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Journal
International Journal of Comparative Psychology, 18(2)

ISSN
0889-3675

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Publication Date
2005

DOI
10.46867/ijcp.2005.18.02.05

International Journal of Comparative Psychology, 2005, **18**, 112-125.

Cocaine and Selective Associations: Investigations into a Biological Constraint on Learning with Drug Self-administration and Shock Avoidance as Reinforcers

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When a tone-light compound was a discriminative stimulus for cocaine-reinforced responding, the light gained most of the control over responding. In contrast, when the compound was an aversive S^D for shock-avoidance, tone control increased. In previous studies, tone control also increased when the tone-light compound was made aversive by signaling food-absence. However, that was not the case in Experiment 2 where tone-light signaled cocaine-absence. Experiment 1 produced an interincentive (cocaine vs. shock) selective association with drug self-administration maintained behavior for the first time. This extends the generality of the selective association biological constraint on learning to self-administered drugs.

In Garcia and Koelling's (1966) original selective association experiment, a compound conditioned stimulus (CS) consisting of a taste and an audiovisual stimulus was paired with a lithium chloride unconditioned stimulus (US) in one group of rats and with an electric shock US in another group. In testing, the taste and the audiovisual stimulus were presented separately. The taste stimulus controlled a stronger conditioned response (CR), reflected in suppression of drinking, when lithium chloride was the US, while the audiovisual stimulus controlled a stronger conditioned response when electric shock was the US. This first demonstration of a selective association showed that (1) the choice of the CS used in conditioning experiments was not as arbitrary as believed, and (2) experimental outcomes might critically depend on the particular combinations of CSs and USs used. Therefore, when a set of stimuli have been given equal opportunity to control a response, the US may determine which stimulus is most effective. Such selective associations have also been called "stimulus-reinforcer interactions" (LoLordo, 1979).

While Garcia and Koelling's (1966) experiment employed classical conditioning, operant conditioning procedures have also been used to study selective associations. LoLordo and associates (Foree & LoLordo, 1973; LoLordo & Furrow, 1976) used a tone-light (TL) compound as a discriminative stimulus (S^D) that occasioned pigeons' treadle-pressing for either food or shock avoidance. When food was the reinforcer, operant responding came under visual control, whereas auditory control increased when responding was maintained by shock avoidance.

Animals were housed and treated in accordance with the policies of the IACUC at American University. This research was supported by NIDA Grant DA-08651 awarded to Stanley J. Weiss and in part by the NIDA Intramural Research Program. Correspondence concerning this article should be addressed to Stanley J. Weiss, Department of Psychology, American University, Washington, DC 20016, U.S.A. (sweiss@american.edu).

The stimulus-reinforcer interaction reported by Foree and LoLordo (1973) is presented in the left frame of Figure 1. Similarly, the right frame of Figure 1 shows that in rats visual control predominated when food was the reinforcer for lever pressing in the presence of a TL compound S^D, while auditory control predominated when lever pressing in TL avoided shock (Schindler & Weiss, 1982).

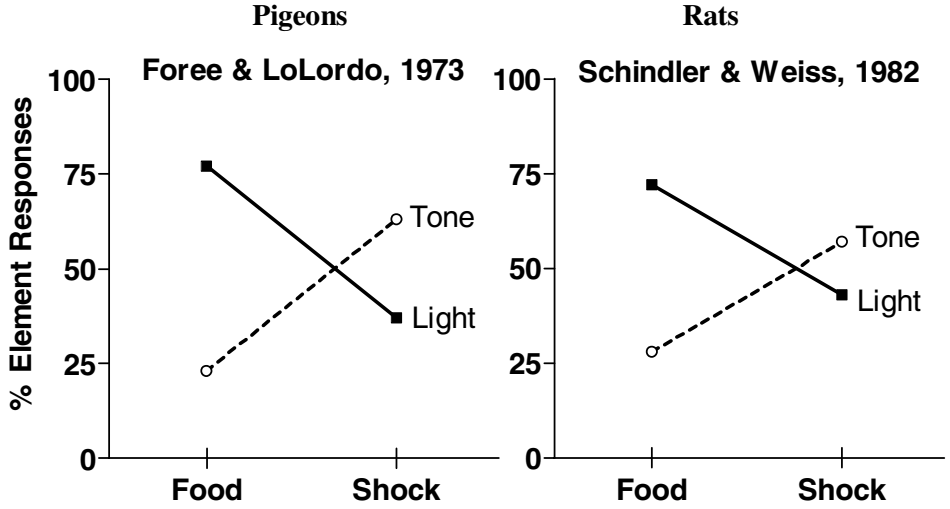

Figure 1. Left: The percentage of total stimulus element responses emitted in tone (open circles) and in light (filled squares) by pigeons for the food and shock avoidance groups of Foree and LoLordo (1973, adapted from their Figure 3). Copyright by the American Psychological Association, reprinted by permission. Right: The same measures for the rats in the food and shock avoidance groups from Schindler & Weiss (1982, adapted from their Figure 3). Copyright by Academic Press, reprinted by permission. These percentages are calculated by dividing the number of responses emitted to the tone or the light conditions on the stimulus-element test by the total responses emitted to the tone and light elements and then multiplying by 100 [responses in tone or light/(responses in tone + responses in light) X 100].

