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Impaired Object Recognition Following Prolonged Withdrawal From Extended Access Cocaine Self-Administration

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Abstract

Cocaine addicts have a number of cognitive deficits that persist following prolonged abstinence. These include impairments in executive functions dependent on the prefrontal cortex, as well as deficits on learning and memory tasks sensitive to hippocampal function. Recent preclinical studies using non-human animals have demonstrated that cocaine treatment can produce persistent deficits in executive functions, but there is relatively little evidence that treatment with cocaine produces persistent deficits in performance on hippocampal-dependent tasks. We recently demonstrated that extended (but not limited) access to self-administered cocaine is especially effective in producing persistent deficits on a test of cognitive vigilance, and therefore, we used this procedure to examine the effects of limited or extended access to cocaine self-administration on recognition memory performance, which is sensitive to hippocampal function. We found that extended access to cocaine produced deficits in recognition memory that persisted for at least 2 weeks after the cessation of drug use. We conclude that the deficits in learning and memory observed in cocaine addicts may be at least in part due to repeated drug use, rather than just due to a pre-existing condition, and that in studying the neural basis of such deficits procedures involving extended access to self-administered cocaine may be especially useful.

Keywords

self-administration; memory; cocaine; object recognition

Cocaine addicts present with a number of cognitive deficits even following prolonged abstinence. These include impaired performance on tasks involving attention and cognitive flexibility that are thought to be mediated by the medial and orbital prefrontal cortex, as well as spatial, verbal, and recognition memory impairments on tasks thought to be mediated by the hippocampus (Manschreck et al. 1990; Ardila et al. 1991; Berry et al. 1993; Beatty et al. 1995; Hoff et al. 1996; Bolla et al. 2003). Given that cognitive deficits are known to negatively impact treatment outcomes (Aharonovich et al. 2003; Aharonovich et al. 2006), the development of an animal model of persistent cocaine-induced cognitive deficits would be useful in exploring the nature of the deficit.

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A number of preclinical studies have reported that treatment with cocaine produces cognitive deficits during the acute withdrawal period (Deller and Sarter 1998; Kondrad and Burk 2004; Santucci et al. 2004; Schoenbaum et al. 2004; Kantak et al. 2005), but only a few have found that cocaine self-administration experience produces persistent deficits, as seen in humans (Burke et al. 2006; Calu et al. 2007; George et al. 2007; Briand et al. 2008). We found that extended (but not limited) access to self-administered cocaine produced performance deficits lasting at least a month on a cognitive vigilance task indicative of impaired cognitive flexibility (Briand, et al. 2008), and similar effects were reported recently by George and colleagues (2007) using a delayed nonmatch-to-sample task. These studies provide clear evidence that chronic cocaine leads to persistent deficits on tasks dependent on medial and orbital frontal cortex function, but to date, there is little preclinical evidence that cocaine produces persistent memory deficits on tasks sensitive to hippocampal function, similar to those seen in addicts. Studies examining the effects of cocaine on spatial memory have found transient deficits (Santucci, et al. 2004) or no deficits at all (Kantak, et al. 2005; Del Olmo et al. 2006). These studies suggest that cocaine treatment does not produce persistent deficits on hippocampal-dependent tasks in animals, and therefore, the deficits seen in addicts may represent a premorbid condition. Alternatively, the cocaine administration procedures utilized in previous studies involved relatively limited access to drug. There is accumulating evidence that extended access to self-administered cocaine may produce a number of symptoms characteristic of addiction that are not seen following more limited drug access, including persistent cognitive deficits (Ahmed and Koob 1998; Paterson and Markou 2003; Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004; Ferrario et al. 2005; George, et al. 2007; Briand, et al. 2008), although the influence of amount of access may be moderated by the use of higher doses (Burke, et al. 2006; Calu, et al. 2007; Kerstetter and Kantak 2007). Thus, the current experiment compared the effects of extended (6 hrs/day) or more limited (1 hr/day) access to cocaine on object recognition memory performance. The object recognition memory task is particularly relevant because human cocaine addicts have been reported to show deficits on recognition memory tasks (Meek et al. 1989; Manschreck, et al. 1990; Mittenberg and Motta 1993; Hoff, et al. 1996), and recognition memory is sensitive to hippocampal damage (Beason-Held et al. 1999; Clark et al. 2000; Zola et al. 2000; Zola and Squire 2001; Broadbent et al. 2004; Rossato et al. 2007), although as with all learning tasks multiple brain structures contribute to performance.

