinical routine. Up to six participants attended 15 twice-a-week group sessions, which lasted 50 min. Sessions were conducted by a psychologist, and the treatment method was based on motivational interviewing. The program's progress and goals emphasized on determining high-risk situations for MA use, providing skills to resolve personal, social and environmental barriers, and enhancing coping methods to prevent relapse. Before the first module, one individual session

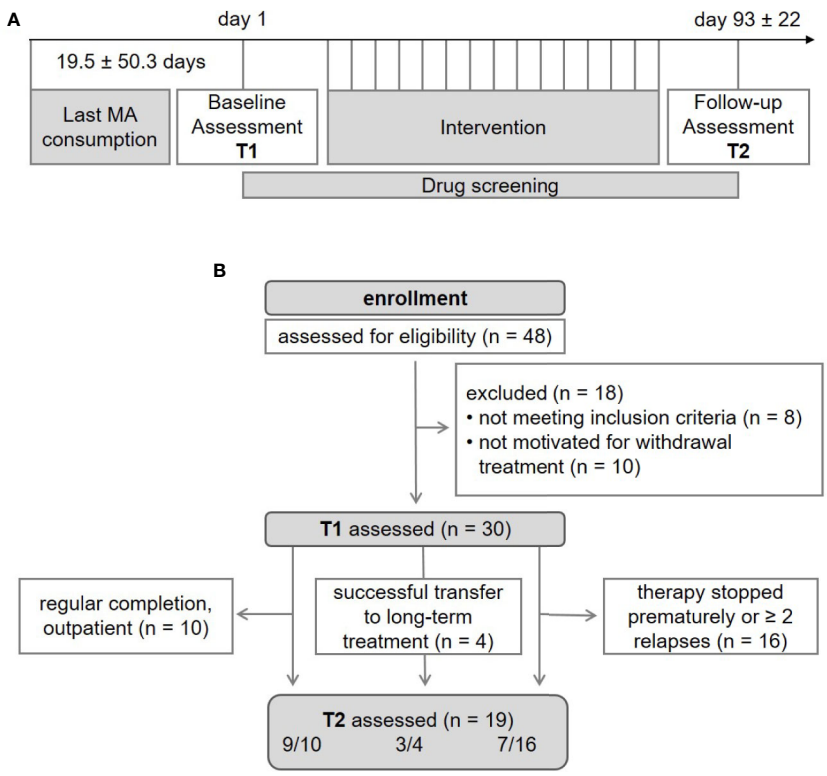

FIGURE 1 | Study overview, recruitment details and sample size of methamphetamine (MA) patients throughout the study process. T1, baseline assessment; T2, follow-up assessment.

took place in which information about the group program and rules was provided, and the willingness to participate was discussed. In detail, the following topics were covered: "Explanation of the Therapeutic Rational" (module 1), "Motivational Clarification" (modules 2 and 6, if necessary repeated throughout therapy), "Craving" (3–5; psychoeducation, identification of triggers, strategies), "Social Risk Situations" (7–9; dealing with social risk situations, rejection training in role plays), "Apparently Harmless Decisions" (10 and 11, psychoeducation and dealing with seemingly harmless decisions), "Personal Risk Situations" (12 and 13, dealing with personal risk situations), "Emergency Plan" (14, preparation of an emergency plan with strategies for coping with high-risk situations), "Change Plan" (15, coping with problems after the end of therapy).

Inpatients provided weekly urine samples. Outpatients were also called unannounced, but randomized in the morning between Monday and Friday with a probability of 1/6 and ordered to provide urine for drug screening. Urine sample delivery took place under personal observation. In addition, manipulations were made more difficult by measuring the urine temperature immediately after delivery. Samples were quantitatively analyzed at the Institute of Legal Medicine at the Technische Universität Dresden and a sum of 300 ng/ml for MA and amphetamines was set as a cut-off for a positive result. Relapse was defined as any positive urine result during the course of treatment.