Experiment 1

To date, the only positive reinforcer that has been used in selective association experiments has been food. The present study sought to explore the generality of the selective association phenomenon over positive reinforcers by using cocaine to maintain responding in TL. This is also the first study investigating selective associations with drugs. One group of rats was trained to lever-press in TL for cocaine infusions and a second group was trained to lever-press in TL to avoid shock. For both groups, no cocaine infusions or shock was received in the absence of tone and light ($\bar{T}\bar{L}$) and responses in $\bar{T}\bar{L}$ had no consequences (extinction). This training established TL as a discriminative stimulus for cocaine self-administration or shock avoidance, respectively. In testing, tone and light were presented separately on a stimulus-element test to assay the degree of control over responding that each of the elements had acquired. Since it is well established that cocaine functions as a positive reinforcer in rats (Weeks & Collins, 1987; Wise, 1987), it is expected that the light would gain predominant control over responding in the cocaine group, just as light does when food is the reinforcer.

Method

Subjects. Eight naïve adult male Long-Evans rats completed the experiment. Rats were housed in individual cages in a colony room with a 12-h light/dark cycle (lights on at 08:00 h). Training sessions were conducted during the light phase. Water was available continuously, except during training sessions. Weights were maintained at approximately 80% of ad lib (mean = 390 g; SEM = 9.8 g) with laboratory chow provided following daily training sessions.

Apparatus. Training took place in operant chambers enclosed in sound attenuation chests (Weiss, 1970). Experimental events were controlled by a MED Associates (St. Albans, VT) computer system from an adjacent room where cumulative recorders were also situated. Each chamber measured 20 cm high, 23 cm long, and 18 cm wide, and was dimly illuminated at all times by a shielded 7.5-W houselight operated at 3W. The level of illumination provided by this houselight assembly was enough to make the rat barely discernible, but did not activate a photometer (Simpson, 408-2).

Each chamber contained a lever operandum and food trough (not used in present experiment) on the front wall. A response on the lever closed a Gerbrands microswitch, requiring a force of 0.14 to 0.18 N (15 to 20 gm). Ambient noise with the exhaust fan running was measured at 70 dB (Realistic SPL meter). An approximately 2000-Hz, 79-dB tone was generated by a BRS AO-201 audio oscillator, amplified by a BRS AA-201 amplifier, and presented through an 8-Ohm, 20-cm speaker mounted in an enclosure 21.5 cm above the training chamber. There were two 15-cm, 25-W, 120-V tubular light bulbs 10 cm behind the two translucent side walls that provided the visual stimulus. These lights were operated at 74 V and produced 0.55 log ft-Lamberts illumination when measured at the center of a side wall.

Shock for each chamber was generated by either a Lehigh Valley Electronics 1531 constant-current shocker or a BRS/LVE SGS-004 solid-state shocker-scrambler. It was delivered through 0.3-cm diameter stainless steel rods spaced 1.3 cm apart, which composed the floor of the chamber. The lever and front wall of the chamber were also in the shock circuit. All components included in the shock circuit were cleaned with a wet paper towel immediately prior to training sessions.

Cocaine (National Institute on Drug Abuse, Bethesda, MD, U.S.A.) in a saline vehicle at a concentration of 2.56 mg/ml was delivered at a rate of 3.19 ml/min through Tygon tubing wrapped in a metal spring. The tubing was suspended through the ceiling from a 22 gauge rodent single-channel fluid swivel (Alice King Chatham Medical Arts, Hawthorne, CA, U.S.A.). Drug infusions were delivered by a MED Associates or Harvard Apparatus model 22 syringe pump, using a 10-ml syringe. Pumps were situated outside the sound attenuation chests. The spring was attached to the plastic screw mounted on the rat's head, reducing tension on the catheter.

Procedure: Cocaine Group. Intravenous catheters were implanted under ketamine (60 mg/kg) and xylazine (10 mg/kg) anesthesia using procedures described in detail earlier (Panlilio, Weiss, & Schindler, 1996). Dose per infusion was controlled by manipulating the duration of infusion. Catheters consisted of approximately 4 cm Silastic tubing (0.044 mm ID, 0.814 mm OD) connected to vinyl tubing (Dural Plastics, 0.5 mm ID, 1.0 mm OD). The vinyl portion of the catheter exited at the back of the neck and was obturated with a modified 23 gauge needle. A 20-mm plastic screw was cemented with dental acrylic to 4 stainless steel jeweler's screws implanted in the skull.

Rats were given one week to recover in their home cages before self-administration training began. Daily self-administration sessions lasted approximately 4 h. The procedures used to produce stimulus control of cocaine self-administration are described in detail in Weiss, Kearns, Cohn, Schindler, & Panlilio (2003). During the first training session, each lever response produced a 1.0 mg/kg infusion of cocaine. TL was present for the entire session. Once lever-pressing developed on this continuous reinforcement schedule, the response requirement was gradually increased from fixed-ratio (FR) 1 to FR 10. Concurrently, the unit dose was gradually decreased from 1.0 mg/kg to 0.32 mg/kg. Once a rat was reliably responding on the FR 10 schedule, a variable-interval (VI) 30-s schedule was introduced. (In all VI schedules employed in this study, intervals ranged from 2 s to three times the mean value, with any interval value equally likely to follow any other value.) As before, TL was present for the entire session. The VI value was gradually increased to VI 60-s over the next several sessions.

