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Incubation of cocaine craving after withdrawal

Jeffrey W. Grimm, Bruce T. Hope, Roy A. Wise, and Yavin Shaham

Behavioral Neuroscience Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, 5500 Nathan Shock Drive, Baltimore, Maryland 21224, USA

Relapse to cocaine addiction is frequently associated with subjective reports of craving, a poorly understood state that precedes and accompanies cocaine-seeking behaviours¹. It has been suggested² that over the first few weeks of withdrawal from cocaine, human addicts become sensitized to drug-associated environmental cues that act as external stimuli for craving, although the evidence for this is inconsistent³. Here we provide behavioural evidence from laboratory animals suggesting that the onset of craving is delayed and that craving does not decay, but rather increases progressively, over a two-month withdrawal period.

We modelled cocaine-craving behaviour by using rats trained to press a lever to receive an intravenous injection of cocaine and then testing them under conditions in which lever-pressing could continue but the cocaine reward was no longer given. In this model, lever-pressing drops to almost zero ('extinguishes') but can be temporarily reinstated by giving the animal an unearned 'priming' injection of the drug⁴, by administering some forms of stress⁵, or by presenting drug-associated cues⁶ — factors that are known to provoke drug craving in human addicts^{1,7,8}.

We trained seven groups of rats to press the lever for intravenous cocaine injection (0.5 mg per kg body weight per lever-press). Individual rats lived in a chamber that had a retractable lever. Each training session began with insertion of the lever and illumination of a red house light. At the end of each session, the house light was turned off and the lever retracted. A 5-second tone–light signal accompanied each earned injection. After 10 days of 3-hour training sessions twice daily, in which the animals came to earn 55.3 ± 2.7 infusions per day, they were withdrawn from cocaine for 1, 2, 4, 7, 15, 29 or 60 days. During the withdrawal period, the lever was retracted and the house light was kept off.

We subsequently tested each group under two extinction conditions in which cocaine reward was withheld. First, we assessed resistance to extinction in the presence of the house light and the lever — cues that during training had indicated drug availability — but in the absence of the light and tone that were previously paired with drug injection. The animals were allowed to lever-press for six to eight 1-hour sessions (separated by 5-min intervals, during which the lever was retracted and the house light turned out) until their response fell to less than 15 presses per session. We found that lever-pressing was minimal in rats that had been deprived of cocaine for a single day and maximal in animals that had been deprived for 60 days (Fig. 1a).

The second test of cocaine seeking was a cue-induced reinstatement test conducted 5 min after the last of the extinction sessions. This test began with a 5-second presentation of the tone–light signal that had previously accompanied cocaine injection; each lever-press in this test resulted in another presentation of the tone–light signal⁶. In this test, the animals were not only exposed to the cues that would normally signal cocaine availability, but they were also exposed

to the conditioned reinforcing cues that previously confirmed cocaine reward. Again, response was minimal after a single day of cocaine deprivation and maximal after 60 days (Fig. 1b). We found a linear increase over 2 months of cocaine withdrawal in the rats' sensitivity to similar drug-associated environmental cues that stimulate cocaine craving in humans¹.

Our results are consistent with clinical observations in humans² and suggest that a delayed-onset craving syndrome develops or 'incubates' during the first 2 months of cocaine abstinence, and probably lasts for longer. Although the mechanisms responsible for this incubation are not known, the intensification of cocaine seeking described here develops over a period when most of the neuroadaptations that accompany withdrawal from chronic cocaine addiction are in progressive decline^{9–11}.

The time course of this intensified drug seeking is similar to that of psychostimulant sensitization, which becomes progressively stronger with increasing abstinence for periods of up to several weeks^{12,13}. Whatever the mechanism by which craving is incubated, our evidence is inconsistent with the view that cocaine craving decays progressively after cessation of drug use. It suggests instead that the individual is most vulnerable to relapse at times well beyond the acute phase of drug withdrawal.

