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Outcome specificity in deepened extinction may limit treatment feasibility: Co-presentation of a food cue interferes with extinction of cue-elicited cocaine seeking

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ABSTRACT

Background: We previously showed that presenting two cocaine cues simultaneously during extinction deepens the extinction of cue-elicited cocaine seeking (Kearns et al., 2012). The present study investigated whether compounding a non-drug appetitive cue with a cocaine cue would similarly deepen extinction.
Methods: In Experiment 1, tone and click were each first established as discriminative stimuli for cocaine-reinforced responding and light was a cue for food-reinforced responding. In an initial extinction phase, all stimuli were presented individually. Then, during an additional compound extinction session, rats received 8 presentations of one of the cocaine cues (counterbalanced over subjects) simultaneously with light and 8 presentations of the other cue alone. A spontaneous recovery test was used to evaluate the effectiveness of the extinction treatments. Experiment 2 was performed under conditions designed to match those of Experiment 1, except food was the reinforcer in tone and click instead of cocaine.
Results: In Experiment 1, the cocaine cue compounded with the food cue during extinction controlled greater spontaneous recovery of cocaine seeking than the cocaine cue always presented alone. In contrast, Experiment 2 demonstrated deepened extinction of responding to a food cue when both compounded cues were food cues.
Conclusions: Results suggest that deepened extinction depends on the compound presentation of cues associated with the same reinforcer. Compound presentation of cues associated with different reinforcers could lead to an enhancement of responding. Care is urged in attempts to deepen the extinction of cue-elicited drug seeking by compounding drug cues with non-drug cues.

1. Introduction

Drug cues play a central role in addiction (Volkow et al., 2012). In humans, drug cues can elicit craving for the drug (Kennedy et al., 2013; Sinha, 2013), activate the brain's reward circuits (Fotros et al., 2013; Volkow et al., 2012), and trigger relapse (Marhe et al., 2013; Prisciandaro et al., 2013). A treatment that neutralizes the power of drug cues could prove very valuable in efforts to manage addiction. Extinction has been used in such an effort. For example, the extinction-based treatment called cue-exposure therapy (Drummond et al., 1995) involves repeatedly presenting cues to addicts without the drug. This extinction should theoretically break the cue-drug association and thereby eliminate the cues' ability to influence behavior. While there have been a few studies suggesting that cue-exposure therapy may have some promise (e.g., Loeber et al., 2006; Rohsenow et al., 2001), in general, results have not been as encouraging as expected (for reviews see Conklin and Tiffany, 2002; Havermans and Jansen, 2003). A method more effective than the standard extinction procedure may help to improve outcomes.

Recently, preclinical studies have shown that there is a way of deepening the extinction of cue-elicited, drug-seeking behavior (Janak et al., 2011; Kearns et al., 2012). Deepened extinction was first reported by Rescorla (2006) in experiments involving non-drug cues. In deepened extinction, cues are first presented individually during extinction training, for several sessions. Then, the cues are presented simultaneously (i.e., compounded) during additional extinction training. We showed that even a single such compound extinction session was capable of reducing the spontaneous recovery of cue-controlled cocaine seeking by approximately 50% as compared to that produced by a cocaine cue that underwent the standard extinction treatment (Kearns et al., 2012). This suggests that the deepened extinction procedure could be a way to more effectively, and more permanently, reduce the power of drug cues over behavior.

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Deepened extinction is accounted for by error-correction learning theories such as the Rescorla-Wagner model (Rescorla, 2006; Rescorla and Wagner, 1972). According to these models, learning is the process whereby the discrepancy (or "prediction error") between expectation and outcome is corrected. In the case of extinction learning, presentation of the cue initially produces expectation for the reward previously associated with that cue. When the reward is not delivered, there is a prediction error. This acts to decrease reward expectation produced by the cue. This process continues until the cue no longer generates expectation for reward. Now, there is no longer a mismatch between expectation (no reward) and outcome (no reward) and, therefore, nothing to drive learning. Rescorla (2006) hypothesized that further extinction learning might be possible at this point if expectation could be restored, temporarily, over the course of additional extinction trials. He discovered that compounding two cues was a way to create such a temporary expectation and thereby produce deepened extinction.

One issue that may limit the potential clinical utility of deepened extinction as a treatment for human drug abusers is the difficulty in controlling the presentation of cues that might be compounded with the problematic target drug cue(s). While it may be possible to expose users in the clinic to small and discrete paraphernalia cues (e.g., a pipe), it may not be feasible to compound these with other relevant drug cues, such as a person or place previously associated with the drug. Further, cue-drug associations are assumed to have been formed in the user's natural environment as a by-product of the drug-taking experience. This means that the conditioning histories of many of these cues are variable or unknown. For example, while it may be assumed that there has been a consistent pairing of a crack pipe with the effects of cocaine, there may have been more irregular pairings, and different kinds of associations formed, between broader contextual cues (e.g., a house or neighborhood) and the effects of cocaine.

A more practical treatment based on deepened extinction would need to provide the practitioner with better control over the cues that are to be presented during extinction in compound with the problematic drug cues. Of course, establishing new drug cues in the clinic would require presentation of the abused drug and this is undesirable. However, if deepened extinction could be produced by compounding the problematic drug cue(s) with other non-drug appetitive cues, a solution might be had. For example, periodic presentation of a shape on a computer screen could be established as a cue predictive of a small monetary reward. This shape should then come to elicit positive feelings, perhaps even a small "rush" or "high" that is associated with winning money. This non-drug appetitive cue could then be simultaneously presented with the target drug cue on compound extinction trials, where no money (or drug) would be presented. If the effects of the prediction error produced by the omission of reward on these compound extinction trials generalized to the drug cue, deepened extinction of the drug seeking elicited by the drug cue could be achieved.