Once stable patterns of responding were observed on the VI schedule, discrimination training began with a multiple (mult) variable-interval (VI) 30-s extinction (EXT) schedule. Under this schedule, responses were reinforced in TL by a cocaine infusion according to a VI 30-s contingency, while responses went unreinforced (EXT) in $\overline{\text{TL}}$. TL and $\overline{\text{TL}}$ components alternated every 60 s on

average (range: 30-120 s). To promote response cessation in $\overline{TL}$, a 10-s response correction contingency was added to the end of each $\overline{TL}$ component. According to this contingency, a lever press during the last 10 s of a $\overline{TL}$ component delayed the presentation of TL so that $\overline{TL}$ did not end until responding had ceased for at least 10 s.

The parameters of the mult VI EXT schedule and the unit dose were gradually adjusted for each rat to produce moderate response rates in TL and cessation of responding in $\overline{TL}$. For subjects S-13 and S-20 a VI 45-s schedule operated in TL on the terminal baseline. For S-43 and S-44, respectively, a VI 90-s and a VI 60-s schedule were used in TL to produce response rates more similar to those obtained with the other rats under the VI 45-s schedule. For all subjects, the final baseline response correction value in $\overline{TL}$ was 30 s (i.e., a lever press during the last 30 s of a $\overline{TL}$ component delayed the presentation of TL so that $\overline{TL}$ did not end until responding had ceased for at least 30 s).

During each session, the first 2 infusions were 1.0 mg/kg, and the dose was reduced to 0.2-0.28 mg/kg for the remainder of the session. The procedure of making the first 2 infusions of each session 1.0 mg/kg was employed to accelerate the cocaine "loading phase" and thereby reduce variability in early session responding. This procedure also prevented the reinforcement of a response incompatible with lever pressing as might occur under the commonly used priming procedure where drug is infused independently of responding at the beginning of a session. On the terminal baseline schedule rats typically earned approximately 100 infusions over the course of the 4-h session.

Procedure: Shock avoidance Group. Initially, with TL present for the duration of the session, rats were shaped to escape a continuous 0.5-mA shock by pressing the lever. Once rats began to regularly press the lever, a free-operant-avoidance (FOA) schedule was introduced. Initially, rats were trained on a response-shock (RS) 25-s shock-shock (SS) 1-s FOA schedule. According to this schedule, each response postponed shock by 25 s. If 25 s elapsed without a response, the SS interval began and a 0.5-mA, 0.5-s shock was delivered every 1 s until a response occurred. Responses made during a shock presentation prolonged the shock for 0.5 s in order to discourage shock-initiated responding. Over sessions, the SS interval was gradually increased from 1 s to 5 s. The shock intensity was adjusted for individual rats to an intensity no greater than the minimum necessary to maintain moderate rates of responding. Initially, sessions lasted until a rat received 200 shocks. As rats became more proficient at avoiding, session length was increased up to 8 h. Because these sessions were so long, rats in the shock group were trained on alternate days.

Once a rat reached an avoidance criterion of receiving no more than 0.6 shocks/min (i.e., avoiding at least 75% of the potential RS interval shocks) on this RS 25-s SS 5-s schedule for three consecutive sessions, discrimination training began on a mult FOA EXT schedule. Now, TL components alternated with the $\overline{TL}$ components every 100 s on average (range: 48-160 s). In TL, the FOA schedule operated and in $\overline{TL}$ no shock was ever delivered (extinction). There was no response correction contingency programmed in $\overline{TL}$ because responses would have been reinforced by delaying the presentation of TL. On the terminal baseline schedule, the frequency of shock delivery in the Shock avoidance Group was different from the frequency of cocaine infusion in the Cocaine Group because the goal of training was to produce comparable baseline behavior over the two groups rather than to match them on frequency of cocaine infusion/shock delivery.

Procedure: Stimulus-Element Test. For subjects in both groups, the training criterion was having response rates in TL at least 10 times higher than in $\overline{TL}$ for three consecutive sessions. The stimulus-element test lasted 72 min and consisted of twelve block-randomized, 60-s presentations of T, L, and TL. That is, in each block, T, L, and TL were presented in random order and twelve blocks were presented over the course of the test. Each test stimulus was separated by a 60-s period when all stimuli were off.

Prior to the start of the test, there was an approximately 2-h warm-up period when rats responded on their normal training baseline schedule. For both groups, the stimulus-element tests were conducted in extinction (i.e., no cocaine or shock was presented during test stimuli). However, for the shock group, there were two reacquisition periods inserted after the fourth and eighth blocks of the test. During these reacquisition periods, the FOA contingency was reinstated during a TL component lasting 300 s. This was followed by a 90-s EXT component in $\overline{TL}$. A light test stimulus followed one reacquisition period and a tone followed the other. Previous studies (Panlilio & Weiss, 1993; Weiss, et al., 1993b) using similar training and testing procedures have used reacquisition periods to increase the number of test responses made by shock-trained rats, who typically make fewer test responses than food-trained rats.