Experimental Procedures

Animals

Sixty-three adult male Wistar rats (Harlan) were individually housed in a temperature and humidity controlled room and maintained on a 14:10 light/dark cycle, with water available *ad libitum*. All animals were food restricted throughout the experiment to maintain at least 90% of their free feeding body weight.

Apparatus

Drug administration took place in 16 operant chambers measuring 22 × 18 × 13 cm (Med Associates, St. Albans, VT, USA) located inside larger sound-attenuating chambers. For the drug self-administration procedure, each operant chamber had two nose-poke holes equipped with cue lights. A tone (2900 Hz) was present inside of the chamber. The floor of the chamber consisted of 19 stainless steel rods (4 mm in diameter) spaced 1.5 cm apart (center-to-center). Med-PC for Windows software (v. 1.1, Med Associates) controlled all drug delivery, tone presentation and data collection in each system via a Pentium PC. Object recognition familiarization and testing took place in a black triangular shaped open field (92cm along each side, 46cm high).

Surgery

Following a week of acclimation to the colony, the animals were anaesthetized using ketamine/ xylazine (77:1.5 mg/ml, intraperitoneal [IP], at 0.1 mL/100 gm of body weight) and silicone catheters were inserted into the right jugular vein and passed subcutaneously to exit from the animals' back (see Caine et al. 1993). Animals were allowed to recover from surgery for a minimum of 3 days prior to drug administration and the catheters were flushed daily with 0.1mL of gentamicin (50 mg/kg, in 0.9% sterile bacteriostatic saline).

Cocaine Self-Administration

Catheterized rats were transported from their home cage to an operant chamber 6 days a week for four weeks, where they were allowed to nose-poke for cocaine (0.4 mg/kg/infusion in 50 μ L of saline administered over 1.6 s) on a continuous reinforcement schedule (FR1) with a time-out of 20 s. A training session commenced with the illumination of the "active" nose-poke hole stimulus light. Responding in this hole resulted in drug delivery and the nose-poke stimulus light was extinguished during the time-out period. Responding in the other nose-poke hole, designated inactive, had no consequences. Following 1 week of 1-hour training sessions, animals were divided into two balanced groups and one group (ShA) continued to receive 1-hr sessions while the other group (LgA) was given 6-hr sessions for the remaining 3 weeks of self-administration. Animals that did not acquire stable self-administration behavior (at least 5 infusions each day for 3 consecutive days) were removed from the study. A third group of rats (no-drug control group, ND) received sham surgery and were transported each day to a novel test room where they were placed into Plexiglas chambers, similar to the operant chambers.

Object Recognition

Experiment I—Fourteen days following the final self-administration session, animals (LgA N=14; ShA N=13; ND N=16) in the first experiment were placed in the black triangular open field containing two identical novel objects (made up of small colorful plastic toys glued together) and were allowed to explore for 5 minutes (object familiarization training). Three hours, 24 hours, and 1 week after exposure to these objects animals were returned to the open field which now contained one object to which they had been previously exposed and one novel object, and allowed to explore the open field for 5 min. The novel objects were changed for each test and randomized across animals and object placement was counterbalanced. Object exploration was defined as the time spent sniffing or touching, but not sitting on, an object and all scoring was done by a observer blind to treatment conditions. Between all trials both the open field and the objects were washed with a 70% ethanol solution.