Treatment was classified as "successful" if the patient was enrolled in a postacute management program or attended at least 8 of 15 group therapy sessions. In addition, maximum one MA relapse until T2 indicated by negative drug tests was allowed, provided the relapse was admitted and self-critically processed. If the therapy was prematurely terminated without following specific long-term treatment or if two relapses occurred, treatment was classified as "unsuccessful". "Retention rate" was assessed as the quotient between number of successful treatment and total number of patients completing T1.

Tasks and Measures

Clinical Data

At T1, MA usage patterns were assessed, which included age of first MA use, total duration of MA use and days of abstinence. Psychiatric comorbidities were recorded according to ICD-10 criteria. A positive family history for the presence of mental disorders in 1st and 2nd degree relatives was systematically inquired according to (53).

Sustained Attention

The sustained attention subtest (SA) of the reliable and valid computer-administered test of Attentional Performance 2.3.1 (54) was used, which takes approximately 15 min. Participants were rapidly presented with individual symbols varying in shape, size, and filling (e.g. a small triangle and a large circle) and asked to press a key if a symbol matched the shape of the symbol presented immediately before. Omissions were recorded as dependent measures, with higher scores reflecting poorer sustained attention (34). Further variables recorded included the number of incorrect answers (errors) and response times.

Impulsive Choice

We used a delay discounting task (DD) in which participants repeatedly needed to choose a smaller immediate amount of money or a greater delayed one (e.g. 2€ now or 8€ in 1 week). Offers were randomly displayed on the left or right side of the screen. There was no time limit for making decisions. To ensure realistic choices and increase task relevance, subjects were informed that at the end of the experiment, one trial would be selected randomly and paid according to the given choice. Monetary rewards ranged from 0.30 to 10€. The subjective evaluation of the offers has been described by a hyperbolic function [e.g. (55)]: $V = A/(1 + kd)$, where V represents the subjective value of the amount A after a delay d (3, 7, 14, 31, 61, 180, or 365 days) and k is a free parameter representing the discount rate. Larger k values represent preference for immediate amounts, which has been interpreted as impulsive choice behavior. To provide behavioral estimates, an adaptive procedure for binary choice presentation was used. For a detailed description of the mathematical framework see (56) and for an application of the task in a clinical cohort of patients with alcohol use disorder see (32). Briefly, a trial-by-trial adaptive approach was chosen to present participants with choice options near their individual indifference point at each trial, thus allowing for fast assessment of individual parameters of behavior. The likelihood of choosing between the two offers followed a softmax probability function: $P(a1|\ k, \beta) = 1/(1 + \exp[\beta (V2 - V1)])$, where V1 and V2 are the subjective values of the offers and $\beta > 0$ serves as a consistency parameter. The algorithm started from liberal prior distributions on the parameters and, after observing a choice at each trial, updates the belief about the parameters using the Bayes' rule: $P(k, \beta|\ choice) \propto P(k, \beta|choice)\ P(k, \beta)$. The procedure continued for 50 trials and the estimates at the final trial were considered the best-fitting parameters for a participant. The distribution of parameter estimates over task progression was plotted and found to converge well, yielding stable final estimates of choice behavior (**Supplementary Figure 1**). Recorded variables included: $\log[k]$ as an estimate of discounting behavior, $\log[\beta]$ as a measure of consistency of choice behavior and for each trial the time to make a decision.

Data Analysis

Data were initially analyzed with SPSS version 25. Histograms, box plots, and Shapiro tests were employed to judge parameter distribution. Differences between groups in socio-demographic and cognitive variables were evaluated using appropriate parametric or nonparametric tests comparing two independent groups as specified in **Tables 1** and **2**. Logistic regression analyses with forward stepwise selection was used for outcome prediction in MA patients as previously described (52). Individual median response times over all trials were used for group-wise analysis. Longitudinal analyses of pre- and posttreatment cognitive assessments were conducted using R 3.2.3 (R Development Core Team, 2015). We used mixed-effects models (lmer, R-package: lme4); for DD: prediction of log[k] out of time, group and their interaction; for SA:

TABLE 1 | Socio-demographic and clinical data at T1 and T2.