Results and Discussion

Baseline training data from the last 3 sessions preceding the stimulus-element test are presented in Table 1. All rats responded in TL at least 10 times faster than in $\bar{T}\bar{L}$ except for S20 (Cocaine Group) who was inadvertently tested after meeting the 10:1 discrimination ratio on 3 non-consecutive (rather than consecutive) sessions. However, this subject achieved the 10:1 discrimination ratio on 2 of its last 4 sessions, including the final session, and achieved an 8:1 ratio on the two other sessions. Therefore, this subject's stimulus control on the terminal baseline was not appreciably different from other subjects in the same group. Although the Cocaine Group had higher response rates, on average, than the Shock- Avoidance Group in both TL and $\bar{T}\bar{L}$, the range of response rates in TL over the two groups overlap each other.

The total number of responses emitted in each of the stimulus conditions of the stimulus-element test, and the percentage of element responses in light [(responses in light/(responses in tone + responses in light) X 100], are presented in Table 2. On average, rats in the Cocaine Group made more responses than rats in the Shock avoidance Group in all three test stimuli. The Cocaine Group responded 1.8 times and 2.5 times faster than the Shock avoidance Group in T and TL, respectively. However, the Cocaine Group responded more than 7 times faster than the Shock avoidance Group in L. For both groups, more responses were emitted in TL than in either element alone.

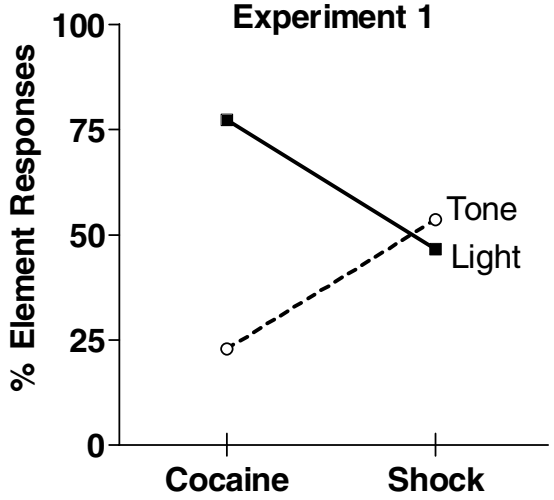

Figure 2. The percentage of total stimulus element responses emitted in tone (open circles) and in light (filled squares) for the Cocaine Group and the Shock avoidance Group in Experiment 1. See Figure 1 for explanation of calculations.

Figure 2 presents the mean percentage of element responses emitted in T and L for both groups. This figure illustrates that the light controlled 77% of test responses in the Cocaine Group, but only 48% of test responses in the Shock avoidance Group. A repeated measures ANOVA performed on test response rates to tone and to light indicated that there were significant effects of reinforcer: group, $F(1, 6) = 22.13$, $p < 0.01$; stimulus, $F(1, 6) = 17.11$, $p < 0.01$; and stimulus-by-reinforcer interaction, $F(1, 6) = 23.81$, $p < 0.01$. Thus, this experiment has demonstrated a cocaine/shock selective association for the first time, thereby extending

research on the biological constraint on learning to another type of reinforcer: self-administered drugs.

Within each group, the percentage of element responses controlled by light was not related to baseline training response rates. For example, in the Cocaine Group, the rat (S-44) with the highest response rate during training (in both TL and $\overline{TL}$) had the lowest percentage of element responses to L for the group, while the rat (S-43) with the second highest training response rates had the highest percentage of element responses to L. Similarly, in the Shock avoidance Group, the two rats nearly tied for the lowest baseline training response rate (S-17 and S-10) had the second-highest and lowest percentages of responses emitted in L for their group. Finally, S-41 in the Shock avoidance Group had a TL response rate, 8.5 responses/min, that was quite similar to the TL response rates of S-13 and S-20 in the Cocaine Group (8.8 and 8.5 responses/min, respectively). However, the percentage of element test responses controlled by L for shock avoidance rat S-41 (59%) was considerably lower than that for cocaine rats S-13 and S-20 (73% and 84%, respectively). Therefore, it seems unlikely that the group difference in modality of stimulus control observed here was influenced by differences in baseline training response rates between the groups.

The 77% light control in the Cocaine Group is very similar to what has been found in previous studies employing training and testing procedures similar to those used in the present experiment where food was the reinforcer instead of cocaine (Panlilio & Weiss, 1993; Schindler & Weiss, 1982; Weiss, Panlilio, & Schindler, 1993a). The 53% tone control in the Shock avoidance Group closely replicates previous findings reported by Schindler and Weiss (1982). In fact, the results of Schindler and Weiss (1982; reproduced in the right frame of Figure 1), whose training and testing conditions were very similar to those of the present experiment, are almost indistinguishable from those presented in Figure 2 of the present experiment, where responding on the mult VI EXT schedule was maintained by cocaine.

