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STIMULUS CONTROL OF COCAINE SELF-ADMINISTRATION

STANLEY J. WEISS, DAVID N. KEARNS, AND SCOTT I. COHN

AMERICAN UNIVERSITY

AND

CHARLES W. SCHINDLER, AND LEIGH V. PANLILIO

NATIONAL INSTITUTE ON DRUG ABUSE

Environmental stimuli that set the occasion wherein drugs are acquired can ''trigger'' drug-related behavior. Investigating the stimulus control of drug self-administration in laboratory animals should help us better understand this aspect of human drug abuse. Stimulus control of cocaine self-administration was generated here for the first time using multiple and chained schedules with short, frequently-alternating components—like those typically used to study food-maintained responding. The procedures and results are presented along with case histories to illustrate the strategies used to produce this stimulus control. All these multicomponent schedules contained variable-interval (VI) components as well as differential-reinforcement-of-other-behavior (DRO) or extinction components. Schedule parameters and unit dose were adjusted for each rat to produce stable, moderate rates in VI components, with minimal postreinforcement (infusion) pausing, and response cessation in extinction and DRO components. Whole-body drug levels on terminal baselines calculated retrospectively revealed that all rats maintained fairly stable drug levels (mean, 2.3 to 3.4 mg/kg) and molar rates of intake (approximately 6.0 mg/kg/hr). Within this range, no relation between local VI response rates and drug level was found. The stimulus control revealed in cumulative records was indistinguishable from that achieved with food under these schedules, suggesting that common mechanisms may underlie the control of cocaine- and food-maintained behavior.

Key words: Stimulus control, drug self-administration, multiple schedules, chained schedules, cocaine, whole-body drug levels, rats

There is a growing consensus that environmental stimuli that set the occasion wherein drugs can be acquired, or are otherwise associated with the drug-taking experience, can come to act as stimuli that ''trigger'' drug-related behavior. For example, it is well established that drug-related stimuli can elicit drug craving in humans (Childress, McLellan, Ehrman, & O'Brien, 1987; Ehrman, Robbins, Childress, & O'Brien, 1992; O'Brien, Childress, McLellan, & Ehrman, 1990). According to some current accounts of drug dependence (Markou et al., 1993; Pert, 1994; Robinson & Berridge, 1993), such craving involves the same type of behavior-increasing ''incentive-motivation'' mechanism as that operating when stimuli are differentially associated with changes in the probability of receiving nondrug reinforcers such as food (Bindra, 1972; Rescorla & Solomon, 1967; Weiss, 1978; Weiss & Schindler, 1987, 1989).

Shulman (1989) used a questionnaire to study ''cocaine triggers'' in 200 addicts receiving treatment. The most frequently cited category leading to drug seeking was *people, places, and things* which included such cue descriptions as ''places you copped,'' ''cocaine paraphernalia,'' and ''people using around me.'' Wallace (1989) found that *environmental stimuli* were cited as the trigger for drug seeking by 34% of a patient population presenting for treatment a second time. These studies, as well as those cited above, suggest that environmental cues are critical in occasioning drug-related behavior in many drug abusers. In spite of this, Bickel & Kelly (1988) concluded that,

> . . . stimulus control is a behavioral process that has not received a great deal of scientific attention, both in relation to the basic processes involved and the application of that knowledge for the socially important prob-

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Correspondence concerning this article should be addressed to Stanley J. Weiss, Department of Psychology, American University, Washington, DC 20016 (e-mail: sweiss@american.edu).

> lems of substance abuse . . . . If we continue to ignore stimulus control processes, our goal of having a behavior analysis of substance abuse will be woefully incomplete. (p. 136).

This observation was reiterated by Bickel & Kelly (1997).

For the most part, the study of stimulus control has focused on behavior maintained by reinforcers, such as food or shock-avoidance, on multicomponent schedules where an operant response is differentially reinforced in the presence of frequently alternating different stimuli. Much has been accomplished with this approach. (For some reviews and research, see Dinsmoor [1995a, 1995b], Harrison [1991], Rilling [1977], Terrace [1966], Weiss & Schindler [1987], and Weiss, Thomas & Weissman [1996].) By investigating how stimulus control is produced and maintained when behavior is reinforced by pharmacological agents in animals, we may gain insight into the process by which environmental stimuli come to control drug abuse in humans.

Goldberg and Kelleher (1976) studied a multiple (mult) fixed-interval (FI) 5-min fixed-ratio (FR) 30 schedule for cocaine reinforcement in primates. Their components switched after every reinforcer and a 100-s timeout followed each injection. They found that responding in each component was appropriate to the multiple schedule, indicating stimulus control. Also in primates, Balster and Schuster (1973) studied a mult FI 9-min extinction (15-min timeout) schedule of cocaine reinforcement. Again, there was one injection per FI component. As with the Goldberg and Kelleher study, responding appropriate to the FI schedule occurred when the stimulus for that component was presented, and cumulative records also revealed that responding was low in the extinction component.

The multiple schedules used in the studies described above differ from those typically used with conventional reinforcers in that (a) only one reinforcer could be earned per discriminative stimulus (S^D), and (b) the component wherein reinforcement was earned always terminated with reinforcer delivery. Therefore, reinforcer delivery itself could have played a larger role in the stimulus control generated in these primates than is customarily the case with more conventional multiple schedules where many reinforcers can be earned per S^D. To promote environmental stimuli gaining maximum control of behavior, in the present study multiple infusions were possible in an S^D.

In most studies using multicomponent schedules of drug self-administration with rats, responding was reinforced by drug in one component and food in another, typically with 30-min or longer components, and there were few components per session (Caine and Koob, 1994a, 1994b; Goeders & Guerin, 1994; Goeders, McNulty, & Guerin, 1993; Shoaib, Swanner, Beyer, Goldberg, & Schindler, 1998; Weissenborn, Yackey, Koob, & Weiss, 1995). For several reasons, long schedule components may not be ideal for generating stimulus control and establishing conditioned effects of drug-related discriminative stimuli. With long schedule components, the delivery of a reinforcer may acquire discriminative properties that are potentially more salient than the exteroceptive stimuli in signaling the availability of further reinforcement. In addition, when only a few components are presented per session, there are few ''trials'' through which to establish conditioned effects. Furthermore, some theories of associative learning (e.g., scalar expectancy theory [Gibbon, 1977; Gibbon & Balsam, 1981]) postulate that excitatory properties are most effectively conditioned to stimuli if these stimuli are presented for a brief period of time relative to total session duration.

To efficiently and effectively generate stimulus control of drug self-administration, the S^Ds need to be presented many times per session, necessitating schedule components of short to moderate duration. Establishing such baselines can be challenging, and few researchers have used multicomponent intravenous drug self-administration schedules with short components. This laboratory, however, has a history of achieving stimulus control with complex schedules wherein responding was maintained by food and/or shock-avoidance (e.g., Weiss, 1964, 1969, 1971; Weiss & Panlilio, 1999; Weiss, Panlilio, & Schindler, 1993a, 1993b; Weiss & Schindler, 1989; Weiss, Thomas, & Weissman, 1996; Weiss & Van Ost, 1974). By applying strategies adapted from this previous work, it has been possible to achieve stimulus control on com-

plex baselines of drug self-administration that is virtually indistinguishable from that achieved with food baselines.

A description of how these techniques can be used to achieve stimulus control of drug self-administration may be of value to other investigators. Therefore, the procedures and the resulting stimulus control established in representative rats will be presented as detailed case histories in an integrated, continuous tutorial style in the tradition of Ferster and Skinner (1957). Examples of the behavioral control established at various stages of training under a variety of complex schedules of drug self-administration will be provided in the form of cumulative records that are representative of a subject's behavior in early, intermediate, and terminal baseline sessions. The terminal baseline stimulus control established in other comparably trained rats is presented in tables.

One of the obstacles to establishing stimulus control with multicomponent schedules of drug self-administration is the fact that each intravenous drug infusion tends to be followed by an extended pause in responding. These postreinforcement pauses could potentially be due to satiation, aversiveness of high cumulative doses, or motor effects that prevent operant responding (Katz, 1989; Lynch & Carroll, 2001). Under the simplest schedule of reinforcement, where drug is delivered each time a response is emitted (continuous reinforcement, crf), the postinfusion pause is a direct function of unit dose (Dougherty & Pickens, 1973; Lynch, LaBounty, & Carroll, 1998; Pickens & Thompson, 1968). Thus, one objective of the training described below was to tailor for each rat the infusion dose that would maintain a steady, moderate response rate and have the rat return to lever pressing directly after an infusion.

Analyses of whole-body drug levels and other drug effects (e.g., dopamine levels in the nucleus accumbens; Petit & Justice, 1989, 1991; Wise, 1999; Wise et al., 1995) under continuous reinforcement (crf) schedules have led to suggestions that animals regulate their intake to maintain levels of drug or some specific drug effect within a narrow range. For example, Tsibulsky and Norman (1999) concluded that cocaine self-administration under a crf schedule continues until a whole-body drug level "satiety threshold" of approximately 1.7 mg/kg is surpassed; responding then resumes when cocaine levels fall below this point. In order to evaluate whether this type of regulated intake or titration of cocaine levels also occurs under complex schedules like those described in the present paper, whole-body drug levels were calculated for all of the sessions for which cumulative records are presented. These analyses were performed retrospectively, with drug levels calculated only after all training procedures had been completed and representative records selected. We examined whether drug level and response rate covaried in the VI components of these schedules.

OVERVIEW OF OBJECTIVE AND METHODS

To determine whether drug reinforcement can produce stimulus control comparable to that produced with food under similar contingencies, we examined several multicomponent schedules. To facilitate the comparison of drug- and food-maintained responding, contingencies and schedule parameters closely approximated those that we have used previously with conventional reinforcers. In addition, the same discriminative stimuli and stimulus/schedule combinations were employed. Stimulus control of cocaine self-administration was established in rats trained with multiple (mult) schedules—where schedule components lasted for specified amounts of time—and chained (chain) schedules—where the operant response caused the components to progress.

The three basic schedules studied here all produced comparable patterns of lever pressing by the end of training. In the presence of a discriminative stimulus (S^D) [tone, light, or tone-plus-light (TL)], variable-interval (VI) schedules were used to maintain responding at stable, moderate rates, with minimal postinfusion pausing. In the absence of these stimuli ($\overline{TL}$), extinction (EXT) or differential-reinforcement-of-other-behavior (DRO) operated, and responding essentially ceased.[1] The goal of training for all schedules

[1] In our laboratory, we have used variable interval (VI) schedules that operated in tone, light, or tone-plus-light (TL) while in the absence of these stimuli ($\overline{TL}$) extinc-

was to produce response rates in VI components that were at least seven times those in EXT or DRO components, the criterion Panlilio, Weiss, and Schindler (1996) employed in the original self-administration study reported from this laboratory. On the terminal baseline schedules, component durations were generally in the 1 to 3 min range.