Characteristic	Group		Comparison	
	MA (n = 30)	HC (n = 24)	*Test value*	*p*
Socio-demographic data				
Age (years)	29.0 ± 6.8	28.8 ± 5.6	0.121[a]	.904
Sex (females)	36.7 (11)	33.3 (8)	0.065[b]	.799
Partnership	43.3 (13)	62.5 (15)	1.962[b]	.161
Migration	2.5 (1)	7.5 (3)	1.634[b]	.201
Children	63.3 (19)	50.0 (12)	–1.335[c]	.182
Education*	76.7 (23)	70.8 (17)	0.236[b]	.627
Unemployment	70.0 (21)	20.8 (5)	13.900[b]	**.001**
Clinical data				
Age of first MA use (years)	19.2 ± 5.2	N/A	N/A	N/A
MA abuse duration (years)	7.0 ± 4.3	N/A	N/A	N/A
Abstinence (days)	19.5 ± 50.3	N/A	N/A	N/A
Psychiatric comorbidities	53.3 (16)	N/A	N/A	N/A
Medication	16.7 (5)	N/A	N/A	N/A
FH+	43.3 (13)	N/A	N/A	N/A

Descriptive statistics (mean ± SD or % (N)) and results of group differences. MA, methamphetamine patients; HC, healthy controls; FH+, positive family history for psychiatric disorders according to first-degree relatives.
**secondary school or lower.*
[a]t (paired t-test).
[b]Pearson chi-square (exact chi-square test).
[c]Z (Wilcoxon matched pairs rank sum test).
In bold: significant at p < 0.05.

prediction of omissions out of time, group and their interactions. Following, we assessed the effect of comorbidity on the results found using mixed-effects models including the factors time and the presence/absence of an additional psychiatric disorder. We report estimates, standard deviations, t-values and p-values derived using Satterthwaite approximations. An alpha level of 0.05 was set for the determination of statistical significance.

RESULTS

Sample Description

Socio-demographic and clinical characteristics of patients and controls are summarized in **Table 1**. Statistical analyses showed no significant difference in age, sex and education. However, unemployment was significantly more frequent in MA patients as expected. Fifty-three percent (n = 16) of participants with MA

TABLE 2 | Summary statistics of experimental parameters.

	T1				
	MA (n = 30)	HC (n = 24)	*Test value*[a]	*p*	*d*
Sustained Attention					
errors	8.93 ± 19.10	10.79 ± 37.02	-0.238	.812	–0.07
omissions	10.63 ± 8.48	4.00 ± 3.65	3.569	**.001**	0.98
response time (ms)	558 ± 130	515 ± 118	1.252	.216	0.34
Delay Discounting					
log[k]	–2.2 ± 2.3	–3.9 ± 2.1	2.565	**.013**	0.70
log[β]	–1.6 ± 1.8	–1.9 ± 1.5	0.808	.423	0.22
deliberation time (s)	2.2 ± 0.8	2.0 ± 0.6	0.935	.354	0.26
	T2				
	MA (n = 19)	HC (n = 17)	*Test value*[a]	*p*	
Sustained Attention					
errors	4.77 ± 5.31	5.61 ± 14.32	–0.231	.818	–0.08
omissions	5.44 ± 7.16	4.11 ± 4.93	–0.650	.520	0.22
response time (ms)	504 ± 107	535 ± 124	–0.796	.434	–0.26
Delay Discounting					
log[k]	–2.3 ± 2.4	–4.1 ± 1.7	2.451	**.021**	0.86
log[β]	–1.8 ± 1.1	–1.7 ± 1.0	–0.451	.655	–0.15
deliberation time (s)	1.8 ± 0.6	1.9 ± 0.5	–1.011	.322	–0.34

MA, methamphetamine patients; HC, healthy controls; d, Cohen's d; log[k], discounting parameter; log[β], consistency parameter.
[a]t (paired t-test).
In bold: significant at p < 0.05.

