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Extended methamphetamine self-administration enhances reinstatement of drug seeking and impairs novel object recognition in rats

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Abstract

Rationale—Methamphetamine is a highly addictive psychostimulant, and chronic methamphetamine users show high rates of relapse. Furthermore, prolonged methamphetamine abuse can lead to psychiatric symptoms and has been associated with various cognitive dysfunctions. However, the impact of self-administered methamphetamine on cognitive dysfunction and relapse has not been concurrently examined in an animal model.

Objectives—The present study determined the effects of short- vs. long-access contingent methamphetamine on self-administration, extinction responding, reinstatement of methamphetamine seeking, and cognitive performance on an object exploration task.

Materials and methods—Long-Evans rats self-administered methamphetamine i.v. (0.02 mg/infusion) or received saline during daily sessions (1 or 2 h) for 10 days, followed by either maintained short- (1 or 2 h) or long-access (6 h) self-administration for 14 days. Lever responding was extinguished prior to reinstatement, which consisted of presentation of drug-paired cues or a priming injection of methamphetamine (1.0 mg/kg). Animals were also tested on an object exploration task prior to self-administration and at 10–12 days after cessation of self-administration, thus providing a comparison of pre-methamphetamine exposure with post-methamphetamine exposure.

Results—Long-access methamphetamine self-administration resulted in escalation of daily intake. Furthermore, animals in both short- and long-access groups showed robust conditioned-cued and drug-primed reinstatement, with long access resulting in enhanced methamphetamine-primed reinstatement. Methamphetamine self-administration also led to access-dependent impairments on novel object recognition but failed to impair recognition of spatial reconfiguration.

Conclusions—Extended methamphetamine self-administration enhances drug-primed reinstatement and decreases novel object recognition, indicating that prolonged contingent methamphetamine increases motivation for drug seeking following withdrawal while increasing cognitive deficits.

Keywords

Cognitive; Extinction; Methamphetamine; Novel object recognition; Reinstatement; Relapse; Self-administration

Introduction

Methamphetamine addiction constitutes a serious problem due to the intensely addictive nature of the drug and the myriad health effects in chronic methamphetamine users (Brecht et al. 2005). Aside from public health concerns (e.g., increased rates of sexually transmitted diseases), methamphetamine addiction poses greater concern than other drugs of abuse, given its capacity to produce deleterious psychiatric symptoms and cognitive impairments. Methamphetamine abuse contributes to depression, aggression, anxiety, attention deficits, and a variety of cognitive deficits (Meredith et al. 2005). Clinical data indicate that long-term methamphetamine users exhibit deficits in specific tests of cognitive function, such as poor recall for both words and pictures (Simon et al. 2000; Woods et al. 2005), impairments of decision making (Paulus et al. 2002), vigilance task performance (London et al. 2005), and verbal encoding and retrieval (Woods et al. 2005). In addition, methamphetamine addicts perform worse than healthy control subjects on tasks requiring attention, working memory, and/or executive function (Kalechstein et al. 2003). However, clinical studies cannot determine a subject's pre-existing cognitive abilities and the true extent of impact from methamphetamine on these measures.

Studies of repeated methamphetamine exposure in animals have demonstrated impairments in sequential motor learning (Daberkow et al. 2005), increased impulsivity (Richards et al. 1999), and decreased novel object recognition (Belcher et al. 2005; Kamei et al. 2006). However, these studies have all utilized non-contingent, short-term drug administration, an approach that does not approximate the contingent, long-term drug use in humans. Furthermore, the use of non-contingent experimental paradigms does not allow for an examination of the relationship between the motivational (i.e., drug seeking) and cognitive aspects of methamphetamine addiction. A considerable number of studies have examined cocaine self-administration and reinstatement of cocaine-seeking behavior, as well as the underlying neural circuitry that mediates relapse to cocaine seeking (McFarland and Kalivas 2001; See 2005; Shalev et al. 2002). In contrast, there are relatively fewer studies of methamphetamine self-administration and reinstatement (Hiranita et al. 2006; Kruzich and Xi 2006; Moffett and Goeders 2007; Shepard et al. 2004), and none of these studies has examined the cognitive consequences of prolonged methamphetamine intake. In addition, most studies using methamphetamine self-administration have employed relatively short daily access to the drug (1 or 2 h/day). Longer daily access (e.g., 6 h/day) to cocaine sometimes results in an escalation of drug intake (Ahmed et al. 2002; Ferrario et al. 2005; Vanderschuren and Everitt 2004) and can increase the magnitude of reinstatement produced by cues or drug priming injections (Kippin et al. 2006). Of particular importance for methamphetamine is the possibility that extended daily drug access may produce cognitive deficits that are akin to those seen in human methamphetamine addicts who undergo repeated binge administration.