Although the stimuli controlled comparable patterns of lever pressing in all three basic schedules, the relation between lever pressing and the delivery of drug reinforcers differed systematically over the three schedules. In the first schedule to be described (mult VI EXT), all cocaine was received in the VI component (tone, light, or TL), where lever pressing was maintained. In the second schedule, mult VI VI DRO, cocaine could be acquired in both VI components (where responding was maintained) and in DRO components (where responding ceased). Finally, in the third schedule, a chain VI DRO, lever pressing in the VI component (tone, light, or TL) did not produce cocaine, but caused the schedule to progress to the DRO component ($\overline{TL}$), where cocaine was received contingent on response cessation. Therefore, under this chain VI DRO schedule, the drug was only received in the component where responding ceased. Thus, across the three respective schedules drug delivery was (a) explicitly paired with, (b) presented nondifferentially with respect to, or (c) explicitly unpaired with the S^D occasioning lever pressing. This variety of stimulus-reinforcer and response-reinforcer relations has never been systematically investigated with drug reinforcement.

The goal of the present study was to determine whether stimulus control of drug self-administration could be achieved under the conditions described above as it has with food reinforcement. At all stages of training, parameters were changed only after the effects of the previous change became apparent in the cumulative records. These changes usually occurred between sessions, but could occur several times over the course of even a single session. If responding became sporadic, the response requirement was reduced and/or the unit dose was increased to its previous level. Although this meant that not every rat received exactly the same training history, the essential contingencies were always consistent with the other rats in the same group. To insure that the stimulus control reported here can be unequivocally attributed to the cocaine contingencies, rats in the present experiment were not pretrained to press the lever for food, as is often done in drug self-administration studies.

tion (EXT) or differential-reinforcement-of-other-behavior (DRO) was programmed. Weiss (1969), Weiss and Emurian (1972), and Tsai and Weiss (1977), however, have shown that comparable control can be achieved with other stimulus/schedule combinations. For example, the VI schedule can operate in tone or in light while TL signals extinction, or the VI schedule can operate in TL and in $\overline{TL}$ while tone or light signal extinction. Those studies were used to investigate the dynamics of Weiss' (1972) composite-stimulus model of stimulus control, but that is beyond the scope of the present report.

EXPERIMENT 1: MULTIPLE VI EXT AND MULTIPLE VI VI EXT SCHEDULES

On a multiple (mult) schedule, different contingencies operate in the presence of specific stimuli and components alternate automatically. Under the two-component mult VI EXT schedule of Experiment 1, a VI schedule of cocaine self-administration operated in tone-plus-light (TL), and no cocaine was available (EXT) in the absence of tone and light ($\overline{TL}$). The procedures used and behavioral progress for a representative rat (S-43) trained on this schedule are described in detail. Terminal baseline data from nine additional rats trained on this schedule are also presented.

The three-component mult VI VI EXT schedule of Experiment 1 was like the two-component mult VI EXT schedule, but a VI cocaine contingency operated when either a tone or a light was present. $\overline{TL}$ was still associated with extinction. The training history of a representative rat (S-16) trained on this mult VI VI EXT schedule is described below, plus terminal baseline data from three additional rats trained on this schedule.

METHOD

Subjects

Seven adult male Sprague-Dawley rats (J-3, J-4, S-9, S-16, S-110, SN-19, and SN-33) and 7 adult male Long-Evans rats (LD-3, LD-20, LD-18, LF-16, LF-10, S-43, and S-44) were used. They were housed in individual cages in a colony room with a 12-hr light/dark cycle (lights

on, 8 a.m. to 8 p.m.). Training sessions were conducted during the light-on cycle. Water was available continuously, except during the 4-hour training sessions. Weights were maintained at approximately 80% of ad lib (348 to 454 gm) with laboratory rat chow provided following training sessions. Training sessions were conducted 7 days a week.

Apparatus

Six operant chambers (Weiss & Schindler, 1989) were 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 lighted at all times by a shielded 7.5-W houselight operated at 3 W. The level of illumination created by this houselight 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 current 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, 85-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 which provided the visual stimulus. These lights were operated at 120 V and produced 130.2 cd/m at the center of a side wall. For rats on the three-component mult VI VI EXT schedule, the tone and the light described above each served as an S^D. For rats on the two-component mult VI EXT schedule, the S^D was a tone-plus-light (TL) compound composed of a 79db 2000-HZ tone and a 0.55 log ft-Lamberts illumination produced by operating the bulbs at 74V.

Intravenous catheters were implanted under ketamine (60 mg/kg) and xylazine (10 mg/kg) anesthesia using procedures described earlier (Panlilio, Weiss, & Schindler, 1996). 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-g needle. A 20-mm plastic screw was cemented with dental acrylic to 4 stainless steel jeweler's screws implanted in the skull during catheter implantation surgery.

Cocaine (National Institute on Drug Abuse, Bethesda, MD) 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). 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.

Calculation of Drug Levels

Whole-body drug levels were calculated for all sessions from which cumulative records are presented. Calculations were based on the sequential interinfusion intervals and the established pharmacokinetic profile of cocaine, using an elimination half-life of 18.1 minutes (Barbieri, Ferko, DiGregorio, & Ruch, 1992). According to the formula, $B_n = (B_{n-1} + D)\ \exp^{-KT}$, where T = time since last infusion, K = 0.0383 min^{-1} based on a half-life of 18.1 minutes for cocaine, D = unit dose in mg/kg, B_{n-1} = calculated amount of drug in the body from previous infusions, and B_n = calculated amount of drug in the body at the time of a given infusion. Although pharmacokinetics can be affected by many factors, this type of model should provide adequate estimates of drug levels for the purposes of the analyses performed here (Lau & Sun, 2002).

Procedure

Two-component mult VI EXT. Initially, 10 rats were trained with a crf schedule where each lever press was immediately followed by a 1.0 mg/kg infusion of cocaine. There was no additional stimulus paired with the drug deliv-

ery, and there was no timeout period following an infusion. TL was present for the entire session. Once lever pressing developed on this crf schedule, the dose per injection was decreased from 1.0 mg/kg to 0.75 mg/kg and then to 0.5 mg/kg. Then, the response requirements were gradually increased to fixed-ratio (FR) 5 or FR 10 as the unit dose was decreased to 0.25 to 0.32 mg/kg. Once a rat was reliably responding on this FR schedule (as judged by response patterns on the cumulative records), a variable-interval (VI) schedule was introduced that allowed a rat to acquire cocaine at approximately the same rate that it had under the FR schedule. The initial VI schedules used ranged from VI 30-s to VI 90-s.

Unit doses were gradually reduced over the course of training. The first two self-administered infusions of every session, however, remained at 1.0 mg/kg to (a) accelerate the cocaine ''loading phase,'' (b) reduce variability in early session responding, and (c) avoid reinforcing a response incompatible with lever pressing, which might occur under the commonly used priming procedure, where drug is infused independently of responding at the beginning of a session.

Once stable patterns of responding occurred on the VI schedule, discrimination training began. Now, the VI schedule continued to operate in TL, while extinction (EXT) operated in $\overline{TL}$. The TL components alternated with $\overline{TL}$ components ($\bar{x}$ = 90 s; range, 45 to 180 s). To reduce responding in $\overline{TL}$, a lever press within the last 10 s scheduled of a $\overline{TL}$ component delayed the presentation of TL until 10 s (the response correction value) passed without a response. The response-correction contingency may contribute to the formation of a discrimination between the VI and EXT components, because (a) it prevents responses in $\overline{TL}$ from being immediately followed by presentation of TL (which might adventitiously reinforce responding in $\overline{TL}$ if TL becomes a conditioned reinforcer due to its pairing with drug delivery), and (b) it increases the likelihood that a response incompatible with lever pressing in $\overline{TL}$ may be reinforced by presentation of TL. The response correction was increased, if necessary, up to 30 s. During discrimination training the unit dose was gradually decreased to approximately 0.2 mg/kg. The VI value was then adjusted for each rat to produce moderate response rates in TL. The final VI values ranged from VI 45-s to VI 90-s.

Three-component mult VI VI EXT. Training on the three-component mult VI VI EXT schedule for 4 rats proceeded in a fashion similar to that described above for the two-component mult VI EXT schedule, with the exception that VI components were signaled by tone and by light rather than by TL. At the outset of training on the three-component schedule, tone components and light components ($\bar{x}$ = 10 min; range, 5 to 20 min) alternated with $\overline{TL}$ components ($\bar{x}$ = 60 s; range, 40 to 90 s). The duration of the tone and the light components were gradually reduced to a mean of 60 s (range, 30 to 120 s) over the course of training. Tone or light components were equally likely to follow $\overline{TL}$, with the restriction that no more than two consecutive VI components were signaled by the same stimulus (tone or light). For both two- and three component multiple schedules, training sessions were generally 4 hr long.

Results

Two-Component Mult VI EXT

By the third session, S-43's unit dose was reduced from 1.0 to 0.75 mg/kg and it began responding approximately once every 20 min. Over the next five sessions, the unit dose was gradually reduced to 0.32 mg/kg, and the response requirement was gradually increased from crf to FR 10. Response rates increased with each progressive decrease in dose and increase in response requirements. On the eighth session, the FR 10 schedule was changed to a VI 90-s schedule. Cumulative record a in Figure 1 is from this session, where S-43 responded at a steady rate (approximately 6 responses/min), and there were no postreinforcement pauses or bursts of responding.

After one more training session on this VI 90-s schedule, mult VI 60-s EXT training began. In Figure 1, the cumulative record labeled b is from S-43's 12th session, where the unit dose was reduced to 0.25 mg/kg. A discrimination was developing, although rates in $\overline{TL}$ were too high. Mean rates in TL and $\overline{TL}$ components were 15.9 and 7.8 responses/min, respectively.