dependence did present psychiatric comorbidities at the time of treatment: five suffered from unipolar depression, two from attention deficit hyperactivity disorder (ADHD), three had drug-induced psychosis before the start of the study, and one patient had posttraumatic stress disorder and dissocial personality disorder. One patient had ADHD combined with a borderline personality disorder. One patient was diagnosed with three comorbidities: ADHD, a unipolar moderate depressive episode and a borderline personality disorder. Of these 16 comorbid patients, five additionally showed a harmful use of cannabinoids and four an alcohol dependence. Five (16.7%) patients were prescribed regular psychotropic medication during the study period: one patient received doxepin, one patient sertraline, one patient olanzapine, one patient a combination treatment of duloxetine and quetiapine, and one patient methylphenidate. Clinically, none of these patients were significantly affected by the medication.

Outcome at Follow-Up

T2 data were obtained from 70% (n = 17) of HC and 63.3% (n = 19) of MA patients initially included. Treatment outcome and participant characteristics of the extended MA patients sample (successful vs. unsuccessful) are reported elsewhere (52). Measures in our subsample (one patient diagnosed with schizophrenia excluded) were comparable. In summary, the treatment was classified as successful in 14 of 30 patients (46.6%). Four of these patients were transferred to a specific long-term treatment and 10 patients into a specific postacute outpatient treatment setting at our department. By contrast, the treatment was considered not successful in 16 cases, i.e., patients had more than one relapse with MA during the study or prematurely terminated the program (**Figure 1B**). Correlational analysis showed trend-level significance for longer regular MA use in men across groups (r = 0.359, p =.051). Moreover, patients with an unsuccessful outcome were predominantly male (81.3%). The abstinence period before baseline (T1) tended to be longer in patients with a favorable outcome (U = 71.500, z = −1.693, p =.093), without being significantly correlated with sex (ρ = −0.100, p =.597) or the duration of regular MA use (ρ = −0.134, p =.479) across groups. Among the demographic and clinical variables, the only predictor significantly increasing the odds of a successful outcome was a shorter period of regular MA use (OR = 1.342, CI 95% for OR = 1.028–1.753, b = 0.294, SE = 0.136, p =.031).

Sustained Attention

Recorded variables and test statistics can be found in **Table 2**. There were no differences between groups in the number of incorrect answers (errors) and response times. Analysis of omissions over groups and time points showed a significant effect of time (Estimate = −4.66, SD = 1.45, t = −3.22, p =.003), group (Estimate = −11.3, SD = 3.31, t = −3.42, p =.001) and a significant interaction effect (Estimate = 4.66, SD = 2.09, t = 2.23, p =.032). At baseline, MA patients had significantly more omissions, indicative of poorer SA. Over time, the patient group showed a steep decline of omissions, while the control group remained on the same level (**Figure 2**). Analysis of MA patients controlling for comorbidity similarly showed a significant effect of time (Estimate = −4.35, SD = 1.71, t = −2.536, p =.002) but no effect of comorbidity (Estimate = 2.49, SD = 2.79, t = 0.892, p =.379) (**Supplementary Fig. 2**). Baseline performance in SA did not significantly differ between patients who finished the program and patients who prematurely stopped treatment (**Supplementary Fig. 3**).