Experiment II—In the first experiment the same familiar object was used for all three of the tests. Therefore, we replicated the experiment using different familiar objects for each test to eliminate the confound of further learning on test days. Thus, for the second experiment, training and testing were identical to Experiment I with the following exceptions. During the training phase animals (LgA N=8; ShA N=11; ND N=11) were presented with two unique sets of novel objects to explore for 5 minutes per set. Each set consisted of two identical objects. These two sets of objects were presented twice in alternation with a 5-minute inter trial interval, for a total of 4 exploration sessions. Animals were then tested after 24 hours and 1 week after training. During each test the animals were presented with only one of the familiar objects, and a novel object, and given 5 minutes to explore.

Statistical Analyses

Cocaine Self-Administration—For each day of self-administration we determined the number of infusions in the first hour, as well as the total number of infusions of each session.

Two-way repeated measures ANOVAs were performed with self-administration session (first vs. last) as the repeated variable, drug group (ShA, LgA) as the independent variable and first hour or total infusions as the dependent variable. When significant main effects or interactions were revealed, Student Newman Keuls post-hoc analyses were performed. For all analyses α was set at 0.05.

Object Recognition—For each object recognition test, the percent time exploring the novel object was calculated by dividing the time spent exploring the novel object by the total object exploration time. One-way ANOVAs were then performed with drug group as the independent variable and percent time exploring the novel object as the dependent variable. When significant main effects were revealed, Student Newman Keuls post-hoc analyses were performed.

Results

Cocaine Self-Administration

Over the 3 weeks of cocaine self-administration animals in the LgA group escalated their intake both in the number of infusions taken during the first hour and the total number of infusions over the course of a self-administration session, whereas in the ShA animals cocaine intake did not change significantly over time (Fig 1).

Object Recognition

Experiment I—There were no group differences in the total time exploring the two objects during the first “training” session ($ND=61\pm3.3s$, $ShA=63\pm4.9s$, $LgA=66\pm4.4s$; ANOVA, main effect of group, $F(2,33)=0.09$, $p=0.92$) nor any group differences in the total amount of time exploring objects during subsequent test sessions (Fig 2d–f). Three hours after training there were no group differences in the percent time spent exploring the novel object. However, when tested 24 hrs after training animals in the LgA group spent less time exploring the novel object than either the no drug control group or the ShA group, which did not differ from one another, suggesting a deficit in recognition memory in animals that 2 weeks previously had extended access to cocaine. When tested 1 week after training both the LgA and ShA groups explored the novel object less than the control group, suggesting a deficit in both.

Experiment II—As in Experiment I, there were no group differences in object exploration time during the training sessions [$ND=186\pm24s$, $ShA=182\pm18s$, $LgA=155\pm20s$; ANOVA, group, $F(2,31)=0.55$, $p=0.58$], nor in the total time exploring objects during the test sessions (Fig. 3c–d). When tested either 24 hrs or 1 week after training the LgA animals spent less time exploring the novel object than did animals in the no drug control group or the ShA group, and these latter two groups did not differ from each other (Fig. 3a–b).

Discussion

Animals are naturally inclined to explore novel objects rather than familiar ones (Ennaceur and Delacour 1988), and therefore, a decrease in the proportion of time spent exploring a novel object relative to a familiar one is often taken to suggest either an initial problem in learning about the objects, or impaired memory for the familiar object. In the present experiment there were no group differences in the time spent exploring the objects during training, nor in the total time spent exploring objects on test days. This suggests that cocaine self-administration experience did not influence the motivation to explore novel objects, nor did it cause generalized changes in behavior (e.g., locomotion) that might have otherwise impaired attention to the objects. It is difficult with the procedures used here to determine if decreased exploration of a novel object on the test day was due to a deficit in initial learning, or in

recollection (memory) on the test day. Whatever the case, the animals were not trained until 2 weeks after the last self-administration session, suggesting that past experience with cocaine produced a persistent deficit in either object learning or memory. Furthermore, extended access to cocaine produced a greater deficit than limited access to cocaine. In Experiment 1 the LgA group showed a deficit when tested either 24 hrs or 1 week after training, and the ShA only showed a deficit when tested 1 week after training. In Experiment 2 the ShA group did not show any deficit when tested at either 24 hrs or 1 week after training, although the LgA group was impaired on both test days. This suggests that even limited access to self-administered cocaine may lead to moderate deficits in recognition memory performance, but they are not always evident, and are clearly less pronounced than the deficits seen following extended access to self-administered cocaine.