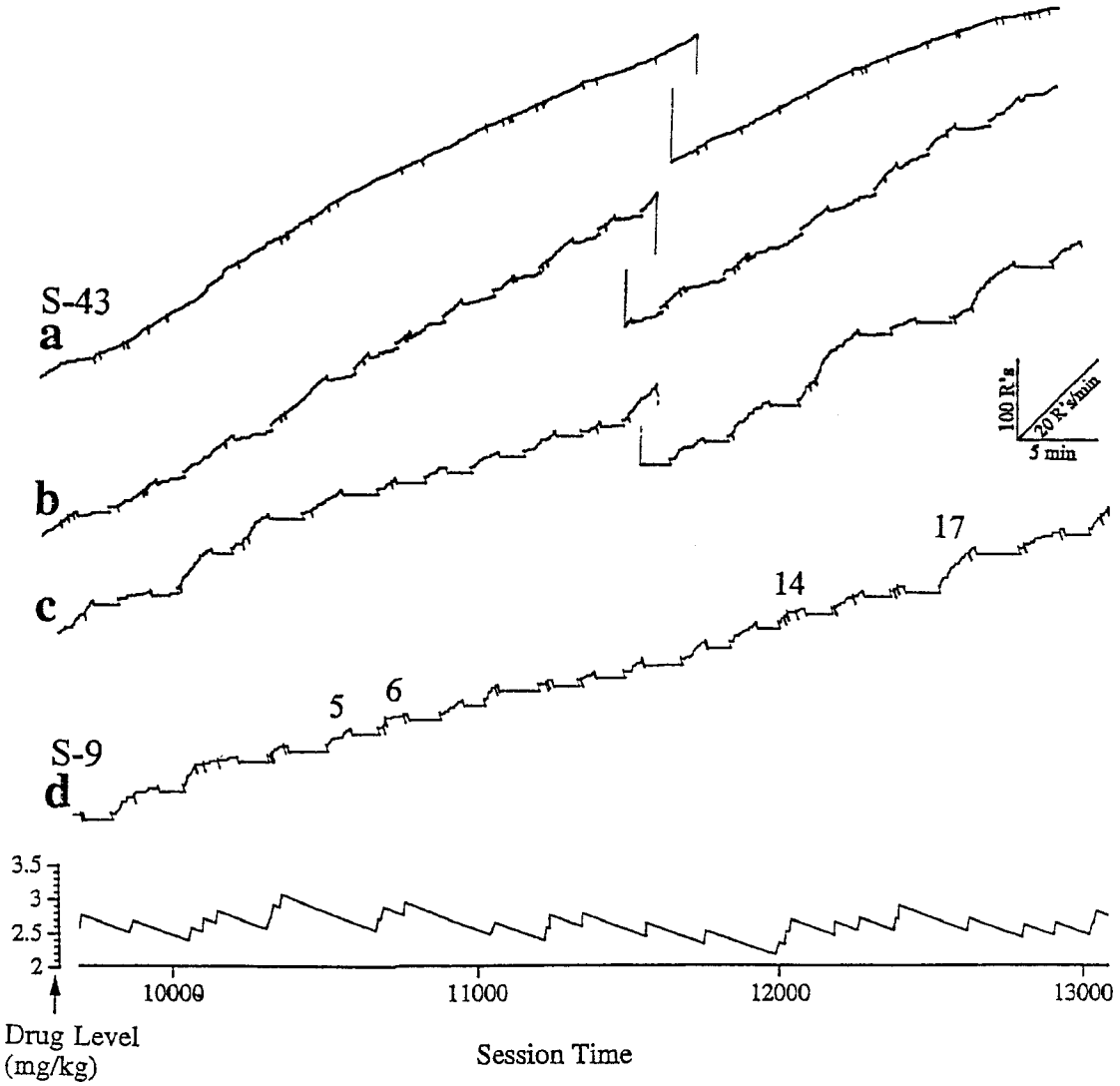

Fig. 1. Cumulative records from rats with mult VI EXT terminal baseline schedules. One-hour cumulative record segments are presented from an early (a), intermediate (b), and terminal baseline training session (c) for S-43. Record d is from a terminal baseline session for S-9. Tone-plus-light (TL) was present when the response pen was in the upper register and absent ($\overline{TL}$) when the response pen was in the lower register. Downward slash marks of the response pen indicate an infusion. The first three records show the responding of S-43 on a: (a) VI 90-s schedule with a 0.32 mg/kg unit dose where TL was present for the entire session (Session 8), (b) mult VI 60-s EXT schedule and a 0.25 mg/kg unit dose (Session 12), and (c) mult VI 90-s EXT schedule and 0.2 mg/kg unit dose (Session 32). Record d is the cumulative record from S-9's 17th session where it was on a mult VI 45-s EXT schedule with a 0.2 mg/kg/infusion dose. Corresponding calculated whole-body drug levels for S-9 are shown below its cumulative record. Numbers in record d identify components referred to in the text. Session time is shown in seconds.

Response rates in $\overline{TL}$ were still higher than desired after three more sessions, so the response correction was increased from 10 s to 20 s on the 16th session and to 30 s on the 22nd session (when the unit dose was decreased to 0.2 mg/kg). Over the next nine sessions, S-43's discrimination improved substantially. The rat, however, would occasionally emit response "bursts" in TL that would carry over into the next $\overline{TL}$ component. To reduce the rate in TL, the VI schedule value was increased from VI 60-s to VI 90-s during

Table 1

For each of the 10 rats trained on the mult VI EXT schedule: Number of sessions, response rates (responses/min) in TL and $\overline{TL}$, reinforcers/min, dose per infusion (mg/kg), and rate of cocaine intake (mg/kg/hr) (all averaged over the last three training sessions). For each rat except S-43 and S-44, the schedule in TL was VI 45-s, while drug was not available in $\overline{TL}$ (mult VI 45-s EXT). For S-43 and S-44, the schedule in TL was VI 90-s and VI 60-s, respectively. For subjects J-4, LD-3, LD-20, LD-18, LF-16, and LF-10, the mean TL and $\overline{TL}$ component durations were 60 s (TL range, 30 to 120 s; $\overline{TL}$ range, 40 to 90 s). For subjects J-3 and S-9, TL and $\overline{TL}$ component durations averaged 90 s (TL range, 45 to 180 s; $\overline{TL}$ range, 60 to 135 s). For S-43 and S-44, TL component durations averaged 120 s (range, 60 to 240 s) and $\overline{TL}$ component durations averaged 75 s (range, 50 to 112.5 s) and 60 s (range, 40 to 90 s), respectively. The response corrections in $\overline{TL}$ were 30 s for all subjects except J-3 and S-9, for whom it was 10 s.

Subject	Sessions	Responses/min		Reinforcers/min	Unit dose (mg/kg)	Rate of intake (mg/kg/hr)
		TL	$\overline{TL}$			
J-3	41	5.9	0.3	0.42	0.2	5.0
J-4	33	4.8	0.2	0.37	0.2	4.4
S-9	18	9.1	0.2	0.45	0.2	5.4
LD-3	30	8.8	0.8	0.39	0.28	6.6
LD-20	18	8.4	1.0	0.42	0.25	6.3
LD-18	21	8.8	0.6	0.43	0.25	6.5
LF-16	20	11.0	0.9	0.43	0.28	7.2
LF-10	15	8.2	0.6	0.38	0.28	6.4
S-43	36	18.6	1.1	0.31	0.2	3.7
S-44	32	20.1	1.7	0.48	0.2	5.8
MEAN	26.4	10.4	0.7	0.41	0.23	5.7

the 30th session. Record c in Figure 1 is from S-43's 32nd session, revealing excellent stimulus control. Responding (a) began promptly with the onset of each TL component, (b) was sustained throughout the component, (c) ceased abruptly when the $\overline{TL}$ component was entered, and (d) did not resume until TL was presented again. During this session, S-43's response rate in TL (21.9 responses/min) was more than 20 times its response rate in $\overline{TL}$ (1.0 responses/min).

Cumulative record d in Figure 1 is that of Rat S-9 which was trained on a two-component mult VI EXT schedule and whose training history was comparable to S-43's. Like S-43's cumulative record in c, S-9's record shows that responding began at the start of each TL component and continued until $\overline{TL}$ was presented, when responding ceased almost completely. Rat S-9 responded more than 40 times faster in TL (10.1 responses/min) than in $\overline{TL}$ (0.2 responses/min). Below S-9's cumulative record (d) in Figure 1 is a plot of its calculated whole-body drug levels during the portion of the session from which the cumulative record is taken. Details of this plot and all of the drug-level plots from Experiments 1 through 3 are presented after Experiment 3.

Stimulus control comparable to that described above for S-43 and S-9 was also achieved in the 8 other rats trained on this mult VI EXT schedule. Table 1 presents terminal baseline data for each of these 10 rats. All were discriminating between TL and $\overline{TL}$. The mean response rate in TL was 15 times that in $\overline{TL}$, with TL controlling rates between 4.8 and 20.1 responses/min. The mean molar rate of drug intake was 5.7 mg/kg/hr, with 7 of the 10 rats within 1.0 mg/kg/hr of the mean. The parameters of the terminal baseline schedule on which each of these rats were trained are presented in the caption of Table 1.

Three-Component Mult VI VI EXT

Initial lever press acquisition training was similar to that described above for the two-component mult VI EXT schedule. Cocaine (1.0 mg/kg/infusion) was available on a crf schedule during 10-min tone or light components that alternated with 60-s $\overline{TL}$ components where no cocaine was available. Over the first seven sessions, the unit dose was gradually de-

creased from 1.0 mg/kg to 0.25 mg/kg and the response requirement in tone and in light was increased from crf to FR 3. Cumulative record a in Figure 2 is from S-16's eighth training session, where responding was maintained by a mult FR-3 FR-3 EXT schedule with a dose of 0.25 mg/kg/infusion. Responses were reinforced according to an FR 3 schedule when tone or light was present, and went unreinforced in $\overline{TL}$. The rat self-administered cocaine on this schedule throughout the session, indicating that the lever press operant had been firmly established.

Cumulative record b in Figure 2 is from S-16's 12th session, where the schedule was mult VI 60-s VI 60-s EXT. By this session, stimulus control was beginning to develop. Typically, many responses were emitted during tone and light components and little responding occurred during $\overline{TL}$. There were still tone and light components where responding was not steady, however, as well as some responding during $\overline{TL}$ components.

Over subsequent sessions, the mean length of the tone and light components was gradually reduced from 10 min to 60 s (range, 30 to 120 s) and a 10-s response correction contingency was added to the $\overline{TL}$ component. The response correction value was increased to 20 s when response rates in $\overline{TL}$ continued to be higher than required to meet the discrimination criterion of 7:1. Cumulative record c in Figure 2 is from S-16's 50th session (see figure caption for schedule parameters). Responding (a) began with the onset of each tone or light component, (b) was sustained at a moderately high rate for the duration of the component, (c) abruptly ceased in $\overline{TL}$, and (d) did not resume until the tone or light was presented. Rates in tone (6.6 responses/min) and in light (6.6 responses/min) were 13 times those in $\overline{TL}$ (0.5 responses/min).

Cumulative record d in Figure 2 shows the performance of Rat S-110, trained on a mult VI 45-s VI 45-s EXT schedule. This rat's training history was similar to S-16's, with the parameters of the schedule presented in record d of Figure 2 identical to S-16's, presented in record c of Figure 2. Record d in Figure 2 reveals that in this session S-110 responded at a faster rate (a mean of 10.2 and 16.0 responses/min in tone and light, respectively) than S-16, but the quality of the stimulus control was comparable for the 2 rats. Responding began promptly with the onset of a tone or a light component and was sustained throughout the duration of the component. Response rates remained low (1.3 responses/min) during $\overline{TL}$ components.

Including S-16 and S-110, 4 rats were trained with the three-component mult VI VI EXT schedule, and all exhibited stimulus control of cocaine self-administration. Table 2 presents the criterion session data for these 4 rats. The parameters of the terminal baseline schedule used for these rats are presented in the caption of Table 2. For 3 of the 4 rats, response rates in tone and in light were within 1.2 responses/min of each other. Although response rates in VI components in Table 2 varied less (6.2 to 10.9 responses/min) than with those rats exposed to the two-component mult VI EXT (a range of 4.8 to 20.1 responses/min) shown in Table 1, the rates in Table 2 overlap those of 80% of the rats in Table 1. Molar rates of drug intake were consistent across rats within the three-component mult VI VI EXT group. All these rats self-administered between 5.7 and 7.1 mg/kg/hr, rates comparable to those of the mult VI EXT rats in Table 1.