The similarity between the selective associations produced between cocaine and shock and those between food and shock suggests that (1) the biological predisposition towards visual control when food is the reinforcer is also operating when cocaine is the reinforcer, and (2) cocaine and food could be related to similar underlying reinforcement mechanisms. Furthermore, the results of the present experiment indicate that the outcomes of conditioning experiments employing cocaine as the reinforcer (or US) might be strongly influenced by the modality of the S^Ds (or CSs) used.

Experiment 2

The results of selective association experiments have traditionally been ascribed to innate propensities for certain sensory modalities to control responding maintained by a particular type of reinforcer (e.g., light with food and tone with shock). For example, LoLordo (1979) referred to these biological constraints as "stimulus-reinforcer interactions." Weiss, Panlilio, and Schindler (1993a) questioned the justification for this specific reinforcer-based attribution of the observed shock-auditory and food-visual selectivity. They pointed out that TL would become hedonically positive when associated with food (Holz, Azrin, & Ayllon, 1963; Le-

itenberg, 1965) and hedonically negative when associated with shock (Verhave, 1962; LoLordo, 1969). Operationally, this means that a subject would be attracted to a food-associated stimulus and repelled from a shock-associated one. Thus, traditional selective association experiments confounded the reinforcer (food or shock) presented in the TL compound with the conditioned hedonic state (positive or negative, respectively) this association would create.

Table 1
Experiment 1 Training Data.

Cocaine Group					
Subject	TL	$\bar{T}\bar{L}$	Infusions/min	Dose	Sessions
S13	8.8	0.8	0.4	0.28	30
S20	8.4	1.0	0.4	0.25	18
S43	18.6	1.1	0.3	0.20	34
S44	20.1	1.7	0.5	0.20	33
Mean	14.0	1.2	0.4	0.23	28.8
Shock avoidance Group					
Subject	TL	$\bar{T}\bar{L}$	Shock/min	mA	Sessions
S17	5.5	0.1	0.6	0.6	26
S10	5.6	0.0	0.6	0.5	19
S40	6.1	0.4	0.6	0.5	42
S41	8.5	0.3	0.6	0.5	29
Mean	6.4	0.2	0.6	0.53	29.0

Note. Table 1 presents for each group, averaged over the last three training sessions, responses per minute in TL and $\bar{T}\bar{L}$, cocaine infusions or shocks per minute in TL, unit dose or shock intensity (mA), and total number of training sessions.

Weiss et al. (1993a) eliminated this confound by using a food-related contingency to make TL positive in one condition and aversive in another condition. To achieve this, they applied formulations from the appetitive-aversive interaction theory of motivation (Dickinson & Pearce, 1977) to the selective-association paradigm. A central assumption of appetitive-aversive interaction theory is that a stimulus signaling the absence of food is in certain ways functionally equivalent, hedonically, to a stimulus that signals shock. There is substantial evidence from a variety of behavioral paradigms that supports this assumption (for reviews see Coughlin, 1972; Leitenberg, 1965).

Weiss et al. (1993a) made TL hedonically positive or negative relative to the absence of TL using only food. (Throughout this experiment, positive, +, and negative, -, are used to denote whether TL should have been made hedonically positive or hedonically negative, respectively, according to the reinforcement contingency operating in TL.) In their TL+ condition, Weiss et al. (1993a) trained rats on a mult schedule wherein responding produced food in the presence of the TL compound but not in its absence. Thus TL signaled the availability of food—a condition appropriate for making TL hedonically positive (TL+). In their TL- condition, rats were trained on a chained schedule where responding in the presence of the TL

compound only produced a terminal link, signaled by the tone and light both being off ($\bar{T}\bar{L}$), where food was delivered contingent on response cessation. Here, where all food was received in $\bar{T}\bar{L}$, TL became a signal for the absence of food. Such conditions would make TL hedonically negative (TL-) relative to $\bar{T}\bar{L}$ (see above).

After stimulus control was well established under each of these conditions, a stimulus-element test was administered, where T and L were presented separately for the first time. On this test (1) visual control predominated in the TL+ condition, where TL was a signal for food, while (2) auditory control was significantly enhanced in the TL- condition, where TL had been associated with the absence of food. These results were subsequently replicated in another study by Weiss et al. (1993b) that used the same chambers and stimuli as the present cocaine study. These findings are important because such auditory enhancement had only been reported previously when TL was an aversive stimulus that controlled shock avoidance. This led Weiss et al. (1993a) to suggest a hedonic model of selective associations wherein hedonically positive conditions favor visual control while hedonically negative conditions increase auditory control.

Since Experiment 1 demonstrated a cocaine/shock selective association, the present study went on to investigate the hedonic hypothesis of selective associations using drug-maintained behavior. To accomplish this, schedules of cocaine self-administration comparable to the TL+ and TL- food schedules just described above were employed in Experiment 2 with cocaine rather than food as the reinforcer. Would these TL+ and TL- schedules of cocaine self-administration—like the TL+ and TL- food schedules on which they were based—influence the relative control by the auditory and visual elements of the TL compound?

Table 2
Experiment 1 Stimulus-Element Test.