Thus, the current study explored the motivational and cognitive consequences of short- vs. long-access methamphetamine self-administration. We hypothesized that greater methamphetamine self-administration would lead to enhanced daily drug intake, impaired novel object recognition performance, and significantly greater reinstatement of drug-seeking behavior. Furthermore, by combining assessment of both motivational and cognitive domains in a valid animal model of methamphetamine addiction and relapse, we hope to improve the ability to test behavioral and pharmacological interventions for methamphetamine abuse and dependence.

Materials and methods

Subjects

Male Long-Evans rats ($n=31$; Charles-River; 275–300 g) were individually housed in a temperature- and humidity-controlled vivarium on a 12-h reversed light–dark cycle (lights off 6 A.M. to 6 P.M.). Animals were provided water ad libitum and maintained on 25 g of standard rat chow (Harlan, Indianapolis, IN, USA) per day until the maintenance phase of self-administration, at which time the animals were maintained on ad libitum food. Procedures were conducted in accordance with the “Guide for the Care and Use of Laboratory Rats” (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, 1996) and approved by the IACUC of the Medical University of South Carolina.

Apparatus and lever training

Testing was conducted in self-administration chambers (30×20×20 cm, Med Associates) linked to a computerized data collection program (MED PC). Each chamber was contained within a sound-attenuating cubicle and equipped with two retractable levers, two stimulus lights, a speaker for tone delivery, and a house light. The house light always signaled the initiation of a session. Prior to surgery, rats were food-deprived overnight and trained to respond on a lever for 45 mg food pellets along a fixed ratio 1 schedule of reinforcement during a single overnight session. After food training, the food pellet hoppers were removed from the test chambers for all subsequent sessions.

Surgical procedures

Rats were anesthetized i.p. with ketamine (66 mg/kg), xylazine (1.3 mg/kg), and equithesin (0.5 ml/kg). Catheters were constructed using previously described methods (Fuchs et al. 2004) by gluing Silastic tubing (12 cm; ID= 0.64 mm; OD=1.19 mm; Dow Corning Corporation) to an external guide cannulae (Plastics One Inc.). The cannulae were then glued to Marlex mesh with cranioplastic cement. The external guide cannulae exited on the rat's back, and the free end of the Silastic tubing was inserted 33 mm into the right jugular vein and secured with 4.0 silk sutures. Both incisions were sutured and treated with antibiotic ointment. An antibiotic solution of cefazolin (10 mg/0.1 ml, IV; Schein Pharmaceuticals, Florham Park, NJ, USA) was infused post-surgery, and each subject received 0.1 ml of heparinized saline (10 U/ml) prior to each session and cefazolin with 70 U/ml heparinized saline following each session. To verify catheter patency, rats occasionally received 0.12 ml of methohexital sodium (10.0 mg/ml i.v.; Eli Lilly, Indianapolis, IN, USA), a short-acting barbiturate that produces a rapid loss of muscle tone.

Methamphetamine self-administration

Infusion tubing for methamphetamine administered intravenously was enclosed in a wire coil and screwed to the external catheter mount on the rat's back. A weighted swivel apparatus (Instech) allowed for free movement within the chamber. Methamphetamine hydrochloride (Sigma-Aldrich Co., St. Louis, MO, USA) was mixed in sterile saline and filtered (0.45 μ m) prior to i.v. administration (0.02 mg/50 μ l bolus). We selected this dose based on previous studies of methamphetamine self-administration in rats (Anggadiredja et al. 2004a; Roth and Carroll 2004a). During daily sessions, a response on the active lever resulted in a 2-s infusion, followed by a 20-s time-out period to prevent overdose. Each infusion was paired for 5 s, with a tone (78 dB, 4.5 kHz) and the white stimulus light over the active lever. Response during the time-out or on the inactive lever was recorded but resulted in no programmed consequences.