EXPERIMENT 2: MULTIPLE VI VI DRO

Like the mult VI VI EXT schedule just described, the mult VI VI DRO schedule was designed to produce moderate and stable rates of responding in tone and in light components and response cessation in $\overline{TL}$ components. On the mult VI VI DRO schedule, however, reinforcers were received in all components (tone, light, and $\overline{TL}$), but on the mult VI VI EXT schedule, where VI and EXT components alternated, reinforcers were received in only half the components (tone and light but not in $\overline{TL}$). Therefore, the overall rate of reinforcement (infusions/min) on the mult VI VI DRO schedule would be substantially higher than the overall rate of reinforcement on the mult VI VI EXT schedule. To compensate for this, the unit dose at each stage of training on the mult VI VI DRO schedule was lower than the unit dose used at corresponding stages of training on the mult VI VI EXT schedule. For example, the initial unit dose used with the mult VI VI DRO schedule was 0.6 mg/kg while the initial dose used with the mult VI VI EXT schedule

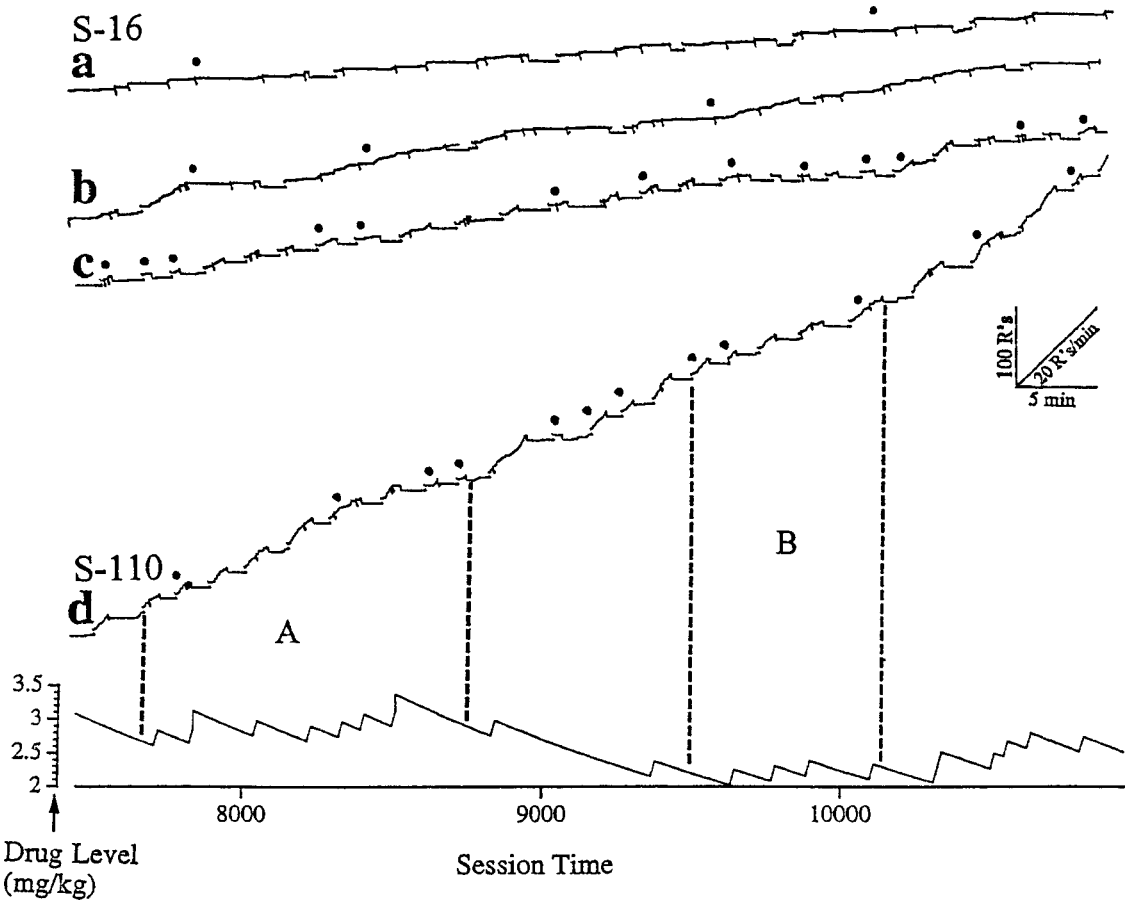

Fig. 2. Cumulative records from rats with mult VI VI EXT terminal baseline schedules. One-hour cumulative record segments are presented from an early (a), intermediate (b), and terminal baseline training session (c) for S-16. Record d is from a terminal baseline session for S-110. Tone or light was present when the response pen was in the upper register (tones are indicated by filled circles) and both were absent ($\overline{TL}$) when the response pen was in the lower register. Downward slash marks on the response pen indicate an infusion. The first three records show the responding of S-16 on a (a) mult FR-3 FR-3 EXT schedule with 0.25 mg/kg unit dose (Session 8), (b) mult VI 60-s VI 60-s EXT schedule with a unit dose of 0.25 mg/kg (Session 12), and (c) mult VI 45-s VI 45-s EXT schedule with a 0.25 mg/kg unit dose (Session 15). Record d is the cumulative record from S-110's 66th session where it was on a mult VI 45-s VI 45-s EXT schedule with a 0.25 mg/kg unit dose. Corresponding calculated whole-body drug levels for S-110 are shown below its cumulative record. Letters in record d identify portions of the record referred to in the text. Session time is shown in seconds.

was 1.0 mg/kg. On the terminal baseline, a 0.08 mg/kg/infusion dose was used for rats trained on the mult VI VI DRO schedule while a 0.25 to 0.32 mg/kg/infusion dose was used on the terminal baselines for rats trained on the mult VI VI EXT schedule. Procedures effective in producing stimulus control of cocaine self-administration on a mult VI VI DRO schedule will be illustrated by the training history of Rat S-11, with the terminal baseline stimulus control of S-21 also presented.

METHOD

Subjects and Apparatus

Two adult male Sprague-Dawley rats (housed and deprived like the rats in Experiment 1) were used. Maintenance conditions for the rats, surgical procedures, apparatus, and drug level calculations were also the same as described in Experiment 1.

Procedure

Initially, rats were trained on a mult crf crf DRO 15-s schedule. Each lever press in tone

Table 2

For 4 rats trained on the mult VI $\overline{\text{VI}}$ EXT schedule: Number of sessions, response rates (responses/min) in tone, light, and $\overline{\text{TL}}$, reinforcers/min, dose per infusion (mg/kg), and rate of cocaine intake (mg/kg/hr) (all averaged over the last three training sessions). For each rat, (a) the schedule in tone and in light was VI 45-s, while drug was not available in $\overline{\text{TL}}$ (mult VI 45-s EXT), (b) the mean tone or light component duration was 60 s (range, 30 to 120 s), and (c) the mean $\overline{\text{TL}}$ component length was 60 s (range, 40 to 90 s). The response corrections in $\overline{\text{TL}}$ were 20, 10, 30 and 30 for subjects S-16, S-110, SN-19 and SN-33, respectively.

Subject	Sessions	Responses/min			Reinforcers/ min	Unit dose (mg/kg)	Rate of intake (mg/kg/hr)
		Tone	Light	$\overline{\text{TL}}$			
S-16	53	6.2	7.2	0.7	0.40	0.25	6.0
S-110	66	7.3	10.9	1.0	0.45	0.25	6.8
SN-19	87	7.3	8.5	0.9	0.38	0.25	5.7
SN-33	44	9.1	8.4[a]	1.3	0.37	0.32	7.1
MEAN	62.5	7.5	8.8	1.0	0.40	0.27	6.4

[a] The 7 : 1 discrimination criterion was exceeded by 25 of the 29 animals reported in this study, with only two, (SN-33 in Table 2 and S-21 in Table 3) falling slightly short of that ratio. These latter animals are included because, after extensive training, the changes in their behavior at stimulus transitions revealed that they were under stimulus control.

or light was immediately followed by a 0.6 mg/kg infusion of cocaine. Thirty seconds after the first infusion delivered in each tone or light component, the $\overline{\text{TL}}$ component commenced. Thus, at least one reinforced response had to be made in each tone or light component to ensure lever pressing in these stimuli.

In $\overline{\text{TL}}$, a DRO 15-s contingency was in effect, where an infusion of cocaine was delivered after 15 s had elapsed without a response. Only one infusion was delivered in a DRO component, followed by a 30-s period where the tone and light remained off and the DRO contingency was discontinued. Then, the tone or light was again presented, on an equal probability basis, with the restriction that no more than three consecutive components were of the same type (tone or light).

Once lever pressing was established on this mult crf crf DRO 15-s schedule, the response requirements in tone and light were gradually increased from crf to FR-10, as the unit dose was gradually decreased from 0.6 mg/kg to approximately 0.15 mg/kg. When responding stabilized on this mult FR-10 FR-10 DRO 15-s schedule, the schedule in tone and light components was changed to VI 15-s. In addition, tone and light components were now scheduled to last a mean of 4 min (range, 2 to 8 min), and $\overline{\text{TL}}$ components (where DRO 15-s was in effect) were 60 s, on average (range: 40 to 90 s). The $\overline{\text{TL}}$ components were now entered automatically, without requiring at least one response in the preceding tone or light component. In addition, the DRO contingency now operated throughout the entire $\overline{\text{TL}}$ component, allowing the subject to earn up to five reinforcers per component. Because of this increased frequency of reinforcement in $\overline{\text{TL}}$, the unit dose was reduced to approximately 0.1 mg/kg. Tone and light components were scheduled to last four times as long as $\overline{\text{TL}}$ components in order to promote responding in tone and light and to counteract generalization of the response decreasing effects of reinforcement contingent on response cessation in $\overline{\text{TL}}$.

Over subsequent sessions, the VI schedule value was gradually increased from 15 s to 45 s and the DRO value in $\overline{\text{TL}}$ was gradually increased from 15 s to 30 s. The mean length of both tone and light components was gradually reduced from 4 min to 90 s (range, 45 to 180 s), while the mean $\overline{\text{TL}}$ component length remained 60 s. The final schedule was mult VI 45 s VI 45 s DRO 30 s with a 0.08 to 0.09 mg/kg unit dose. Daily sessions generally were 4 hr in duration.

RESULTS

By the fourth training session, S-11 began to regularly press the lever during tone and during light components. By Session 10, S-11 was on an FR 10 with each infusion 0.13 mg/kg. Cumulative record a in Figure 3 shows a portion of S-11's tenth session. The