The persistent deficit in recognition memory performance seen in the LgA animals is consistent with work demonstrating that extended access cocaine self-administration leads to persistent deficits in other cognitive arenas, such as cognitive flexibility and working memory (George, et al. 2007; Briand, et al. 2008). As previous work has focused on tasks sensitive to prefrontal cortex function, the current experiments extend these findings to a task for which the hippocampus is important (Beason-Held, et al. 1999; Clark, et al. 2000; Zola, et al. 2000; Zola and Squire 2001; Broadbent, et al. 2004; Rossato, et al. 2007). Cocaine-induced alterations in hippocampal function is also consistent with reports of alterations in hippocampal PET activation in cocaine abusers while making risky decisions in a decision-making task (Fishbein et al. 2005).

Although we found that cocaine self-administration produced persistent deficits on a task sensitive to hippocampal function, others have not. For example, Del Olmo and colleagues (2006) did not find deficits on a spatial memory task, and Katak and colleagues (2005) found no deficits on a hippocampally-dependent win-shift task, following cocaine self-administration. Santucci et al. (2004) found spatial memory deficits following cocaine administration in adolescent animals, but these deficits did not persist in adulthood. Recently, Mendez et al. (2008) reported that experimenter-administered cocaine produced deficits on water maze performance, but the pattern of deficits was “not consistent with major deficits in spatial learning and memory” (p. 185). In the previous experiments involving cocaine self-administration total cocaine intake was on the order of ~120–400 mg/kg, which is not that much more than in animals given limited access in the present study (~100 mg/kg total intake). However, this is considerably less than seen in animals given extended access to cocaine, who took a total of ~1,000 mg/kg. Given that animals allowed limited access had only moderate and inconsistent effects on recognition memory it is possible that more aggressive treatment regimens, and especially ones that better model the changes in brain and behavior that occur in addiction, would lead to consistent deficits on hippocampal-dependent tasks. Indeed, the extended access self-administration protocol used in this study has been shown to produce a number of symptoms characteristic of addiction that are not seen following more limited drug access (Ahmed and Koob 1998; Paterson and Markou 2003; Deroche-Gamonet, et al. 2004; Vanderschuren and Everitt 2004; Ferrario, et al. 2005; Briand, et al. 2008). On the other hand, we need to acknowledge that it is not possible to conclude conclusively that the deficits described here are due to cocaine compromising hippocampal function (Zola, et al. 2000; Baxter and Murray 2001; Mumby 2001; Zola and Squire 2001), because a number of other brain regions have been implicated in recognition memory, including the nucleus accumbens (Sargolini et al. 2003; Ferretti et al. 2005), prefrontal cortex (Hotte et al. 2006), and perirhinal cortex (Barker et al. 2007).

In summary, this study suggests that in addition to producing deficits in executive functions mediated by the prefrontal cortex, extended access to self-administered cocaine self-administration also produces persistent deficits on a recognition memory task that involves the

hippocampus, as well as other brain regions. This is consistent with the hypothesis that similar deficits in addicts may be in part due to repeated exposure to cocaine itself, rather than reflecting a preexisting condition. The fact that limited access to cocaine did not produce deficits comparable to those seen after extended access further suggests that extended access procedures may be advantageous in elucidating the cellular and the molecular changes in brain responsible for cognitive deficits in addicts. The relationship between cognitive deficits and negative treatment outcomes (Aharonovich, et al. 2003; Aharonovich, et al. 2006), make the development of treatments that target the cognitive deficits caused by drugs of abuse of particular importance.

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Figure 1.