Animals were tested in two cohorts, but the timeline was identical for each rat as shown in Fig. 1. In the first experiment, self-administration occurred in daily 2-h sessions for 10 days, after

which the rats were assigned to stay on 2-h access or proceed with long-access (6 h) sessions for 14 days. In the second experiment, self-administration occurred in daily 1-h sessions for 10 days, after which the rats were assigned to stay on 1-h access or proceed with long-access (6 h) sessions for 14 days. Rats were distributed to access conditions such that no a priori differences existed in prior drug self-administration for short- vs. long-access groups. Subsequent analyses showed no differences in the 6-h group due to the initial daily access experience (1 or 2 h). The second cohort also included yoked saline controls, whereby rats were attached to an infusion line identical to that used for methamphetamine self-administration; however, the yoked subjects received 50- μ l infusions of 0.9% saline during daily 1- ($n=2$) or 6-h ($n=4$) sessions whenever the matched self-administering subject received a methamphetamine infusion. Thus, the whole study consisted of three chronic drug self-administration groups: 1 ($n=6$), 2 ($n=8$), and 6 h ($n=11$), plus the non-contingent yoked saline control group ($n=6$).

Extinction

After the last day of self-administration, rats experienced daily 1-h extinction sessions. Responses on either the active or inactive lever were recorded but resulted in no programmed consequences [i.e., no infusions and no conditioned stimulus (CS) presentations]. Animals continued under extinction conditions until they reached a criterion of a minimum of 10 days and <25 lever presses per session for two consecutive days.

Reinstatement procedures

Following extinction, rats underwent two reinstatement tests with a minimum of 2 days of extinction between each test. During the conditioned-cued reinstatement test, rats were placed into the chambers for 1 h, and each active lever press resulted in a 5-s CS presentation in the absence of drug reinforcement. For the drug-primed reinstatement test, a single, non-contingent dose of methamphetamine (1 mg/kg, i.p.) was administered 30 min prior to the 1-h session, and lever responses had no programmed consequences. Conditioned-cued reinstatement was always conducted first, followed by drug-primed reinstatement, in order not to affect conditioned-cued reinstatement with prior non-contingent methamphetamine exposure. Multiple reinstatement trials of this type have been successfully utilized by our laboratory (Fuchs et al. 2004; Kippin et al. 2006) and others (Shaham et al. 2000).

Object exploration task

All animals were tested on an object exploration task just prior to self-administration and once again 2 days prior to the first reinstatement test, allowing for comparison of pre-methamphetamine exposure with post-methamphetamine exposure. The procedures were adapted from those used previously (Lee et al. 2005; Rogers and Kesner 2007). The test apparatus consisted of a round wood board (121-cm diameter, 3.5-cm thickness, 65 cm above the floor, painted white) and a video camera positioned above the board collected data, which was electronically scored using Smart software (version 2.5, Panlab s.l.). A total of 12 toy objects were used: six objects prior to self-administration and six new objects prior to reinstatement testing. As seen in Fig. 2, the task consisted of seven sessions lasting 6 min each, with an inter-session interval of 3 min, during which the rat was returned to its home cage. During session 1 (familiarization), each rat was introduced to the board without any objects present. In session 2 (object introduction), five objects (A–E) were placed at pre-determined locations, and the rat was allowed to explore freely. Sessions 3 and 4 involved the same object orientation as session 2. Session 5 (spatial reconfiguration) was a reconfiguration of some of the stimuli, whereby object E moved to the position of object D, and object D was displaced to a new spatial location. Session 6 (habituation) involved the same orientation of objects as session 5. Session 7 (novel object introduction) involved the introduction of a novel object,

whereby object A' replaced object A, with the remaining objects staying the same as in session 6. The distance traveled during each session (in centimeter) allowed for determination of general locomotor activity. Time spent actively exploring the displaced objects relative to the non-displaced objects in session 5 measured spatial reconfiguration time. Finally, time spent actively exploring the novel object relative to the original objects during session 7 measured novel object recognition time.