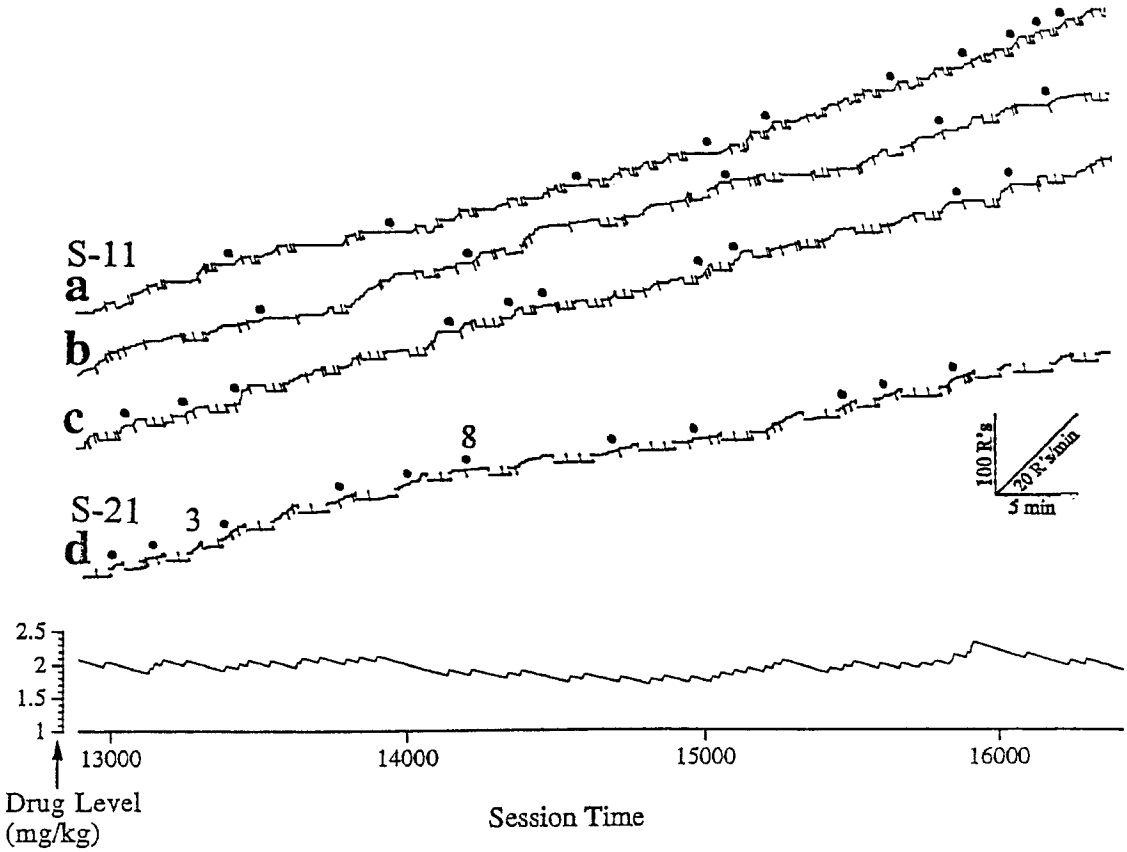

Fig. 3. Cumulative records from rats with mult VI VI DRO terminal baseline schedules. One-hour cumulative record segments are presented from an early (a), intermediate (b), and terminal baseline training session (c) for S-11. Record d is from a terminal baseline session for S-21. Tone or light was present when the response pen was in the upper register (tones are indicated by filled circles) and both were absent ($\overline{TL}$) when the response pen was in the lower register. Slash marks by the response pen, either upward or downward, indicate infusions. The first three records show the responding of S-11 on a: (a) mult FR-10 FR-10 DRO 15-s schedule with a 0.13 mg/kg unit dose (Session 10), (b) mult VI 45-s VI 45-s DRO 30-s schedule with a 0.08 mg/kg unit dose (Session 15), and (c) mult VI 45-s VI 45-s DRO 30-s schedule with a 0.08 mg/kg unit dose (Session 75). Record d is the cumulative record from S-21's 96th session where it was on a mult VI 45-s VI 45-s DRO 45-s with a 0.09 mg/kg unit dose. Corresponding calculated whole-body drug levels for S-21 are shown below its cumulative record. Numbers in record d identify components referred to in the text. Session time is shown in seconds.

customary FR response pattern, bursts of responding followed by postreinforcement pauses, occurred during tone and during light components. There was little responding during $\overline{TL}$ components.

On the next session, a VI 15-s schedule was introduced in tone and in light components that were now scheduled to last a mean of 4 min (range, 2 to 8 min), and $\overline{TL}$ components (where the DRO 15-s was in effect) were a mean of 60 s (range, 40 to 90 s). Over the next four sessions, the VI schedule was gradually increased from 15 s to 45 s and the DRO in $\overline{TL}$ was gradually increased from 15 s to 30 s. Cumulative record b in Figure 3 shows a portion of S-11's 15th session (see figure caption for schedule parameters). Rat S-11's rates were 5.6, 7.0, and 0.8 responses/min in tone, light, and $\overline{TL}$ components, respectively, revealing that a discrimination was developing.

Over subsequent sessions, the mean length of both tone and light components was gradually reduced from 4 min to 90 s (range, 45 to 180 s), while the mean $\overline{TL}$ component length remained at 60 s. At this point in train-

Table 3

For 2 rats trained on the mult VI VI DRO schedule: Number of sessions, response rates (responses/min) in tone, light, and $\overline{TL}$, reinforcers/min, dose per infusion (mg/kg), and rate of cocaine intake (mg/kg/hr) (all averaged over the last three training sessions). For both of the subjects, (a) the contingency in tone and in light was VI 45-s, (b) the mean tone or light component length was 90 s (range, 45 to 180 s), and (c) the mean $\overline{TL}$ component duration was 60 s (range, 40 to 90 s). A DRO 30-s and a DRO 45-s contingency operated in $\overline{TL}$ for S-11 and S-21, respectively.

Subject	Sessions	Responses/min			Reinforcers/min	Unit dose (mg/kg)	Rate of intake (mg/kg/hr)
		Tone	Light	$\overline{TL}$			
S-11	75	12.4	7.2	0.6	0.97	0.08	4.7
S-21	96	7.0[a]	7.5[a]	1.2	0.84	0.09	4.5
MEAN	85.5	9.7	7.4	0.9	0.92	0.09	4.6

[a] The 7 : 1 discrimination criterion was exceeded by 25 of the 29 animals reported in this study, with only two, (SN-33 in Table 2 and S-21 in Table 3) falling slightly short of that ratio. These latter animals are included because, after extensive training, the changes in their behavior at stimulus transitions revealed that they were under stimulus control.

ing, the rat began to exhibit much higher response rates in tone than in light components. To raise response rates in light components, training sessions were administered where 80 to 100% of the VI components were signaled by light. This was successful, but took considerable time. After 20 such sessions, the response rate in light components increased substantially, but was still lower than in tone. Tone and light components were again presented on an equal probability basis. Cumulative record c in Figure 3 presents a portion of S-11's 75th session. Responding is almost entirely absent in $\overline{TL}$ components and generally begins promptly with the onset of each tone or light component. During this session, the rat responded in tone at 10.5 responses/min and in light at 6.6 responses/min, rates more than 10 times those in $\overline{TL}$ (0.6 responses/min).

Cumulative record d in Figure 3 shows the performance of Rat S-21. It was trained under procedures similar to those described above for S-11. The parameters of S-21's schedule were mult VI 45-s VI 45-s DRO 45-s. A DRO 45-s in $\overline{TL}$ was used for S-21 rather than a DRO 30-s because this rat often emitted many responses in $\overline{TL}$ when a DRO 30-s was used. Like S-11, S-21 typically began responding shortly after the onset of a tone or light component and continued throughout the duration of the component. In Figure 3d, mean response rates in tone, light, and $\overline{TL}$ components were 7.0, 7.5, and 1.2 responses/min, respectively.

Table 3 summarizes the criterion session data for both rats. The parameters of the terminal baseline schedule used for these rats are presented in the caption of Table 3. Despite the differences in contingencies between Experiments 2 and 1, lever pressing rates and the quality of stimulus control revealed by the cumulative records were similar over the two experiments. Although lower unit doses were used under the mult VI VI DRO schedule because cocaine was available in all three schedule components, molar rates of drug intake (4.6 mg/kg/hr) were only slightly lower than in the two groups in Experiment 1 (5.7 and 6.4 mg/kg/hr).

EXPERIMENT 3: CHAINED VI DRO SCHEDULES

On a chained schedule, fulfilling the schedule requirements in each successive link is necessary before reinforcement can be earned in the final link. Each link is correlated with a different stimulus, and the schedule operating in each may be the same or different from those operating in other links of the chain (Ferster & Skinner, 1957). Each of the chained schedules used in Experiment 3 had two links. The terminal link, where reinforcement was earned, is denoted S_1, and the initial link is denoted S_2.

Chained schedules have some similarities to second-order schedules of brief stimulus presentation (see recent review by Schindler, Panlilio, & Goldberg, 2002). Both involve sequential changes in exteroceptive stimuli produced by relatively long sequences of re-

sponses. Thus, they may be useful for modeling the long sequences of behavior that are typically required for humans to acquire, prepare, and ingest drugs of abuse. Although stimulus control of drug-maintained behavior has not been reported with traditional chained schedules like those described above, second-order schedules have been used extensively to study the conditioned reinforcing effects of drug-paired environmental stimuli on the control of drug-taking in both primates (Goldberg, Schindler, & Lamb, 1990; Schindler, Katz, & Goldberg, 1988) and rodents (Arroyo, Markou, Robbins, & Everitt, 1998; Everitt & Robbins, 2000).

On these second-order schedules, responding on a simple schedule (usually a short FR) produces a brief stimulus (usually a light) that had been paired with the primary reinforcer. In this context, completion of the FR is called the *unit response*. The unit response is then applied to a second schedule of reinforcement. For example, Goldberg (1973) trained primates under a second-order schedule where (a) the unit response was an FR 30 such that every 30th response on a lever produced a brief flash of light, and (b) the first unit response completed after an FI 5-min timed out produced both the light flash and a drug infusion. This type of second-order schedule maintained higher response rates than a simple FI 5-min schedule, providing evidence that the brief stimulus (which is intermittently paired with drug) functions as a conditioned reinforcer.

The main difference between chained and second-order schedules is that under a chained schedule, a different exteroceptive stimulus is presented during each successive link until the response requirement for that link is satisfied. Thus, while second-order schedules reveal primarily the conditioned reinforcing effects of the briefly presented stimulus, in a chained schedule each stimulus is not only a conditioned reinforcer but a discriminative stimulus for the behavior emitted in the current link (Gollub, 1977; Kelleher, 1966; Kelleher & Gollub, 1962). Therefore, it might better emulate those situations where different behavior sequences are necessary to gain the primary reinforcer, as the case may be in human drug-taking situations.

During the first chain VI DRO schedule to be described, the S_2 link of the chain was signaled by TL. Responding in TL produced S_1, signaled by $\overline{TL}$, according to a VI schedule. In $\overline{TL}$, a DRO schedule operated wherein responding had to cease for a specified time for a cocaine infusion to be presented. As with the two-component mult VI EXT schedule in Experiment 1, the goal of training on this chain VI DRO schedule was to produce moderate and stable response rates in TL and cessation of responding in $\overline{TL}$. A description of the training procedures used for one rat (S-31) to produce stimulus control of cocaine self-administration on this chain VI DRO schedule is presented below, with the terminal baseline stimulus control of 7 other rats trained on this schedule also reported.

The second chain VI DRO schedule reported here was like that just described except that S_2 components were signaled by tone or light (rather than by TL), with tone or light equally likely to follow $\overline{TL}$. The training procedures and progress of representative rat S-15, successfully trained to self-administer cocaine on this schedule, are described below, with the terminal baseline stimulus control of 4 other rats trained on this schedule also reported.

Method

Subjects and Apparatus

Five adult male Sprague-Dawley rats (N-4, S-15, N-5, J-20 and S-99) and 8 adult male Long-Evans rats (S-25, S-30, S-31, S-32, S-33, LD-21, LF-5, and LF-21) (housed and deprived like the rats in Experiment 1) were used. Maintenance conditions for the rats, surgical procedures, apparatus, and drug level calculations were the same as those in Experiment 1.

Procedure

Chain VI DRO with TL as S_2. Initially, rats were trained on a chain crf DRO 5-s schedule wherein 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 schedule. That is, the cocaine was not infused until 5 s had elapsed without a response. During this initial chained schedule training, one infusion per $\overline{TL}$ period was presented, followed by a 55-s period wherein the tone and the light remained off and the DRO contingency was discontinued. When this 55-s period end-

ed, TL commenced. Thus, only one infusion could be earned in each $\overline{TL}$ component.