Cocaine Group				
Subject	Tone	Light	TL	%L
S13	1.0	5.3	7.2	84
S20	1.3	3.7	5.6	73
S43	1.6	7.9	9.1	83
S44	2.8	6.1	12.4	68
Mean	1.7	5.7	8.6	77.2
Shock avoidance Group				
Subject	Tone	Light	TL	%L
S17	0.5	0.6	2.8	54
S10	1.7	0.6	4.3	26
S40	0.7	0.6	3.6	47
S41	1.0	1.4	3.1	59
Mean	1.0	0.6	3.5	46.5

Note. Table 2 presents responses per minute of T, L, and TL and the percentage of element responses in L from stimulus-element tests for the Cocaine and Shock Avoidance groups. Each test stimulus was presented 12 times for 60 s periods over the course of the block-randomized test.

Method

Subjects. Fifteen adult male Long-Evans rats completed Experiment 2, with 7 rats in the TL+ Group and 8 rats in the TL- Group. The TL+ Group included the 4 rats from the *mult* VI EXT Cocaine Group of Experiment 1, since the training and testing procedures used for the TL+ Group of Experiment 2 were identical to those of the mult VI EXT group of Experiment 1. Rats were housed and maintained and surgically prepared as described in Experiment 1.

Apparatus. All experimental equipment used was the same as that in Experiment 1.

Procedure: Design Overview. Two groups of rats were trained with either the TL+ or TL- schedule, wherein they received cocaine in TL or the absence of TL ($\overline{TL}$), respectively. Under both schedules, training continued until a rat was responding at stable, moderate rates in TL and ceased responding in $\overline{TL}$. To achieve this baseline behavioral control, the schedule parameters were gradually adjusted for each rat over sessions, as described below. Each rat was trained 7 days per week, with sessions lasting approximately 4 h. Once the training criteria were met, the stimulus-element test was administered wherein T and L were presented separately to determine the extent to which each stimulus controlled responding.

Procedure: TL+ (mult VI EXT) Group. The procedure used for this group was the same as that described for the Cocaine Group of Experiment 1.

Procedure: TL- (chain VI DRO) Group. In the TL- condition, rats were initially trained with a chain FR 1 differential-reinforcement-of-other-behavior (DRO) 5-s schedule. Under this schedule, a lever-press in TL immediately produced $\overline{TL}$. In $\overline{TL}$, a 1.0 mg/kg infusion of cocaine was delivered according to a DRO 5-s contingency. That is, cocaine was not infused until 5 s had passed without a response. After each injection during this initial chained schedule training, a 55-s timeout occurred during which responses were recorded but had no programmed consequences. When the timeout ended, TL was presented. One infusion per $\overline{TL}$ period was delivered during this phase of training. For the first two chained schedule sessions, if a rat failed to respond in TL within 400 s on average (range: 350-450), $\overline{TL}$ was presented automatically with the DRO 5-s contingency in effect. Once the lever-pressing response was acquired, the unit dose was gradually decreased over sessions from 1.0 mg/kg to approximately 0.2 mg/kg, and the length of the postinfusion TO was gradually decreased from 55 s to approximately 20 s.

Once regular responding occurred on this chain FR 1 DRO 5-s schedule, a VI contingency was introduced in TL such that $\overline{TL}$ was produced by the first leverpress emitted after the amount of time specified by the current VI interval passed in TL. The parameters of this chain VI DRO schedule were gradually adjusted to produce moderate, sustained rates of responding in TL and cessation of responding in $\overline{TL}$. Under this schedule, infusions were no longer followed by TO. Rather, $\overline{TL}$ durations were programmed such that up to 2 infusions could be received per $\overline{TL}$ component if the rat ceased responding during the component. Over sessions, the VI schedule in effect during TL was increased from 15 to 30, to 45 and, finally, to 60 s. Concurrently, the DRO contingency in effect during $\overline{TL}$ was gradually increased from 15 to 20 to 30 s, while $\overline{TL}$ component lengths were correspondingly increased from 30 to 45 to 60 s, respectively. For all rats, the final parameters of this schedule were chain VI 60-s DRO 30-s, with $\overline{TL}$ component lengths ranging from 40-90 s. The first 2 infusions of each session were 1.0 mg/kg, but thereafter the dose was reduced to 0.2-0.25 mg/kg for the remainder of the session. For additional information on producing stimulus control with cocaine on a chain schedule, see Experiment 3 in Weiss et al. (2003).

Procedure: Stimulus-element Test. Rats in both groups were given a stimulus element test once they met the criterion of responding at least 10 times faster in TL than in $\overline{TL}$ for three consecutive sessions or for three out of four sessions, including the final two sessions. The testing procedure was the same as that described for the Cocaine Group of Experiment 1.

Results

Table 3 presents training data for individual subjects. Mean response rates in TL and $\overline{T}\overline{L}$ for the TL+ Group were comparable, respectively, to the response rates in TL and $\overline{T}\overline{L}$ for the TL- Group. All subjects clearly exceeded the 10:1 discrimination ratio between rates in TL and $\overline{T}\overline{L}$. The rates of reinforcement in the schedule component in which cocaine was available (i.e., TL in the TL+ Group and $\overline{T}\overline{L}$ in the TL- Group) were also comparable. Finally, the number of training sessions required to meet criterion were similar over groups.