In all of the deepened extinction studies to date, the compounded cues were previously associated with the same reinforcer. That is, either 2 drug cues (Janak et al., 2011; Kearns et al., 2012) or 2 food cues (Janak and Corbit, 2010; Rescorla, 2006; Leung et al., 2012) were compounded with each other. It is unknown whether compounding cues associated with different reinforcers will also result in deepened extinction. The present study will test this possibility in a preclinical model by investigating whether compounding a food cue with a cocaine cue will lead to the deepened extinction of the cocaine seeking elicited by the latter. Finding such an outcome would suggest that a version of deepened extinction treatment for drug abuse involving compounding non-drug cues with drug cues could be possible.

2. Methods and materials

2.1. Subjects

Naïve adult male Long-Evans rats served as subjects. Thirteen rats completed Experiment 1 and 12 rats completed Experiment 2. Rats were individually housed in plastic cages with wood chip bedding and metal wire tops. They were maintained at 85% of their free-feeding weights (approximately 350–450 g). The colony room where the rats were housed had a 12-h light:dark cycle with lights on at 08:00 h. Training sessions were conducted 5–7 days per week during the light phase of the light:dark cycle. Throughout both experiments, rats were treated in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences, 2011) and all procedures were approved by American University's Institutional Animal Care and Use Committee (IACUC).

2.2. Apparatus

Training took place in six operant chambers. Each chamber was 20 cm high, 23 cm long, and 18 cm wide and had aluminum front and rear walls, white translucent plastic side walls, a clear plexiglass ceiling, and a grid floor. A response lever and food trough were located on the front wall of the chamber. A click stimulus (approximately 15 clicks/s and 64–78 dB), created by a BRS CL-201 click generator and amplified by a BRS AA-201 amplifier, was presented through a 20-cm diameter speaker located in an enclosure mounted approximately 21 cm above the chamber. A tone stimulus (approximately 4500 Hz and 64–66 dB) was delivered by a model SC628HR Sonalert (Mallory Sonalerts, Indianapolis, IN) that was mounted on top of the chamber ceiling. A light stimulus was provided by two 15-cm, 25-W, 120-VAC tubular light bulbs located 10 cm outside each of the side walls of the chamber. These light bulbs were operated at 103 VAC. Each chamber was housed inside a sound attenuation chest (Weiss, 1970) that had a continuously operating ventilation fan. A shielded houselight provided a low level of continuous illumination during all sessions. Experimental procedures were controlled by Med-Associates software (Med-PC, St. Albans, VT) running on a PC located in an adjacent room.

Cocaine (provided by the National Institute on Drug Abuse) in a saline solution at a concentration of 2.56 mg/ml was infused at a rate of 3.19 ml/min by 10-ml syringes driven by Harvard Apparatus (South Natick, MA) or Med-Associates (St. Albans, VT) syringe pumps located outside of the sound attenuation chests. Tygon tubing extended from the 10-ml syringes to a 22-gauge rodent single-channel fluid swivel and tether apparatus (Alice King Chatham Medical Arts, Hawthorne, CA) that descended through the ceiling of the chamber. Cocaine was delivered to the subject through Tygon tubing that passed through the metal spring of the tether apparatus. This metal spring was attached to a plastic screw cemented to the rat's head to reduce tension on the catheter.

2.3. Procedure: Experiment 1

The present procedure was similar to that previously used by Kearns et al. (2012) except that one of the S^Ds – the light – was established as an S^D for food-reinforced responding rather than cocaine-reinforced responding.

2.3.1. Lever-press acquisition. With the light stimulus continuously illuminated, rats were trained to lever press for food pellets (45 mg, Rodent Grain-Based Diet, BioServ, Frenchtown, NJ) in sessions lasting approximately 60 min. Food pellets were available for lever pressing on a fixed-ratio 1 (FR-1) schedule and were also presented non-contingently every 120 s if a lever press was not made. Rats were trained until 100 responses were emitted within a session.

2.3.2. Light/no-light discrimination training. During 2-h sessions, light S^D components lasting 180 s on average (range: 150–210 s) were presented, during which food pellets were available for lever pressing according to a variable-interval (VI) 15-s schedule. These light components alternated with S^Δ components lasting 60 s on average (range: 30–90 s) where the light was off and responding did not result in food pellet delivery. A 30-s response correction contingency operated during the final 30 s of each S^Δ component. According to this contingency, a 30-s S^Δ-termination clock was reset to zero by a response. This contingency was designed to reduce response rates during S^Δ components. Rats were trained with the schedule parameters described above for 1 session. Then, the VI schedule that operated during S^D components was increased to VI 60 s and sessions were continued until a minimum of 4 further sessions were completed and until rats responded at least 3 times faster in light than in light-off for 2 consecutive sessions.

2.3.3. Surgery. Rats were then surgically prepared with chronic indwelling jugular vein catheters, using a modification of the procedure originally developed by Weeks (1962). In brief, under ketamine (60 mg/kg) and xylazine (10 mg/kg) anesthesia, approximately 3 cm of Silastic tubing (0.044 mm i.d., 0.814 mm o.d.) was inserted into the right jugular vein. This Silastic tubing was connected to 8 cm of vinyl tubing (Dural Plastics; 0.5 mm i.d., 1.0 mm o.d.) that was passed under the skin around the shoulder and exited the back at the level of the shoulder blades. The vinyl tubing was threaded through a section of Tygon tubing (10 mm long, 4 mm diameter) that served as a subcutaneous anchor. Six stainless steel jeweler's screws were