During the first two chained schedule sessions, if a rat failed to respond within approximately 400 s (range, 350 to 450 s) of TL commencing, TL was turned off and the DRO 5-s schedule went into effect. Once reliable responding occurred on this schedule, the unit dose was gradually reduced from 1.0 mg/kg to 0.2 mg/kg and the postinfusion period where the DRO contingency was discontinued was gradually reduced from 55 s to 20 s.

When responding stablized, a VI 15-s schedule was introduced in TL. Now, $\overline{TL}$ was produced by the first lever press emitted after the current VI interval ($\bar{x}$ = 15 s) timed out. The parameters of the chain VI DRO schedule were gradually adjusted (see below) to produce moderate sustained rates of responding in TL and cessation of responding in $\overline{TL}$. Under this schedule, the DRO contingency operated throughout the entire $\overline{TL}$ component and $\overline{TL}$ durations were programmed such that up to two infusions could be received per $\overline{TL}$ component. Over sessions, the value of the VI schedule in effect during TL was increased from 15 to 30, to 45, and finally to 60 s, and the DRO schedule value in $\overline{TL}$ was gradually increased from 15 to 20 to 30 s. Concurrently, $\overline{TL}$ component lengths were correspondingly increased from 30 to 45 to 60 s, respectively. The final parameters of this schedule were chain VI 60-s DRO 30-s, with $\overline{TL}$ component lengths lasting a mean of 60 s (range, 40 to 90 s).

Chain VI DRO with tone or light as S_2. Training on this schedule proceeded as described above with the exception that S_2 VI components could be signaled by tone or by light (rather than by TL). A DRO schedule operated in $\overline{TL}$ components. Tone components and light components were equally likely to follow $\overline{TL}$ components, with the restriction that either stimulus (tone or light) occur in no more than two consecutive S_2 components. In Experiment 2, the daily sessions were generally 4-hr in duration.

Results

Chain VI DRO with TL as S_2. By the second session on the chain crf DRO 5-s schedule, S-31 frequently self-administered cocaine and more than 400 s rarely passed in TL without a response. Because the rat had acquired the lever press, the unit dose on the second session was gradually reduced from 1.0 mg/kg to 0.2 mg/kg. With this reduction in dose, the postinfusion TO was gradually reduced from 55 s to 20 s. On the third session, $\overline{TL}$ was no longer presented automatically after 350 to 450 s had passed in TL without a response.

On the fourth session, a VI 15-s schedule was introduced in TL. Now, $\overline{TL}$, where a DRO 15-s schedule operated, was produced only by the first response after the current VI value timed out and $\overline{TL}$ components were scheduled to last 30 s, on average (range, 20 to 45 s). A portion of a cumulative record from this session is presented in Section a of Figure 4. The record shows that with these schedule values, the rat rarely responded before the VI interval timed out, making this schedule functionally a chain crf DRO 15-s schedule. To increase responding in TL, the value of the VI schedule therein was increased from 15 s to 30 s on the next session. This change increased the response rate in TL, although response rate also increased in $\overline{TL}$.

Over the next three sessions, the value of the VI schedule in TL was increased from 30 s to 45 s and finally to 60 s and the DRO schedule value in $\overline{TL}$ was increased from 15 s to 20 s and finally to 30 s. The mean length of $\overline{TL}$ components was correspondingly increased from 30 s to 45 s and finally to 60 s (range, 40 to 90 s) in order to allow for up to two infusions in some $\overline{TL}$ components. Cumulative record b in Figure 4 shows S-31's second session on this chain VI 60-s DRO 30-s schedule. Although responding is higher in TL components ($\bar{x}$ = 6.0 responses/min) than in $\overline{TL}$ components ($\bar{x}$ = 3.2 responses/min), the rat's responses emitted in $\overline{TL}$ caused it to lose many reinforcers on the DRO contingency.

After 10 more sessions on this chain VI 60-s DRO 30-s schedule, excellent stimulus control had developed. Cumulative record c in Figure 4 shows a portion of S-31's 19th session wherein rates in TL were more than 10 times those in $\overline{TL}$. Responding was initiated soon after the onset of each TL component, ceased abruptly with TL offset, and was virtually absent in $\overline{TL}$.

Cumulative record d in Figure 4 is a portion of a terminal baseline session from another rat (S-32) trained with procedures similar to those described above for S-31. The

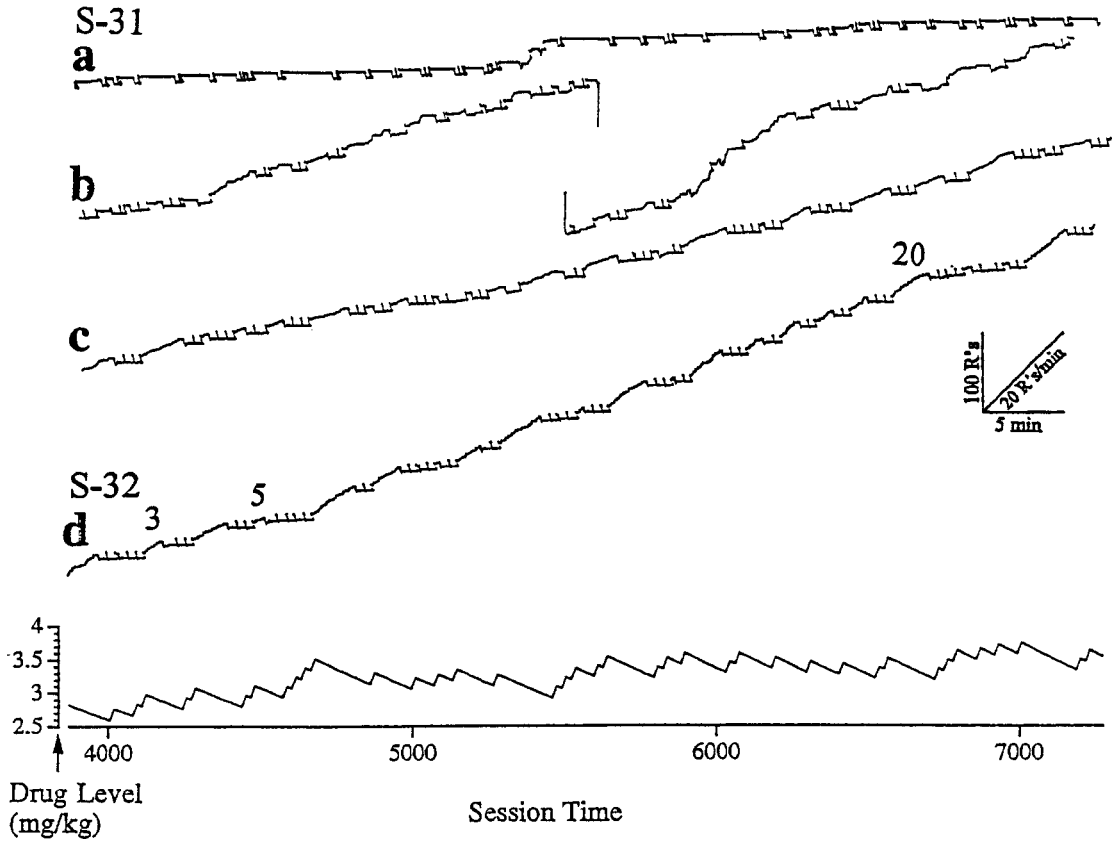

Fig. 4. Cumulative records from rats with chain VI DRO terminal baseline schedules. One-hour cumulative record segments are presented from an early (a), intermediate (b), and terminal baseline training session (c) for S-31. Record d is from a terminal baseline session for S-32. Tone-plus-light (TL) was present when the response pen was in the upper register and absent ($\overline{TL}$) when the response pen was in the lower register. Upward slash marks on the response pen indicate an infusion. The first three records show the responding of S-31 on a: (a) chain VI 15-s DRO 15-s schedule with 0.2 mg/kg unit dose infusions (Session 4), (b) chain VI 60-s DRO 30-s schedule with a 0.2 mg/kg unit dose (Session 9), and (c) chain VI 60-s DRO 30-s schedule with a 0.2 mg/kg unit dose (Session 19). Record d is the cumulative record of S-32's 21st session where it was on a chain VI 60-s DRO 30-s schedule with a 0.2 mg/kg unit dose. Corresponding calculated whole-body drug levels for S-32 are shown below its cumulative record. Numbers in record d identify components referred to in the text. Session time is shown in seconds.

schedule was a chain VI 60-s DRO 30-s with a 0.2 mg/kg/infusion dose of cocaine. Rat S-32 responded faster in TL components (14.4 responses/min) than S-31 did, but the quality of the stimulus control is similar for both rats. Responding typically commenced with TL onset and continued until $\overline{TL}$ was presented, wherein it essentially ceased until TL appeared.

A total of 8 rats (including Rats S-31 and S-32) were trained with the chain VI DRO schedule where S_2 was TL. Terminal baseline data for all of these rats is presented in Table 4. The parameters of the terminal baseline schedule used for these rats are presented in the caption of Table 4. Response rates in TL ranged from 3.9 to 14.5 responses/min, with all rats exceeding the 7:1 discrimination criteria. Molar session rate of cocaine intake, which was 6.5 to 7.2 mg/kg/hr for 7 of the 8 rats, was similar to that of the rats trained on the multiple schedule in Experiments 1 and 2.

Chain VI DRO with tone or light as S_2. Training for Rat S-15 proceeded much like that for Rat S-31 described above, but S_2 was signaled by a tone and by a light. Cumulative record a in Figure 5, taken from S-15's eighth train-

Table 4

For 8 rats trained on the chain VI DRO schedule with TL as S_2: Number of sessions, response rates (responses/min) in TL and $\overline{TL}$, reinforcers/min, dose per infusion (mg/kg), and rate of cocaine intake (mg/kg/hr) (all averaged over the last three training sessions). For each rat, the terminal baseline schedule was chain VI 60-s DRO 30-s. The mean $\overline{TL}$ component duration was 60 s (range, 40 to 90 s) for all subjects except S-33, for which it was 45 s (range, 30 to 67.5 s).

Subject	Sessions	Responses/min		Reinforcers/ min	Unit dose (mg/kg)	Rate of intake (mg/kg/hr)
		TL	$\overline{TL}$			
S-25	22	4.6	0.2	0.57	0.2	6.8
S-30	19	3.9	0.2	0.58	0.2	7.0
S-31	22	7.6	0.6	0.55	0.2	6.6
S-32	22	14.1	0.8	0.56	0.2	6.7
S-33	16	10.4	0.4	0.59	0.2	7.1
LD-21	20	5.0	0.2	0.60	0.2	7.2
LF-5	22	12.9	0.7	0.54	0.2	6.5
LF-21	32	14.5	0.8	0.56	0.25	8.4
MEAN	21.9	9.1	0.5	0.57	0.21	7.0

ing session, shows performance on a chain crf DRO 5-s schedule with a dose of 0.2 mg/kg/infusion. Responses and infusions were distributed throughout the session, revealing that the rat had acquired the lever press operant and that the 0.2 mg/kg/infusion of cocaine was functioning effectively as a reinforcer despite the short delay between the response and infusion.

Cumulative record b in Figure 5 shows S-15's responding on its first session of training on a chain VI 15-s DRO 5-s schedule. In this record, the overall response rate has increased substantially from the session depicted in Figure 5a. The rat responded in tone, light, and $\overline{TL}$ components at 2.7, 6.8, and 5.0 responses/min, respectively, however, indicating that stimulus control remained to be established.