The total number of responses emitted in each of the stimulus conditions of the stimulus-element test and the percentage of element responses in light [(responses in light/(responses in tone + responses in light) X 100] are presented in Table 4. Overall, the rats made a similar number of responses in TL in both the TL+ (88.3 responses) and TL- (72.4 responses) Groups, and in both groups these test rates in TL were slightly less than the sum of the rates in the T and L elements.

Figure 3 presents the mean percentage of element responses in L and in T from the stimulus-element tests for both groups. The mean percentage of responses controlled by L was nearly the same for the two groups: 69.6 for the TL+ Group and 65.8 for the TL- Group. A repeated measures ANOVA performed on the test response rates to tone and to light revealed that there was no significant effect of group, $F < 1$, or stimulus-by-group interaction, $F = 1$, but there was a significant effect of stimulus, $F(1, 13) = 13.1$, $p < 0.01$.

General Discussion

In Experiment 1, an interincentive (cocaine vs. shock) selective association was produced for the first time with behavior maintained by drug self-administration. When TL was an S^D for cocaine-reinforced responding, the L element gained predominant control over responding. In contrast, when TL was an S^D for shock avoidance, T control increased. This suggests that cocaine might function comparably to food in terms of its inherent associability with different types of stimuli.

However, in Experiment 2, an intraincentive (cocaine) selective association was not observed between groups where TL was established as a signal for cocaine vs. a signal for the absence of cocaine. This result was unexpected because intraincentive selective associations have been produced solely by (1) food-generated appetitive excitors and inhibitors in four previous studies and in two different species (rats: Panlilio & Weiss, 1993; Weiss et al., 1993a, 1993b; pigeons: Panlilio & Weiss, 2005), and solely by (2) shock-generated aversive excitors and inhibitors in three previous studies with two different species (rats: Panlilio & Weiss, 1993; Weiss et al., 1993b; pigeons: Panlilio & Weiss, 2005). Thus, the predictions of Weiss et al.'s (1993a, 1993b) hedonic model of have been confirmed previously across four different experiments and in two different species.

The fact that an intraincentive selective association is produced with food, but not with cocaine, is especially surprising because in those earlier experiments that employed food as the reinforcer, training and testing procedures were comparable to those used in Experiment 2 of the present study. The food study of Weiss et al. (1993b) also used the same gender and strain of rats (male Long-Evans),

training chambers, and training stimuli as Experiment 2 of the present study. What does a direct comparison of the results of Experiment 2 of the present (cocaine) study with those of Weiss et al's. (1993b) food study reveal?

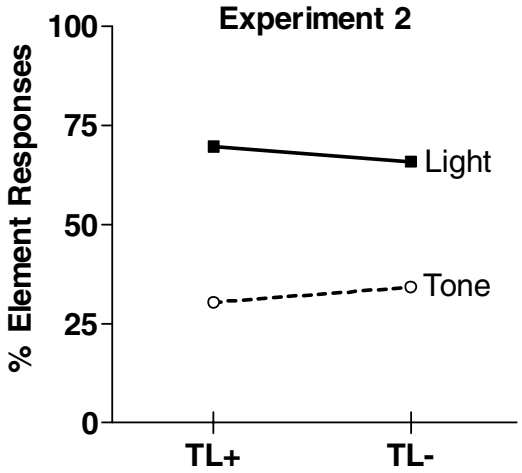

Figure 3. The percentage of total stimulus element responses emitted in tone (open circles) and in light (filled squares) for the TL+ and TL- Groups of Experiment 2. . See Figure 1 for explanation of calculations.

Table 3
Experiment 2 Training Data.

Subject	TL	$\overline{TL}$	Reinf./min	Dose	Sessions
TL+ Group					
S13	8.8	0.8	0.39	0.28	30
S10	8.2	0.6	0.38	0.28	17
S16	11.0	0.9	0.43	0.28	20
S18	8.8	0.6	0.43	0.25	21
S20	8.4	1.0	0.42	0.25	18
S43	18.6	1.1	0.31	0.20	34
S44	20.1	1.7	0.48	0.20	33
Mean	12.0	1.0	0.41	0.25	24.7
TL- Group					
S15	12.9	0.7	0.54	0.20	22
S12	5.0	0.2	0.60	0.20	21
S21	14.5	0.8	0.56	0.25	33
S25	4.6	0.2	0.57	0.20	22
S30	3.9	0.2	0.58	0.20	20
S31	7.6	0.6	0.55	0.20	22
S32	14.1	0.8	0.56	0.20	20
S33	10.4	0.4	0.59	0.20	17
Mean	9.1	0.5	0.57	0.21	22.1

Note. For each group, averaged over the last three training sessions, responses per minute in TL and $\overline{TL}$, reinforcers per minute in the reinforced component (TL in the TL+ Group, $\overline{TL}$ in the TL- Group), unit dose, and total number of training sessions.