A. Mean ($\pm$ SEM) number of cocaine infusions during the first hour of the first and last self-administration session in Experiment I. Following the 3 weeks of differential access to cocaine self-administration, animals given extended access (long access, 6 hr sessions; LgA) took significantly more infusions than animals allowed only limited access (short access, 1 hr sessions; ShA) [main effect of group, $F(1,27)=10.94$, $p=.003$; main effect of session, $F(1,27)=30.77$, $p<.0001$; interaction, $F(1,27)=18.76$, $p=.0002$; *, differs from ShA group as determined by Student Newman Keuls post-hoc tests] B. The mean ($\pm$ SEM) number of cocaine infusions over the entire session on the first and last day of self-administration for the long access (LgA) and short access (ShA) groups in Experiment I. In addition to an increase

in intake during the first hour, animals in the long-access group exhibited an increase in total session intake over the 3 weeks, while the ShA animals did not [main effect of drug, $F(1,27) = 74.93$, $p < .0001$; main effect of withdrawal time, $F(1,27) = 10.35$, $p = .003$; interaction, $F(1,27) = 9.27$, $p = .005$; * differs from ShA group as determined by Student Newman Keuls post-hoc tests; # differs from Day 1 as determined by Student Newman Keuls post-hoc tests]. C. Mean ($\pm$ SEM) number of cocaine infusions during the first hour of the first and last self-administration session in Experiment II. Following the 3 weeks of differential access to cocaine self-administration, animals given extended access (LgA) took significantly more infusions than animals allowed only limited access (ShA) [main effect of group, $F(1,17) = 26.18$, $p < .0001$; main effect of session, $F(1,17) = 36.37$, $p = .02$; interaction, $F(1,17) = 15.37$, $p = .001$; *, differs from ShA group as determined by Student Newman Keuls post-hoc tests]. D. The mean ($\pm$ SEM) number of cocaine infusions over the entire session on the first and last day of self-administration for the long access (LgA) and short access (ShA) groups in Experiment II. Similar to Experiment I, animals in the long-access group exhibited an increase in total session intake over the 3 weeks, while the ShA animals did not [main effect of drug, $F(1,17) = 33.24$, $p < .0001$; main effect of withdrawal time, $F(1,17) = 17.31$, $p = .0007$; interaction, $F(1,17) = 19.56$, $p = .0004$; * differs from ShA group as determined by Student Newman Keuls post-hoc tests; # differs from Day 1 as determined by Student Newman Keuls post-hoc tests].

Figure 2.

The effect of extended vs. limited access to self-administered cocaine on performance on the novel object recognition memory task following a 14-day withdrawal period in Experiment 1. The top three panels (a–c) show the percent novel object exploration time (as a function of the total object exploration time) at the three retention intervals. Panel a shows that there were no differences between the three drug conditions 3 hours after the familiarization training (ANOVA, group, $F(2,42)=1.33$, $p=.28$). However, after 24 hours (panel b), there was a significant decrease in the time spent exploring the novel object in LgA animals relative to both the No Drug and ShA groups, which did not differ from one another (ANOVA, group, $F(2,42)=10.89$, $p=.0002$, *, differs from ShA and No Drug groups as determined by Student Newman Keuls post-hoc tests). One week following the familiarization training (panel c), both drug groups (LgA, ShA) spent less time exploring the novel object relative to the No Drug control group (ANOVA, group, $F(2,42)=5.98$, $p=.005$, *, differs from the No Drug group as determined by Student Newman Keuls post-hoc tests). The bottom three panels show the total object exploration time during the three test sessions. No differences were seen between the groups on this measure at any of point in time.

Figure 3.

The effect of extended vs. limited access to self-administered cocaine on performance on the novel object recognition memory task following a 14-day withdrawal period in Experiment 2. The top two panels show the percent novel object exploration time (as a function of the total object exploration time) at the two retention intervals. At both the 24-hour (a) and 1-week (b) retention intervals, the LgA animals showed a significant decrease in time spent exploring the novel object relative to both the No Drug and ShA groups, which did not differ from one another [(a), ANOVA, group, $F(2,29)=3.98$, $p=.03$; (b), ANOVA, group, $F(2,29)=6.19$, $p=.006$; *, differs from ShA and No Drug groups as determined by Student Newman Keuls post-hoc tests). The bottom two panels (c–d) show the total object exploration time during the three test sessions. No differences were seen between the groups on this measure at any point in time.