Supplemental Information

Detailed Methods

All procedures were approved by the University of Michigan Committee on the Use and Care of Animals.

Subjects

A total of 100 (Exp. 1 initial N = 50, Exp. 2 initial N = 50) male Sprague-Dawley rats weighing 250-300 g upon arrival were used. Rats were housed individually in hanging acrylic cages (8 x 8 x 9 cm) and kept on a 12-hr light/12-hr dark cycle (lights on at 0800 hr) in a temperature and humidity controlled colony room. Water and food were available *ad libitum*, (i.e., animals were *not* food deprived at any time). Behavioral testing was conducted in sixteen standard (22 x 18 x 13 cm) test chambers (Med Associates Inc., St. Albans, VT, USA) located inside sound-attenuating cabinets. A ventilating fan masked background noise. For Pavlovian training each chamber had a food magazine located in the center of one wall, 3 cm above a stainless steel grid floor. Head entries into the food cup were recorded by breaks of an infrared photobeam located inside the magazine. A retractable lever illuminated from behind was located 2.5 cm to the left or right of the food cup, approximately 6 cm above the floor. The location of the lever with respect to the food cup was counterbalanced across animals. On the wall opposite the food cup, a red house light remained illuminated throughout all experimental sessions. For self-administration sessions, the food cup and lever were removed and replaced with two nose-poke ports located 3 cm above the floor on the wall opposite the house light. A nose poke into the port designated the active port, detected by an infrared photobeam inside the hole, resulted in an infusion of cocaine, delivered by an external pump through a tube connected to the animal's catheter back port. The infusion tube was suspended into the chamber via a swivel mechanism, allowing the animal free movement about the chamber. Active and inactive nose-poke ports were counterbalanced to control for side bias. All dependent measures were collected and recorded using Med Associates software.

Pavlovian training

Pavlovian training procedures were similar to those described previously (1). For two days prior to the start of training, 10 banana-flavored pellets (45 mg, BioServe, #F0059; Frenchtown, NJ, USA) were placed in the home cages to familiarize the rats with this food. After 1 week to acclimate to the colony room, rats were placed in the test chambers, with the lever retracted, and trained to retrieve pellets from the food cup by presenting fifty 45-mg banana pellets on a variable interval (VT) 30-s schedule during sessions lasting ~ 25 min, and it was determined whether the rats were reliably retrieving the pellets. After 2 days of pretraining, Pavlovian training commenced. Each trial consisted of insertion (and simultaneous illumination) of the lever (CS) into the chamber for 8 s, after which the lever was retracted and a single food pellet (US) was immediately delivered into the food cup. Each of three daily test sessions consisted of 25 trials in which CS-US pairing occurred on a random interval (RT) 90-s schedule (the time between CS presentations varied randomly between 30 and 150 s). Lever deflections, magazine entries, latency to the first lever deflection, magazine entries during the intertrial interval, and latency to magazine entry during CS presentation were measured. The average number of lever presses across training sessions was used to distinguish sign-tracking (lever-directed) and goal-tracking (food tray-directed) behavior (1). Using this indicator, animals were divided into two groups, sign-trackers (ST, top 33% lever presses) and goal-trackers (GT, bottom 33% lever presses). The intermediate group (middle 33% lever presses) was excluded from further study.

Surgery

After Pavlovian training animals were prepared with intravenous catheters as described previously (2) under ketamine hydrochloride (100 mg/kg i.p.) and xylazine (10 mg/kg i.p.) anesthesia. Following surgery catheters were flushed daily with 0.2 ml sterile saline containing gentamicin (5 mg/ml). During self-administration testing catheters were flushed with this solution before and after each session. Once a week, catheter patency was tested by injection of 0.1 ml sodium thiopental (20 mg/ml in sterile water, i.v.). Only rats that become ataxic within 5 s were considered to have patent catheters and included in the analysis.

Self-administration

Self-administration sessions began one week after surgery in chambers outfitted with two nose ports as described above. A nose poke into the active port resulted an intravenous infusion of cocaine HCl (US; 0.5 mg/kg/infusion in 25 µl delivered in 1.6 s) on a fixed ratio (FR) 1 schedule. After an infusion there was 20-s timeout period, during which nose pokes were recorded, but they had no programmed consequences. During the timeout period the active nose poke port was illuminated. Thus, this light served as the CS signaling cocaine delivery. The initial training dose (0.5 mg/kg) was chosen because it has been reported to produce relatively rapid acquisition of self administration while maintaining moderate response levels (3). To guarantee that all animals received exactly the same number of drug injections, and therefore the same number of CS-US pairings, all animals were initially allowed to take 5 infusions (i.e., the length of the session was determined by how long it took to take 5 injections). This infusion criterion (IC) was then increased to 10, 15, 25, 40, and finally 80 infusions. Animals were tested at each IC for two consecutive sessions. At IC 40, the dose was lowered to 0.2 mg/kg, to produce increased response rates necessary to result in sessions lasting approximately 1-2 hrs. This lower dose was used for the remainder of testing, and was chosen because doses in this range have been found to be sensitive to the presence or absence of a CS (4). Animals who failed to acquire self administration (ST = 2, GT = 2), or for whom catheter patency was not maintained (ST = 3, GT = 5), were removed from the analysis.

1. Flagel SB, Watson SJ, Robinson TE, Akil H (2007): Individual differences in the propensity to approach signals vs goals promote different adaptations in the dopamine system of rats. *Psychopharmacology (Berl)* 191: 599-607.

2. Crombag HS, Badiani A, Maren S, Robinson TE (2000): The role of contextual versus discrete drug-associated cues in promoting the induction of psychomotor sensitization to intravenous amphetamine. *Behav Brain Res* 116: 1-22.

3. Carroll ME, Lac ST (1997). Acquisition of i.v. amphetamine and cocaine self-administration in rats as a function of dose. *Psychopharmacology (Berl)* 129: 206-214.

4. Schenk S, Partridge B (2001). Influence of a conditioned light stimulus on cocaine self-administration in rats. *Psychopharmacology (Berl)* 154: 390-396.