Statistical methods

Daily methamphetamine intake (milligram per kilogram) and rates of lever responding during methamphetamine self-administration sessions were analyzed using repeated measures analysis of variance (ANOVA). Lever responding during extinction and on tests of reinstatement was also assessed by ANOVA. Post hoc comparisons between individual groups were conducted using the Tukey's test for pairwise comparisons. For object exploration, a one-way ANOVA compared the group effects during spatial reconfiguration or novel object recognition. Activity levels were compared using repeated measures ANOVA, with group (between subjects) and session (within subject) as variables. In order to assess relationships between tests, nonparametric Spearman rank correlations were used to assess associations between novel object recognition on the post-test and first hour intake, maintenance self-administration intake, cue-induced reinstatement, and drug-primed reinstatement. Furthermore, a separate assessment was conducted between drug-primed reinstatement and first-hour intake, maintenance self-administration intake, and cue-induced reinstatement. Tests on novel object recognition on the post-test and drug-primed reinstatement were considered separate a priori hypotheses, so a Bonferroni adjustment was used within the group of tests for each of these outcomes. Thus, four comparisons were made for novel object recognition and three for drug-primed reinstatement. Since a log10 transformation normalized drug-primed reinstatement data, we also considered univariate linear regressions, with log10 prime as the outcome and each of the variables above as predictors in order to quantify the linear effect of each predictor on prime.

Results

Methamphetamine self-administration varies over time based on daily access

Prior to being assigned to short- or long-access groups, rats were allowed to self-administer methamphetamine for 1 or 2 h/day for 10 days in order to achieve stable self-administration prior to being allocated to different access conditions. Active lever responding for the last 3 days of this acquisition phase was 39.3 ± 3.1 for subjects on 1 h/day and 59.8 ± 2.7 for subjects on 2 h/day. Daily methamphetamine intake was 1.32 ± 0.10 mg/kg for subjects on 1 h/day and 2.31 ± 0.09 mg/kg for subjects on 2 h/day.

Figure 3a shows active (drug-paired) lever responding across the 14 days of methamphetamine maintenance. Repeated measures ANOVA revealed no significant effects of time for the 1-h group, but a significant main effect for the 2- ($F_{13, 91} = 2.25, p < 0.05$) and 6-h ($F_{13, 116} = 4.98, p < 0.001$) groups. Post hoc analyses comparing lever responding on day 1 with subsequent days showed significant increases ($p < 0.05$) for day 8 in the 2-h group and for days 11–14 for the 6-h group. Similar to lever responses, daily methamphetamine intake (mg/kg/session) increased across the 14 days of maintenance as seen in Fig. 3b. There were no significant effects of time for the 1-h group but a significant main effect for the 2- ($F_{13, 91} = 2.00, p < 0.05$) and 6-h ($F_{13, 129} = 8.31, p < 0.001$) groups. Comparisons of methamphetamine intake on day 1 with subsequent days showed significant increases ($p < 0.05$) for day 14 in the 2-h group and for days 5–6 and 8–14 in the 6-h group. Finally, Fig. 3c illustrates the amount of methamphetamine intake (milligram per kilogram per hour) during the first hour of each session. No significant escalation was seen for the 1-h group, but significant main effects were found for the 2-

($F_{13, 91}=8.31, p<0.01$) and 6-h ($F_{13, 129}=3.54, p<0.001$) groups. Although there was an overall increase in first hour drug intake in these two groups, the effect magnitude was rather small. Post hoc analyses only showed significant increases ($p<0.05$) for days 9 and 10 in the 2-h group and day 12 in the 6-h group.

Long-access methamphetamine exposure does not alter extinction responding or conditioned-cued reinstatement but enhances methamphetamine-primed reinstatement

When methamphetamine was no longer available, lever responding readily declined across daily extinction sessions, as seen in Fig. 4 (top panel). Since the extinction session duration was the same for all access groups (1 h), we used a 2-way ANOVA, which revealed a significant main effect for day ($F_{9, 198}=1.95, p<0.05$), but there was no effect for access condition nor was there an interaction of day $\times$ access condition. Thus, all groups extinguished equally prior to reinstatement testing. Figure 4 (bottom left) shows responding on the previously drug-paired lever during the last 2 days of extinction (open bars) and the conditioned-cued reinstatement tests (hatched bars). All three access condition groups showed robust conditioned-cued reinstatement as compared to extinction baseline ($*p<0.01$). However, reinstatement did not significantly differ between animals with different access histories. As seen in Fig. 4 (bottom right), all access groups also showed significant methamphetamine-primed reinstatement ($*p<0.01$). However, in contrast to conditioned-cued reinstatement, a significant difference between groups was seen during drug-primed reinstatement ($F_{2, 24}=6.82, p<0.01$). Post hoc analysis revealed that long-access methamphetamine exposure led to significantly greater reinstatement ($\dagger p<0.05$) when compared to short-access (1 or 2 h) groups.