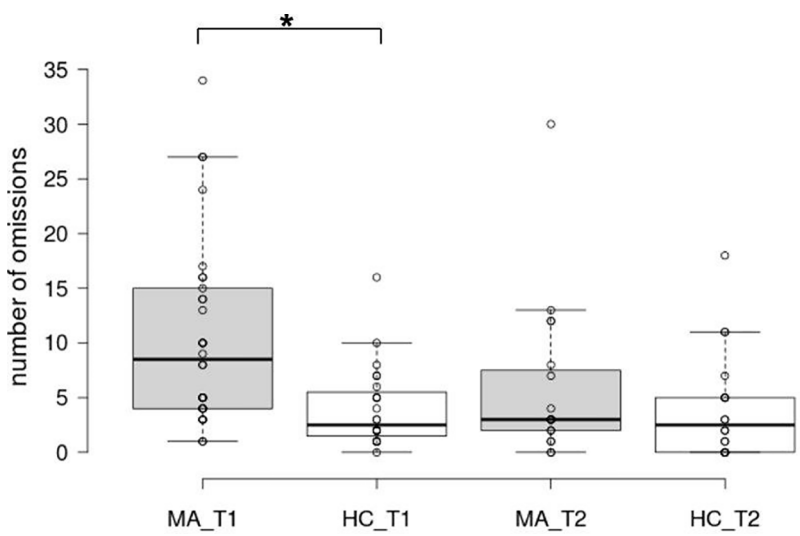

FIGURE 2 | Box plots of omissions in the sustained attention task. The horizontal line represents the median; the boxes extend to the 1st and 3rd quartile, while whiskers extend to the max/min or the corresponding quartile + 1.5 IQR. Additionally, each data point is visualized. MA_T1, MA patients at baseline; HC_T1, control group at baseline; MA_T2, MA patients at follow-up; HC_T2, control group at follow-up; *, significant main effect of group.

Impulsive Choice

Estimates of choice behavior and deliberation times as well as test statistics can be found in **Table 2**. Analysis showed a group effect for DD (Estimate = −2.02, SD = 0.99, t = −2.04, p = 0.04) with MA patients having significantly higher estimates, indicating that they chose the immediate option more often and thus were more impulsive (**Figure 3**). For discounting estimates, there was neither a significant change in time from T1 to T2 (Estimate = 0.11, SD = 0.41, t = 0.26, p = 0.791) nor a significant interaction effect (Estimate = 0.42, SD = 0.59, t = 0.71, p = 0.487). Analysis of MA patients controlling for comorbidity similarly showed no significant effect of time (Estimate = 0.02, SD = 0.49, t = 0.04, p = 0.973) and comorbidity (Estimate = 0.59, SD = 1.44, t = 0.415, p =.681). No significant differences between groups were observed for consistency of choices and deliberation times.

DISCUSSION

The main aim of the present study was to determine whether cognitive impairments in attention and impulsive choice behavior in recently detoxified MA patients recover during a 3-month program, which included psychotherapy and regular drug screening. Our results showed that baseline performances in sustained attention, which were inferior compared with those of controls, improved so much during this period that they were no longer impaired at the follow-up session. In contrast, more impulsive delay discounting in MA patients compared to controls did not change over time.

Baseline differences between groups in both cognitive domains tested in this study are in line with a range of prior studies (13, 22, 24, 26, 28, 33, 43, 57–59). Thus, attentional deficits and choice behavior favoring immediate rewards are consistently associated with MA use. On the other hand, decision speed of MA patients has been found unaltered previously (25, 60) as well as in our sample in which performance demonstrated no group effect. Observed heightened impulsive behaviors may predict drug use or can be a consequence of repeated drug exposure and withdrawal (61). However, impulsivity is a multifaceted construct and impulsive choice behavior might undergo a developmental change that parallels drug consumption as directly observed in rodent studies [e.g. (62)] and suggested from human work in addiction [c.f. (32)]. On the neurobiological level, neurotoxic effects of MA and adaptive changes in the structure of brain regions involved in motivation, reward and the top-down control of behavior may be causal (21, 23, 27, 63–65). This is complemented by functional magnetic resonance imaging findings of lower activation in the frontal cortices in MA users during attention (66) and decision-making tasks (24, 25, 35, 67), reflective of reduced resources to process information and subsequent performance deficits. In addition, as MA users often lack appetite and therefore stop regular eating, nutritional effects on brain metabolism may also contribute to the observed cognitive dysfunctions (68). Our data thus further support the notion that chronic MA abuse is linked to cognitive dysfunction and may cause cognitive decline (69, 70).

