Brief Communication

Withdrawal from cocaine self-administration produces long-lasting deficits in orbitofrontal-dependent reversal learning in rats

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Drug addicts make poor decisions. These decision-making deficits have been modeled in addicts and laboratory animals using reversal-learning tasks. However, persistent reversal-learning impairments have been shown in rats and monkeys only after noncontingent cocaine injections. Current thinking holds that to represent the human condition effectively, animal models of addiction must utilize self-administration procedures in which drug is earned contingently; thus, it remains unclear whether reversal-learning deficits caused by noncontingent cocaine exposure are relevant to addiction. To test whether reversal learning deficits are caused by contingent cocaine exposure, we trained rats to self-administer cocaine, assessed cue-induced cocaine seeking in extinction tests after 1 and 30 d of withdrawal, and then tested for reversal learning more than a month later. We found robust time-dependent increases in cue-induced cocaine seeking in the two extinction tests (incubation of craving) and severe reversal-learning impairments.

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To explore whether long-lasting deficits in reversal learning occur after contingent exposure to cocaine, we trained rats to self-administer cocaine, tested for time-dependent increases in cue-induced cocaine seeking (i.e., incubation of craving; Grimm et al. 2001), and then assessed reversal learning using procedures identical to those we have used previously to test effects of noncontingent cocaine exposure and orbitofrontal lesions (Schoenbaum et al. 2003, 2004). All testing was conducted at the University of Maryland School of Medicine in accordance with University and NIH guidelines. Male Long-Evans rats (n = 7, 300–350 g, Charles River Labs) were implanted with jugular venous catheters, using published procedures (Lu et al. 2004a, 2005b). Silastic catheters were inserted into the jugular vein and passed subcutaneously to the top of the skull, where they were attached to a modified 22-gauge cannula (Plastics One) and mounted to the rat’s skull with dental cement. After a one-week recovery period, these rats were trained to lever press for cocaine infusions, using published procedures Lu et al. 2004a,b; Lu et al. 2005a,b. Briefly, self-administration was conducted in chambers from Coulbourn Instruments equipped with two levers. Pressing on the active lever resulted in infusion of cocaine-HCl (0.75 mg/kg/infusion) accompanied by a 4-sec tone-light cue, with a 40-sec
Lever on both days showed that the rats pressed significantly more on the active extinction sessions. A 3-factor ANOVA (lever pressing on the active lever did not result in drug infusion, pressing behavior during extinction sessions, using published procedures) showed a significant three-way interaction between lever, hour, and day. One and 30 d after the end of cocaine self-administration, we assessed lever pressing behavior during extinction sessions, using published procedures. These procedures were identical to those used in self-administration training except that pressing on the active lever did not result in drug infusion, though it did earn presentation of the tone-light cue that had been associated with drug infusion during training. Figure 1B shows pressing on the active and inactive levers during these extinction sessions. A 3-factor ANOVA (lever × hour × day) showed that the rats pressed significantly more on the active lever on both days (F(1,15) = 49.9, P < 0.001) and significantly more on the active lever on day 30 than on day 1, as indicated by a significant three-way interaction between lever, hour, and day (F(1,20) = 6.4, P < 0.01). A direct comparison of responding on the active lever on days 1 and 30 revealed a significant increase across days in the first hour (F(1,10) = 19.1, P < 0.01) and also over the entire 3-h test period (F(1,10) = 14.4, P < 0.01).

Approximately one month after completion of late withdrawal (day 30) testing, the rats were water-deprived and then trained in an odor-guided go, no-go odor discrimination task. Odor discrimination testing was conducted in custom chambers that differed from those used for self-administration training. Procedures were identical to those we have used previously to assess the effects of lesions and passive exposure to cocaine. Briefly, rats sampled an odor on each trial and then had 3 sec to decide whether to respond at a nearby fluid well; the "positive" odor predicted delivery of an appetitive 10% sucrose solution and the "negative" odor predicted delivery of an aversive 0.02 M quinine solution. The rats were trained until they met a criterion of 18 correct responses in a moving block of 20 trials. After reaching criterion on several problems, they were tested on two serial reversals of the final problem. For this, the rats were first required to demonstrate retention of the original problem (S1+/S2−), by meeting the behavioral criterion again, and then they were required to meet this same criterion again after the odor-outcome associations were disrupted. The rats were then required to demonstrate reversal of the original problem (S1−/S2+). After the rats acquired the first reversal, retention of the reversed problem (S1−/S2+) was assessed the following day, after which the rats had to acquire a re-reversal of the problem (S1+/S2−). Note that rats also had to perform at 80% correct over a 60-trial block in order for reversals to proceed to further ensure accurate performance over a large number of trials. Their performance was compared to a group of male Long-Evans control rats (n = 11, 300–350 g, Charles River Labs) that underwent discrimination and reversal testing using identical procedures in conjunction with a separate study. This group of rats did not receive jugular venous catheters or self-administration training but otherwise had handling, surgical experience (anesthesia, skull exposure), and training (discrimination training and also exposure to the self-administration training environment for 1 h per day) that was similar to that of our experimental group. These rats acquired the problem to be reversed at the same rate as the rats trained to self-administer cocaine in the current study (P > 0.5) suggesting that training history, including instrumental training in the drug-treated rats several months earlier, did not interfere with discrimination performance prior to reversal. Moreover, as we will show next, their reacquisition rates were identical to those of the rats trained to self-administer cocaine.

Reversal performance of the rats in these two groups is illustrated in Figure 2. Rats that had been trained to self-administer cocaine required many more trials than controls to acquire the reversals. A 2-factor ANOVA (group × retention/reversal) confirmed this impression, revealing significant main effects of group (F(1,15) = 16.7, P < 0.001) and retention/reversal (F(1,15) = 158.4, P < 0.001) and a significant interaction (F(1,15) = 25.4, P < 0.001). Subsequent contrasts showed no difference in performance during retention of the problems (P > 0.10), indicating that both groups learned the original discriminations to the same degree, but a significant impairment in acquiring the reversals (P < 0.001).

We have replicated our prior finding that cocaine exposure causes long-lasting impairments in reversal learning in rats. Previously, deficits were demonstrated in rats, approximately a month and a half after 14 d of exposure to experimenter-administered cocaine (30 mg/kg/d, i.p.). In the present study, we show reversal-learning deficits in rats, ~3 mo after 14 d of exposure to self-administered cocaine (18.4 mg/kg/
Alcohol and drug exposure.

The reversal deficit was demonstrated in rats that exhibited a robust time-dependent increase in cue-induced cocaine seeking after withdrawal. This phenomenon termed incubation of cocaine craving (Grimm et al. 2001; Lu et al. 2004b). Reversal deficits are linked to orbitofrontal-amygadalar dysfunction (Rolls et al. 1994; Chudasama and Robbins 2003; Schoenbaum et al. 2003, 2006; Izquierdo et al. 2004; Stalnaker et al. 2006a), brain regions that show long-lasting effects of psychostimulants on neuroplasticity (Crombag et al. 2004; Goussakov et al. 2006). Notably, these same areas are also implicated in drug craving in humans and rats and in incubation of craving in rats (Volkow and Fowler 2000; Goldstein et al. 2001; Fuchs et al. 2004; Dom et al. 2005; Kalivas and Volkow 2005; Lu et al. 2005b). Since reversal learning was not assessed during early withdrawal from cocaine, the current report does not address whether or not these phenomena are directly related. It would be of great interest to determine whether the decision-making deficits demonstrated here reflect effects of cocaine on a similar neural substrate that mediates cocaine craving or incubation of craving.

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