Long-access methamphetamine exposure selectively decreases novel object recognition

Figure 5 (left panel) compares the active exploration for pre- vs. post-self-administration tests on the spatial reconfiguration test (session 5) for objects E and D. The difference scores were calculated by subtracting the time spent exploring an object during the pre-test from the post-test. Thus, negative scores reflect decreased object exploration. Active exploration was operationally defined as the total time (seconds) spent in the pre-defined zone around the object minus the time spent engaged in other activity or resting. No significant differences were seen between groups for spatial reconfiguration testing. Figure 5 (right panel) shows the exploration of the novel object (session 7) for pre- vs. post-methamphetamine tests. There was a significant group difference ($F_{3, 30}=3.02, p<0.05$), with an access-dependent decrease in time spent exploring the novel object. Post hoc analyses revealed that the 6-h access group explored the novel object significantly less during the post-test as compared to saline-treated animals ($p<0.05$). All rats, regardless of access condition, traveled the same amount of distance during each session. ANOVA revealed a significant main effect for session ($F_{6, 162}=13.88, p<0.001$); however, there was no significant main effect for treatment condition or the condition $\times$ session interaction. Thus, prior methamphetamine exposure did not have any apparent effects on general activity at 10–12 days after chronic self-administration.

Methamphetamine intake predicts drug-primed reinstatement but not novel object recognition

We predicted that methamphetamine intake during self-administration would be a determining factor for reinstatement to drug seeking, as well as cognitive performance. A significant correlation between methamphetamine intake during maintenance self-administration and drug-primed reinstatement was seen ($r=0.52, p<0.01$). However, drug-primed reinstatement was not correlated with conditioned-cued reinstatement. Univariate linear regression analysis confirmed that drug-primed reinstatement was predicted by maintenance self-administration intake ($\beta=0.003, p<0.05$) but not conditioned-cued reinstatement. Contrary to our hypothesis, recognition of the novel object was not significantly related to methamphetamine

self-administration, first hour intake, or drug-primed reinstatement; however, novel object recognition was significantly correlated with conditioned-cued reinstatement ($r=0.45$, $p<0.05$).

Discussion

The current study demonstrates that extended methamphetamine i.v. intake leads to enhanced drug seeking following a subsequent priming injection and that the magnitude of drug seeking is directly related to the amount of intake during chronic methamphetamine self-administration. In addition, prolonged methamphetamine administered intravenously can retard an animal's ability to detect novel stimuli in the environment without affecting the ability to attend to spatial attributes. Of additional note is the lack of a difference in locomotor activity levels between groups, suggesting that the observed effects are not due to generalized motor deficits.

The current study varied daily access to methamphetamine in order to mimic the high levels of methamphetamine obtained during binge administration in humans that may affect cognitive function and propensity to relapse. The rats in the 6-h long-access group self-administered levels of methamphetamine similar to those reported recently in rats (Kitamura et al. 2006). Furthermore, the long-access rats showed significantly greater intake during the later days of maintenance self-administration as compared to the first few days. While this escalation was not seen in the 1-h group, there was a very slight trend towards increased intake in the 2-h access group. It has been previously argued that the escalation of drug intake during prolonged access sessions observed in animal models mimics the "loss of control" over drug use observed in human addicts (Koob et al. 2004; Morgan and Roberts 2004). Most studies that have examined differential access regimens have focused on cocaine i.v. intake, with reports of escalated increases (Ahmed and Koob 1998; 1999; Mantsch et al. 2004; Morgan et al. 2002) or no changes (Dalley et al. 2005; Kippin et al. 2006; Roth and Carroll 2004b) over time. In addition to cumulative changes in drug intake, it has been argued that increased intake seen during the first hour of daily long-access self-administration of cocaine or heroin reflects allostatic decreases in reward function (Ahmed and Koob 2005). The current results found only a very modest change in first hour intake of methamphetamine. Increased overall intake in the absence of specific changes in first hour intake has also been reported with cocaine (Kippin et al. 2006). Regardless of the intake patterns, the long-access animals in the current study achieved very high levels of methamphetamine exposure. Indeed, the cumulative dose amounts over the 14-day maintenance period in the long-access group (>90 mg/kg) surpassed doses administered in non-contingent "binge" paradigms, which typically employ acute injections in a single day (ranging from one to four single doses of 1 to 10 mg/kg) that produce cumulative totals of 4 to 40 mg/kg (Itzhak et al. 2002; O'Dell et al. 1991; Zhu et al. 2006).