Our main finding suggests an improvement of sustained attention performance when compared to levels of control subjects, while performance in controls did not improve over time. Observed effects may be specific to the treatment or represent a subgroup of patients completing treatment. The design of the present study did not include a control group for the intervention. Nevertheless, *post hoc* analysis showed that baseline performance in sustained attention was not divergent

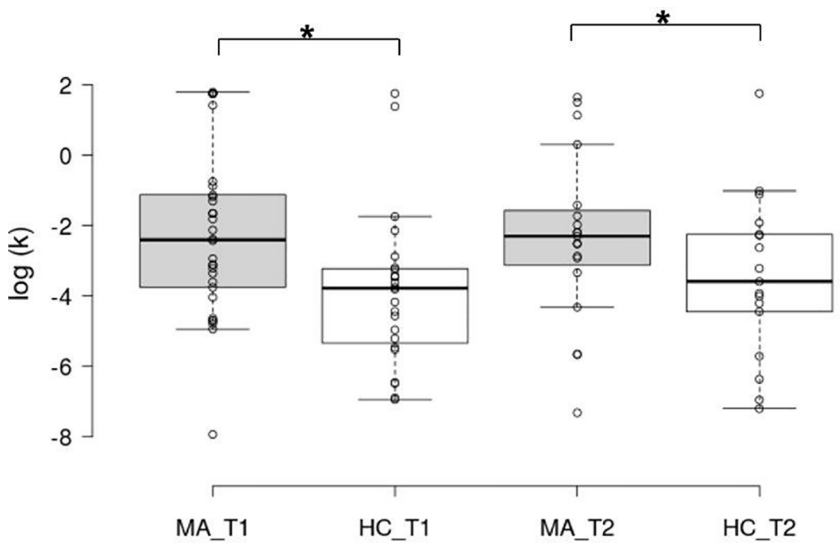

FIGURE 3 | Box plots of the decision-making parameter from the delay discounting task in log scale. The horizontal line represents the median; the boxes extend to the 1st and 3rd quartile, while whiskers extend to the max/min or the corresponding quartile + 1.5 IQR. Additionally, each data point is visualized. MA_T1, MA patients at baseline; HC_T1, control group at baseline; MA_T2, MA patients at follow-up; HC_T2, control group at follow-up; *, significant main effect of group.

between patients who finished the program and those who prematurely stopped treatment, which allows supportive evidence for a treatment effect. This speculation however warrants further assessments. Existing cross-sectional studies already illustrate comparable neuropsychological test performance in MA users and non-MA–using controls following periods of abstinence, i.e. ≥ 8 months (16, 43, 71), reflecting that there may indeed be recovery of cognitive functioning following protracted abstinence (38). Other studies evaluating subjects with shorter periods of abstinence (5 days to 3 months) report observable deficits in a number of cognitive domains such as attention, episodic memory and executive functions (39, 41). Yet, these findings likely align with baseline deficits observed in our study with mean days of abstinence at baseline assessment in the range of these reports. Longitudinal studies that have examined the effects of abstinence on cognitive functioning in MA users when tested in early abstinence and again in later abstinence, similarly yield some evidence for functional recovery. In short observation periods (≤ 3 weeks), MA-dependent individuals have been found to improve their performance on neuropsychological tests including attention (42) and executive functioning (40). Longer periods of abstinence may also improve motor and verbal memory (36, 72). However, these studies did not include a control group for re-test effects, thus limiting conclusions on the causal role of abstinence in performance changes. The inclusion of such a control group clearly represents an important advance of the present study, strengthening our findings of attentional improvements. In support, normalization of global cognitive function in MA-dependent participants after an average of 1 year abstinence from MA has been reported in one study, which also included a control group for longitudinal effects (73).