Over the next several sessions, schedule values were gradually changed to yield a chain VI 60-s DRO 30-s. Cumulative record c in Figure 5 shows S-15's responding after extended training on this schedule. Responding was initiated promptly in each tone or light component and was sustained throughout the component. Rat S-15's responding in tone or light produced $\overline{TL}$, where responding ceased abruptly and the cocaine infusions occurred under the DRO 30-s schedule. Response cessation continued in $\overline{TL}$ until the next tone or light component was presented. During this session, rates in tone, light, and $\overline{TL}$ were 7.5, 10.3, and 1.1 responses/min, respectively.

Cumulative record d in Figure 5 shows responding of another rat (S-99) trained to self-administer cocaine on a chain VI DRO schedule where S_2 was signaled by a tone or by a light. Rat S-99's training history was similar to S-15's described above. The values of the terminal baseline schedule presented in record d were chain VI 90-s DRO 30-s with a 0.2 mg/kg unit dose. Rat S-99 responded at a sustained rate throughout tone and light components (some of which lasted more than 3 min) without cocaine infusions because cocaine was presented only in $\overline{TL}$ after the DRO contingency was satisfied. Responding was virtually absent in $\overline{TL}$ components. Rat S-99 emitted 6.8 responses/min in tone, 8.8 responses/min in light, and less than 1 response/min in $\overline{TL}$.

Summary data for the 5 rats exposed to the chain VI DRO schedule (including Rats S-15 and S-99) are presented in Table 5. The parameters of the terminal baseline schedule used for these rats are presented in the caption of Table 5. The rats trained on this schedule required almost three times as many sessions to reach their terminal baseline stimulus control as rats trained on the chain VI DRO schedule where S_2 components were associated with TL (see Table 4). This faster learning under multiple versus single cue learning situations is consistent with previous findings (e.g., see Eninger, 1952). Nevertheless, the quality of the terminal baseline stimulus control is essentially the same for the rats

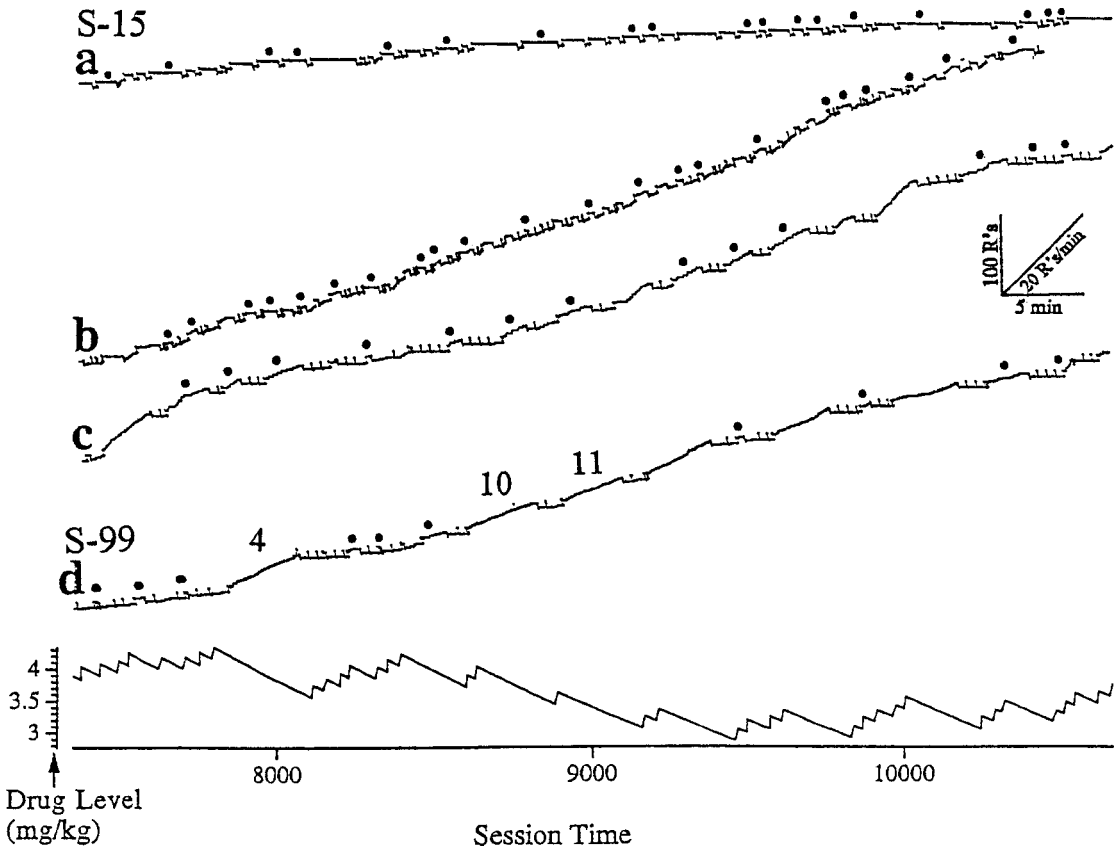

Fig. 5. Cumulative records from rats with chain VI DRO terminal baseline schedules where the VI component could be signaled by a tone or by a light. One-hour cumulative record segments are presented from an early (a), intermediate (b), and terminal baseline training session (c) for S-15. Record d is from a terminal baseline session for S-99. Tone or light was present when the response pen was in the upper register (tones are indicated by filled circles) and both were absent ($\overline{TL}$) when the response pen was in the lower register. Upward slash marks on the response pen indicate an infusion. The first three records show the responding of S-15 on a (a) chain crf DRO 5-s schedule with 0.2 mg/kg unit dose infusions (Session 8), (b) chain VI 15-s DRO 5-s schedule with a 0.2 mg/kg unit dose (Session 11), and (c) chain VI 60-s DRO 30-s schedule with a 0.2 mg/kg unit dose (Session 61). Record d is from S-99's 64th session where it was on a chain VI 90-s DRO 30-s schedule with a 0.2 mg/kg unit dose. Corresponding calculated whole-body drug levels for S-99 are shown below its cumulative record. Numbers in record d identify components referred to in the text. Session time is shown in seconds.

trained on the chained schedule as presented in Table 4 and in Table 5 with respect to (a) response rates in VI components, (b) response rates in DRO components, (c) reinforcers/min, and (d) molar rates of session cocaine intake. Furthermore, the baseline stimulus control of these chained-schedule trained animals is indistinguishable from that of the multiple-schedule trained animals in Tables 1 through 3.

Calculated whole-body drug levels and response rates. The panels at the bottom of Figures 1 through 5 present calculated whole-body drug levels during the portions of the session corresponding to the cumulative records (d) presented directly above them. The ranges of whole-body drug levels (mg/kg) for individual subjects in these Figures were 2.1 to 3.0 for Rat S-9; 2.0 to 3.4 for Rat S-110; 1.7 to 2.3 for Rat S-21; 2.6 to 3.9 for Rat S-32; and 2.9 to 4.3 for Rat S-99 (mean range = 2.3 to 3.4 mg/kg). Thus, the ranges of drug levels within individuals were as large as 1.4 mg/kg, a 70% change for S-110. Drug levels never approached zero, however, and there were no consistent trends (increasing or decreasing) in drug level over these records.

Within the range of drug levels maintained

Table 5

For 5 rats trained on the chain VI DRO schedule with tone or light as S_2: Number of sessions, response rates (responses/min) in tone, light, and $\overline{TL}$, reinforcers/min, dose per infusion (mg/kg), and rate of cocaine intake (mg/kg/hr) (all averaged over the last three training sessions). For each rat, the terminal baseline schedule was chain VI 60-s DRO 30-s, except for S-99 for which the schedule was chain VI 90-s DRO 30-s. The mean $\overline{TL}$ component duration was 60 s (range, 40 to 90 s).

Subject	Sessions	Responses/min			Reinforcers/min	Unit dose (mg/kg)	Rate of intake (mg/kg/hr)
		Tone	Light	$\overline{TL}$			
N-4	42	5.0	4.2	0.6	0.45	0.2	5.4
S-15	55	8.3	10.9	1.0	0.52	0.2	6.2
N-5	72	13.4	13.1	1.6	0.53	0.2	6.4
J-20	66	6.7	9.3	0.8	0.60	0.2	7.2
S-99	65	8.0	9.8	0.8	0.68	0.2	8.2
MEAN	60	8.3	9.5	1.0	0.56	0.2	6.7

under these schedules, drug levels were not systematically related to response rates. In many cases, although a rat's whole-body drug level was similar when different schedule components were entered, its response rates differed markedly between the components. This can be seen in (a) cumulative record d in Figure 1, where rat S-9 entered Components 6 and 17 with a drug level of approximately 2.75 mg/kg, while its response rate during Component 6 was 10.0 responses/min and that during Component 17 was 20.0 responses/min, (b) cumulative record d in Figure 3, where S-21's drug level remained within 1.8 and 2.3 mg/kg, while its response rate during VI components ranged from 20.0 (Component 3) to 3.4 responses/min (Component 8); and (c) cumulative record d in Figure 4, where S-32 entered both Components 3 and 5 with a drug level of 3.0 mg/kg while rates in Component 3 were 2.4 times those in Component 5.

Conversely, there were also components where the whole-body drug levels were different but response rates were the same. This is exemplified in (a) cumulative record d in Figure 1 where S-9 responded at the same rate (11.4 responses/min) in components it entered with its highest and lowest whole-body drug levels, 2.85 mg/kg (Component 5) and 2.3 mg/kg (Component 14), respectively; (b) cumulative record d in Figure 2 where the range of S-110's drug levels in Segment A (2.65 to 3.4 mg/kg) is higher than its range of nonoverlapping drug levels in Segment B (2.0 to 2.5 mg/kg), while its response rates in Segments A and B were essentially the same (13.8 and 13.5 responses/min, respectively), and (c) cumulative record d in Figure 4 where S-32 entered Components 3 and 20 with drug levels of 3.0 and 3.65 mg/kg, respectively, yet its response rate was identical in both components (12.0 responses/min).

Perhaps the most convincing evidence for a lack of relation between drug levels and response rates comes from the relatively long S_2 chain components, where drug levels were dropping while response rates remained stable. For example, during Components 10 and 11 in cumulative record d of Figure 5, S-99's drug level dropped by 26% (0.95 mg/kg) over approximately 7 min while its responding remained remarkably stable at approximately 8.0 responses/min. Here, a nearly 1.0 mg/kg decrease in whole-body drug level did not affect response rate.