Only a few studies have examined persisting neuronal effects of chronic methamphetamine self-administration. Transient down regulation of dopamine D1 and D2 receptors was reported 1 day after chronic methamphetamine self-administration in rats (Stefanski et al. 1999), but this effect was not seen after 7 or 30 days of withdrawal, nor were there any persisting effects on dopamine transporter numbers (Stefanski et al. 2002). Similar transient effects were seen for tyrosine hydroxylase, with increased mRNA and protein levels in midbrain dopamine cell regions reported at 1 day, but not 30 days, after cessation of methamphetamine self-administration (Shepard et al. 2006). A recent study examined markers of neurogenesis and gliogenesis in the medial prefrontal cortex of rats that had experienced prolonged short- or long-access methamphetamine self-administration (Mandyam et al. 2007). Interestingly, decreased proliferation and survival, along with increased cell death, were seen after both regimens, although intermittent self-administration failed to produce the same effects. It will be important to further characterize various measures of neuronal integrity and function after chronic methamphetamine self-administration in order to determine the potential substrates of cognitive impairments that may or may not be related to overt neurotoxicity.

The general pattern of extinction responding after methamphetamine self-administration was similar to that seen after chronic cocaine or heroin self-administration in rats (Feltenstein et al. 2007; Fuchs et al. 2006; Fuchs et al. 2002; Rogers and See 2007). Resistance to extinction reflects, at least in part, motivated behavior to obtain drug reinforcement. If greater drug experience increases drug desire, higher responding during extinction might be expected in animals with a history of long access to the drug. Despite the increase in methamphetamine self-administration seen after longer access conditions, the present results showed no differences between groups in the levels of extinction responding, a finding similar to that previously found after long-access cocaine self-administration (Kippin et al. 2006; Knackstedt and Kalivas 2007). In addition to no differences in extinction responding between access groups, the present results failed to find differences in conditioned-cued reinstatement. We previously reported that long-access cocaine self-administration led to significantly greater drug seeking following drug-paired cues than short-access cocaine self-administration (Kippin et al. 2006). However, this effect was not dependent on contingent access since animals with short-access + additional yoked, non-contingent cocaine exposure also showed greater drug seeking when compared with animals that experienced short access alone. One possibility for the lack of differences in conditioned-cued reinstatement after varied methamphetamine access regimens may be the extensive overtraining that all animals experienced regardless of daily access (total of 24 days). Thus, the strongly entrained drug-cue association in all three access groups may have masked any discernible differences in response to the cue presentation during reinstatement. It is possible that repeated testing of conditioned-cued reinstatement may reveal access-dependent differences over time. Alternatively, other types of cues or presentation parameters (e.g., contextual cues) of methamphetamine-paired cues may reveal potential access-dependent differences.

In contrast to conditioned-cued reinstatement, long-access methamphetamine animals showed significant enhancement of drug-primed reinstatement, a finding similar to that seen after chronic cocaine self-administration (Kippin et al. 2006; Mantsch et al. 2004). Furthermore, we found that methamphetamine intake and drug-primed reinstatement were significantly correlated. A recent report using self-administration and reinstatement in mice reported the same effect, whereby methamphetamine intake during self-administration was positively correlated with drug-primed reinstatement but not with conditioned-cued reinstatement (Yan et al. 2007). The enhanced reinstatement and the correlation between intake and drug seeking for drug-primed reinstatement is likely related to the differences in the neural circuitry that mediates reinstatement of drug seeking produced by drug- vs. cue-induced reinstatement. Studies on the neural substrates that maintain cocaine seeking have shown that the circuitries for different forms of reinstatement consist of partially overlapping yet distinctly different sets of brain nuclei (Feltenstein and See 2008). Interestingly, the opioid receptor antagonist, naltrexone, attenuated methamphetamine-primed but not conditioned-cued reinstatement (Anggadiredja et al. 2004b), implicating a potential role for the opioid system in methamphetamine-primed reinstatement.

