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.
Figure 1. Cocaine self-administration and incubation of cocaine craving. (A) Mean ± SEM number of cocaine infusions, responses (both infusion + timeout responses) on the active, cocaine lever, and responses on the inactive lever during the three 1-h cocaine self-administration sessions. (B) Total responding per hour on the active and the inactive levers in the same rats during three 1-h extinction sessions conducted 1 and 30 d after cocaine self-administration training. (*) Different from Day 1 or from the inactive lever, P < 0.05.

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 (Schoenbaum et al. 2003, 2004). 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 3-h session. Figure 2 shows 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 (Schoenbaum et al. 2004).
Reversal learning after contingent cocaine


Goldstein, R.Z., Volkow, N.D., Baler, R.D., Jentsch, J.D., Olausson, P., De La Garza, R., and Taylor, J.R. 2002. Plasticity of reward neurocircuitry linked to orbitofrontal-amygdalar 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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