The percentage of element responses controlled by L in the TL+ Group of Experiment 2 of the present cocaine study and that of the food-trained TL+ Group of Weiss et al. (1993b) were almost identical: 69.6% and 70.3%, respectively. Even the standard deviations of these percentages were close: 13.1 and 10.0, respectively. However, the results of the TL- Groups were not nearly as similar over these studies. For the cocaine-trained TL- Group of the present study, L controlled 65.8% of their element responses (SD = 19.4), a percentage not significantly different from that observed in the TL+ Group. In Weiss et al.'s (1993b) study, the TL- food group emitted only 53.3% of their element response to L (SD = 12.4), a percentage that was significantly lower than that observed in their TL+ food group. This pattern of results suggests that TL failed to act as a hedonically negative condition (relative to $\bar{T}\bar{L}$) in the TL- Group of the present study.

Table 4
Experiment 2 Stimulus-Element Test.

TL+ Group				
Subject	Tone	Light	TL	%L
S13	1.0	5.3	7.2	84
S10	1.5	1.3	6.2	47
S16	2.8	4.2	8.5	60
S18	0.6	1.7	2.6	71
S20	1.3	3.7	5.6	73
S43	1.6	7.9	9.1	83
S44	2.8	6.1	12.4	68
Mean	1.7	4.3	7.4	69.6
TL- Group				
Subject	Tone	Light	TL	%L
S15	5.3	1.8	8.6	26
S12	1.7	5.3	6.3	76
S21	1.3	3.6	6.3	73
S25	1.6	2.8	6.4	63
S30	0.3	3.8	4.3	94
S31	2.4	3.2	6.1	57
S32	1.8	3.7	5.3	68
S33	1.5	3.6	4.9	70
Mean	2.0	3.4	6.0	65.8

Note. Responses per minute in Tone, Light, and TL and the percentage of element responses in Light from stimulus-element tests for the Cocaine and Shock avoidance Groups. Each test stimulus was presented 12 times for 60 s periods over the course of the test.

A potential explanation for the failure of TL to act as a hedonically negative condition may be provided by an analysis of the time course of the effects of cocaine. The elimination half-life of intravenously administered cocaine, about 18 min (Barbieri, Ferko, Di Gregorio, & Ruch, 1992), is much longer than the 1-3 min component durations used in the present experiment. Thus, when a rat in the TL-

Group received one (or more) cocaine infusions in a $\overline{TL}$ component, there would have been substantial tissue levels of cocaine remaining when TL was presented again. This situation may have acted to reduce the size of any difference between TL and $\overline{TL}$ in terms of relative hedonic value. In contrast, when food was the reinforcer, there would not have been this reinforcer "spillover" effect from one component to the next. That is, for the TL- food group of Weiss et al. (1993b), each food reinforcement episode was a discrete event confined to the $\overline{TL}$ component, thereby making TL, where food was never received, hedonically negative.

The dynamics related to the time course of cocaine's effects should also have been operating for the TL+ Group of the present cocaine study. That is, the effects of cocaine infusions received in TL should have been experienced to some extent during $\overline{TL}$ components as well. This would have made TL less hedonically positive than if the effects of cocaine were restricted to TL components. However, the mean percentage of responses controlled by L is nearly identical for the TL+ Group of the present study (69.6%) and for Weiss et al.'s (1993b) TL+ food group (70.3%). This close correspondence in degree of L control suggests that TL in fact was hedonically positive in the TL+ Group of the present study. It is possible that the spread of the reinforcing effects of cocaine over components created a situation where TL and $\overline{TL}$ were hedonically positive conditions in both groups with only small differences between TL and $\overline{TL}$ in terms of relative hedonic value. Such a situation would be expected to produce predominantly visual control in both the TL+ and TL- groups—which is exactly what was observed.

Future experiments are necessary to systematically investigate the effect that the potential "spillover" of the reinforcing effects of cocaine across components might have had on the results of Experiment 2. It would be informative to see if predominantly visual control occurs when food is received in both TL and $\overline{TL}$ when the contingencies create a discrimination between the two conditions. If predominant visual control results when rats are trained on a procedure where food was received for lever-pressing in TL and also for response cessation in $\overline{TL}$ (e.g., on a mult VI DRO schedule), support for the cocaine spillover hypothesis would be provided.

It is also possible that food and cocaine function in a qualitatively different manner on the chained schedule that was employed for the TL- Group of Experiment 2. Specifically, the results of that group are consistent with the notion that components of a chain schedule removed from reinforcement are not as aversive when cocaine is the reinforcer as when food is the reinforcer. Further experiments with cocaine reinforcement on the chained schedule might explore this possibility by evaluating relative preference for the various links in a chain when the reinforcer is food or cocaine.

While the resolution of the potential reasons for the ambiguous results of Experiment 2 awaits the outcome of future research, Experiment 1 has provided convincing evidence of an interincentive cocaine/shock selective association for the first time. This simultaneously extends the generality of this biological constraint on learning to self-administered drugs while demonstrating cocaine as a positive reinforcer through a new reinforcement-related phenomenon, selective associations.

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Received July 8, 2004.
Revision received December 20, 2004.
Accepted February 16, 2005.