The use of the object recognition task allowed for assessment of cognitive performance both before and after chronic methamphetamine self-administration. This procedure offers several advantages in the assessment of object recognition, particularly the ability to measure recognition of novelty based on both spatial reconfiguration and novel object attributes (Kesner and Rogers 2004). Furthermore, animals can be tested in a single multi-session test without prior training, new sets of objects can be used for retesting, and general locomotor activity can be simultaneously determined. Using this test, we found a selective deficit in novel object recognition performance after progressively longer methamphetamine access conditions. Recognition of the spatial reconfiguration was spared, and there were no effects on overall locomotor activity between groups. The present findings are congruent with previous reports of impairments in novel object recognition resulting from acute, non-contingent

methamphetamine injections (Belcher et al. 2005; Bisagno et al. 2002; Schroder et al. 2003). While the reduced interaction with the novel object can be interpreted as a deficit in recognizing a novel object, it is also possible that animals with a history of chronic methamphetamine intake have reduced motivation to interact with a novel object during the task. Using a new and more powerful tracking system that allows for better detailed assessment of subject contact with objects, we have begun studies to further characterize not only object recognition performance but also additional cognitive tasks that may be affected by chronic methamphetamine self-administration, including attentional set-shifting performance.

In sum, the present findings suggest that extended self-administration of methamphetamine leads to increased methamphetamine-primed reinstatement of drug seeking, as well as decreased recognition of a novel object. Future studies will pursue the relationships between various motivational and cognitive consequences of contingent methamphetamine use. Of particular interest will be the determination of the persistence of methamphetamine-induced deficits, as well as assessment of potential biological substrates that underlie both motivational and cognitive dysregulation. By gaining a greater understanding of these critical domains in a valid model of methamphetamine addiction, potential targets for therapeutic intervention may be identified and tested.

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Surgery & Recovery	OET	Self-administration		Extinction 10 days	OET	Cue Test	Extinction 2+ days	Meth Test
		Acquisition 10 days	Maintenance 14 days					

Fig. 1.

Experimental timeline. Following recovery from surgery, baseline object exploration task (*OET*) performance was assessed. After chronic methamphetamine self-administration, rats experienced daily extinction sessions, followed by a second *OET*. The following day, animals underwent conditioned cue-induced reinstatement in the absence of drug (*Cue Test*). After further 2–3 days of extinction, animals experienced drug-primed reinstatement (*Meth Test*)

Fig. 2.

Object exploration task procedure (see text for full apparatus description). Each session lasted 6 min, with a 3-min inter-session interval. *Session 1* consisted of familiarization with the open field. In *sessions 2–4*, five objects remained in the same locations. *Sessions 5 and 6* determined response to spatial reconfiguration. *Session 7* involved novel object recognition, whereby novel object A' replaced object A in the same location

Fig. 3.

Methamphetamine self-administration. **a** Active (drug-paired) lever responding across the 14 days of chronic maintenance self-administration. **b** Methamphetamine intake (milligram per kilogram per session) across 14 days of maintenance. **c** Amount of methamphetamine intake (milligram per kilogram) during the first hour of each self-administration session. Significant increases over day 1 within each group are indicated ($*p < 0.05$)

Fig. 4.

Extinction and reinstatement of drug seeking. *Top* Decreased lever responding on the previously methamphetamine-paired lever over daily extinction trials. No significant differences were seen across access conditions. *Bottom left* Conditioned-cued reinstatement of responding ($*p < 0.01$ compared to extinction responding). *Bottom right* Methamphetamine-primed reinstatement ($*p < 0.01$ compared to extinction responding; $†p < 0.05$ compared to 1- and 2-h access groups)

Fig. 5.

Left Object exploration during the test of spatial reconfiguration (session 5) for objects *D* and *E* expressed as the difference in scores between pre- and post-chronic methamphetamine self-administration. No significant differences were seen between groups. *Right* Object exploration during the test of novel object recognition expressed as the difference between pre- and post-chronic methamphetamine self-administration. The 6-h access methamphetamine group explored the novel object significantly less during the post-test as compared to saline-treated animals (* $p < 0.05$)