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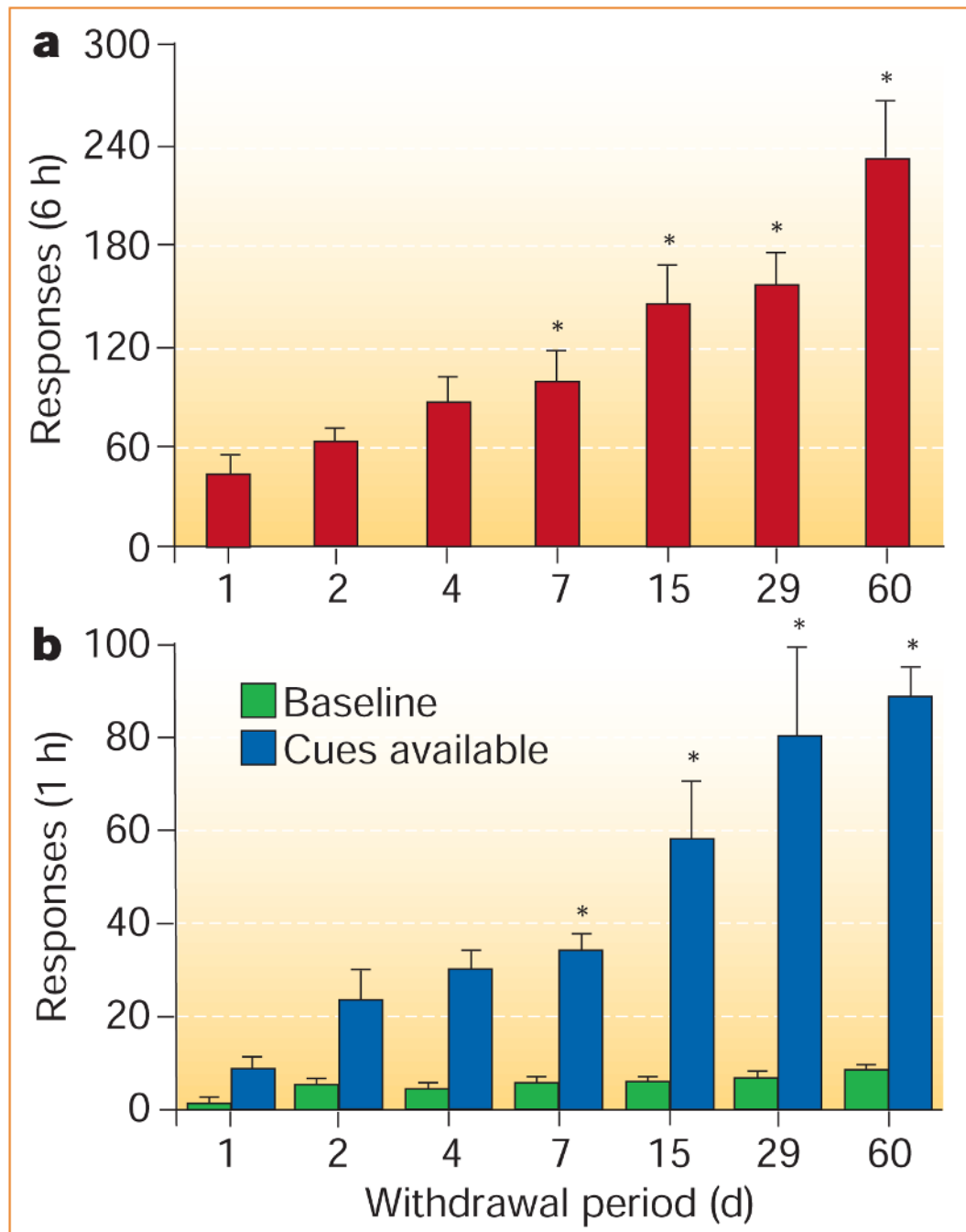


Figure 1.

Persistence of a cocaine-seeking habit as a function of time since the last day of self-administration of cocaine. **a**, Mean (\pm standard error) number of non-reinforced responses on the lever previously associated with cocaine, from six extinction sessions in the presence of the house light and lever cues that were previously associated with cocaine availability. **b**, Mean (\pm standard error) number of non-reinforced responses on the lever previously associated with cocaine in the subsequent presence of the light-tone signal (conditioned reinforcer) that was previously associated with earned cocaine injections. Baseline data are from the previous extinction session. *Different from day 1 ($P < 0.01$).