Finally, relevant to improvements in function, there is evidence for some of the MA-associated changes on the neurobiological level to recover following periods of abstinence. This has been illustrated in human studies for MA-associated brain metabolism and monoamine system abnormalities (36, 40, 72, 74, 75) and structural alterations, e.g. prefrontal grey-matter deficit (71). Similar results have been obtained in primate (76) and rodent studies (77). Nonetheless, discordant findings in the literature examining cognitive functions and neurobiological alterations in MA users following abstinence exist [see (23)] and have been discussed to reflect differences, e.g. in study design but also important clinical characteristics such as length of abstinence. Meta-analyses, however, do not imply such an association between length of abstinence and functional impairments in MA users (58, 60).

An alternative explanation is provided if not global cognitive function but single performance domains recover over different time scales following periods of abstinence while others may even persist. This idea was put forward together with the notion that neurobiochemical alterations in the monoamine system are likely most pronounced and persistent in e.g. dopamine rich regions (72). In light of the present study this implies that performance in sustained attention, which is highly related to activity measures in the prefrontal cortices (78) and moderately innervated by dopaminergic fibers, follows an early path of recovery, while impulsive choice and decision-making are additionally dependent on high striatal activity (79), the main target of dopamine fibers. This is also in line with the idea of delay discounting representing "more" trait-like features, while sustained attention is highly state-dependent. For discounting to change, conditions must change, and the individual must adapt to the new state, which may take time but may also be drug-dependent (80).

Clinical Relevance

Attentional ability is a critical aspect in processing environmental stimuli during decision-making and highly relevant for long-term treatment success. Pharmacological treatment studies using modafinil or ibudilast have shown some positive effects on the attentional capacity in recently detoxified MA patients (20, 81). Our data provide the first evidence that sustained attention can substantially improve during a 3-month MA-specific relapse prevention program based on cognitive behavioral therapy and motivational interviewing. This is in line with available clinical and preclinical evidence suggesting that cognitive stimulation may provide a valuable adjuvant intervention for drug addiction (82). Interestingly, a recent review shows that individual rates of delay discounting can decrease through behavioral training, endorsing context-dependent and changeable attributes in impulsive choice behavior. The most promising avenues in this regard seem to be acceptance-/mindfulness-based trainings and manipulations involving future orientation (83). Thus, we cannot exclude that impulsive choice, which did not normalize after 3 months in our study, would have improved after a longer recovery time or after implementing the aforementioned treatment modules. Although studies are required to identify explicit modules and their mechanisms, interventions that improve such cognitive domains or target activity in relevant networks are promising for the long-term reduction of MA intake and prevention of relapse.

Limitations

It should be emphasized that this work can only be considered as a pilot study. Firstly, our findings are limited by the relatively small sample size providing low power for within-subject analyses. The small sample size additionally limited analysis to evaluate effects of medication and comorbid diagnoses. The presence of a dual diagnosis in MA users can worsen craving (84) and may thus affect behavior and relapse. While the evaluation of specific comorbid diagnoses was impossible, we could confirm our main results when including the presence/absence of psychiatric comorbidity in our model. Moreover, the number of cases with medication was too small for systematic investigations on medication effects, which represents a shortcoming as medications have been found to modulate attention performance in patients and animal models (85, 86). Secondly, no control group for intervention was included and we thus encourage similar research to address specific intervention effects. Finally, multiple measures are required to inform more rigorously about the nature and degree of deficits in different

domains of attention and their developmental course under therapy. These include focused, selective, alternating and divided attention in which problems—if they significantly persist into abstinence and recovery—could result in treatment failure and return to regular MA use (87). On the other hand, our study has several strengths, exemplified by the longitudinal HC group and a naturalistic sample of MA patients with comorbid psychiatric disorders and drug abuse histories.

CONCLUSION

The current study in MA patients shows that sustained attention significantly improved under treatment conditions. Our work thus lends support to the recommended psychotherapeutic interventions. Further measures of sustained attention may even present a valuable tool of parallel clinical monitoring informing treatment progress.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethics committee of the Technische Universität Dresden. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP and UZ designed the study. NB, SP, and MS developed the delay discounting task. CG, AS, and MP contributed to study management, data collection and processing. RM-P, NB, JP, and SP analyzed the data. NB, JP, and MP wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00581/full#supplementary-material

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