GENERAL DISCUSSION

Stimulus Control of Behavior Maintained by Drug and by Nondrug Reinforcers

Studies of drug self-administration that specifically focus on stimulus control—especially within multicomponent schedules with short components that are comparable to those used with conventional reinforcers—are extremely rare. The present data demonstrate that it is possible to maintain patterns of responding under multiple and chained schedules of cocaine self-administration that are virtually indistinguishable from behavior maintained by nondrug reinforcers under

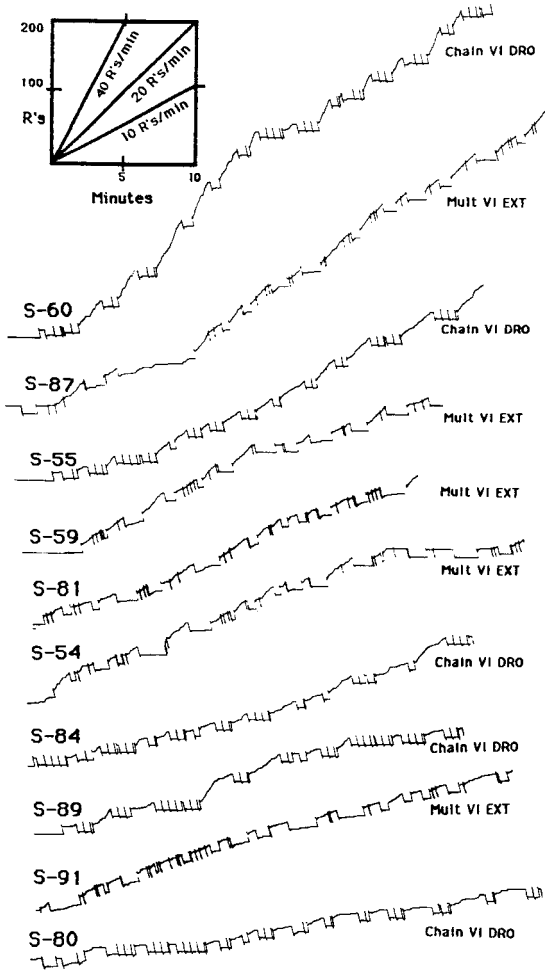

Fig. 6. Cumulative records of rats trained on mult VI EXT and chain VI DRO food-reinforced schedules from Weiss, Panlilio and Schindler (1993a). Records are presented in order of decreasing response rate. The rat's baseline schedule, chain VI DRO or mult VI EXT, is indicated to the right of each record. The pen in the upper register indicates a tone-plus-light (TL) component. During the absence of TL, the pen was in its lower register. Upward or downward slashmarks indicate food deliveries.

comparable schedule parameters (e.g., Weiss, 1964, 1969, 1971; Weiss & Panlilio, 1999; Weiss et al., 1993a, 1993b; Weiss & Schindler, 1989; Weiss et al., 1996; Weiss & Van Ost, 1974). A comparison of the terminal baseline cumulative records in Figures 1, 2, 4 and 5 with those in Figure 6 supports this conclusion. Figure 6 presents cumulative records from Weiss et al. (1993a, Fig. 2) of the responding of food-trained animals on chain VI DRO and mult VI EXT schedules like those of the present experiment. (Training chambers and stimuli were also the same). Five of the rats in Figure 6 were trained on mult VI 60 s EXT and 5 on chain VI 60 s DRO 30 s.

A comparison of the record of cocaine-trained Rat S-9 (Figure 1, record d) with that of food-trained Rat S-54 (Figure 6) illustrates this comparable stimulus control under a mult VI 60-s EXT schedule. Their response rates in the VI component were 9.1 and 11.7 responses/min, respectively, and response patterns were similar, as reflected by the records' fine grain. A comparison of the record of cocaine-trained Rat S-32 (Figure 4, record d) with that of food-trained Rat S-55 (Figure 6) illustrates comparable stimulus control under a chain VI 60-s DRO 30-s schedule. Their response rates in the VI component were 14.1 and 15.9 responses/min, respectively, again with similar fine grain in both records. There are comparable similarities over the remaining food-reinforced and drug-reinforced rats in these figures. (For representative records of rats responding for food on three-component mult VI VI EXT, mult VI VI DRO, and chain VI DRO schedules like those used in the present experiment see Weiss, 1971, Fig. 4 and Weiss & Van Ost, 1974, Fig. 1.)

The between-subject ranges of response rates in VI components were also comparable over rats trained with drug and with food reinforcers. On the mult VI EXT schedule, response rates in the VI component ranged from 4.8 to 20.1 responses/min for the drug animals (see Tables 1 and 2) and from 6.2 to 19.1 responses/min for the food rats (see Weiss et al., 1993a, Table 1). On the chain VI DRO schedule, response rates ranged from 3.9 to 14.5 responses/min for the drug rats (see Tables 4 and 5) and from 4.9 to 26.5 responses/min for the food rats (with 4 of these latter 5 rats between 4.9 and 15.9 responses/min) (see Weiss et al., 1993a, Table 1). In addition, response rates in DRO or EXT components were negligible whether the reinforcer was food or cocaine.

The procedures used here to produce stimulus control of drug-maintained behavior that was indistinguishable from that exhibited by rats reinforced with food on these multicomponent schedules, can be summarized as follows:

1. Schedule parameters (e.g., VI value,

DRO value, as well as durations of VI, DRO, and EXT components) were adjusted gradually and customized for each individual rat, within the limits of the basic contingencies of the schedules, to maintain responding in the VI components and reduce responding in the DRO and EXT components.

2. High doses (usually 1.0 mg/kg/infusion) were used during acquisition of self-administration, which animals acquired without shaping or prior food-reinforced bar pressing.

3. Once lever pressing was acquired, the unit dose was gradually adjusted on a subject-by-subject basis to produce moderate response rates and minimal postreinforcement pausing in VI components of the schedules. These adjustments consistently led to unit doses that resulted in the rats self-administering cocaine at approximately 6 mg/kg/hr over the session on their terminal baseline schedules (see Tables 1 through 5).

4. Successive changes to each rat's schedule and unit dose were guided by the effects of the previous change, as revealed through reviews of the cumulative records.

Whole-Body Drug Levels, Response Rates and Stimulus Control

The relation between drug levels (or levels of drug effect) and self-administration responding is currently a topic of much interest (e.g., Ahmed & Koob, 1999; Lynch et al., 1998; Norman, Norman, Hall, & Tsibulsky, 1999; Tsibulsky & Norman, 1999; Wise, 1999). Studies of this relation have traditionally used continuous reinforcement schedules where every response produces the drug (cf., Nicola & Deadwyler, 2000). Under such conditions, animals often maintain drug levels within a relatively narrow range, which has led to the suggestion that self-administration may be controlled by an automatic, homeostatic-like mechanism (Ahmed & Koob; Lynch & Carroll, 2001; Tsibulsky & Norman). Until now, however, drug levels have not been reported under complex, intermittent schedules of reinforcement like those described in the present paper, where intake is influenced by both the demands and limits set by the schedule.

In the present study, drug levels were maintained within a relatively narrow range by each subject. According to titration theory, maintenance of drug levels within a certain range occurs because there is a threshold below which self-administration responding occurs and above which responding ceases. Thus, intake on a crf schedule is essentially regulated by the duration of postinfusion pauses. In the intermittent schedules of the present study, unit doses were chosen to minimize postreinforcement pauses, which would suggest that drug levels were not allowed to surpass the hypothetical satiety threshold. Drug intake and the drug levels achieved under these schedules, however, were not substantially different from those obtained under crf. Both the whole-body drug levels (approximately 2.3 to 3.4 mg/kg) and the molar rates of intake (approximately 6 mg/kg/hour) under the final training schedules in the present study were similar to the values observed in the same rats during earlier crf training. These values were also similar to those of rats trained only with crf in an earlier study (Panlilio, Katz, Pickens, & Schindler, 2000). In that study, unit doses of cocaine comparable to those used on the terminal baselines of the present study produced mean whole-body drug levels around 2 mg/kg and mean molar rates of intake slightly less than 6 mg/kg/hour. Therefore, through the process of adjusting unit doses with the goal of maintaining robust responding without postinfusion pausing, it appears that a situation was created where drug levels were maintained close to, but possibly just below, the threshold where responding would have ceased.

The fact that whole-body drug levels were stable and did not drop substantially during periods of drug unavailability makes it unlikely that changes in absolute drug levels contributed to the development of stimulus control in this study. Moreover, because the three basic schedules covered a broad spectrum of response-reinforcer relations, responding in a particular component could not have been automatically determined by whether drug was available during that component. That is, across the three basic schedules, responding had three completely different relations to drug administration. Under the mult VI EXT schedule, responding occurred only in the component where drug was received; under the chain VI DRO schedule, responding occurred only in the com-

ponent where drug was *never* received; finally, under the mult VI DRO schedule, responding only occurred in one component, even though drug was received in both components.

There is also no evidence that local response rates were influenced by the current whole-body drug level. There were (a) components where whole-body drug levels differed while response rates remained the same, as well as (b) components where drug levels were the same but response rates differed. Thus, although it is possible that responding may only occur while drug levels are within a certain range, variations in drug levels inside of this range did not affect response rates.

In contrast to changes in absolute drug levels, which had no observable effect on schedule-controlled responding in the present study, it is likely that relative changes in drug level exerted a powerful influence. In the plots of calculated whole-body drug levels in record d of Figures 1 through 5, (a) the positive slope of the whole-body drug level is steep upon infusion, while (b) after infusion the slope of the decline in whole-body drug level is shallow. This shows that, in contrast to the relatively slow clearance of cocaine, each infusion increased whole-body drug levels abruptly. A similar rapid increase/slow decrease pattern has been reported when rats' intra-accumbens cocaine concentrations, rather than whole-body drug levels, were modeled during cocaine self-administration (Nicola & Deadwyler, 2000). In the present experiments, the rapid increases in whole-body drug level may have functioned both as an operant reinforcer and as a Pavlovian unconditioned stimulus in a manner analogous to the delivery of a food pellet. This is consistent with studies showing that drug reinforcement depends on immediate increases in drug levels following a cocaine infusion, rather than the absolute amount of drug delivered (Balster & Schuster, 1973; Panlilio, Goldberg, Gilman, Jufer, Cone, & Schindler, 1998).

Drug Abuse and Stimulus Control

There is a developing consensus that environmental stimuli associated with the drug-taking experience can acquire the capacity to increase drug-related behavior (e.g., drug craving, seeking, and consumption) through an incentive motivational mechanism involving classical conditioning (Markou et al., 1993; Pert, 1994; Robinson & Berridge, 1993). Panlilio, Weiss, & Schindler (1996, 2000) supported these assumptions in an experiment where animals were trained on a schedule functionally similar to the mult VI VI EXT schedule described in Experiment 1.

In the Panlilio et al. (1996, 2000) experiments, motivational properties would have been established to a tone and to a light because these stimuli set the occasion wherein rats could work for cocaine (Panlilio et al., 1996) or heroin (Panlilio et al., 2000), while drug was not available in the absence of these stimuli. After this training, compounding the tone and the light tripled cocaine as well as heroin seeking. In addition, compounding tone and light doubled intake of both drugs over the baseline titrated levels controlled by either S^D alone. No other animal model of drug abuse has so powerfully revealed the influence of environmental drug-related cues in producing ''loss of control.'' This ''stimulus compounding model of drug abuse'' demonstrates that exteroceptive stimuli can exert profound control over drug self-administration, and that this control is lawful and predictable. Further research involving multicomponent schedules, using training tactics like those described here, may provide further insights into how environmental, drug-related stimuli influence drug abuse.

Reiterating the sentiment of Bickel and Kelly's (1988, 1997) commentary presented in the introduction, Kirby, Lamb, & Iguchi (1997) concluded:

> Strategies addressing stimulus control have been incorporated into drug-abuse treatments, but stimulus control as a behavioral process in drug abuse has not received much explicit scientific attention. Much more research is needed before we will have a basic understanding of the processes involved and the necessary tools for systematically applying that knowledge to the treatment of substance abuse. (p. 181)

The research presented here demonstrated how stimulus control of drug self-administration could be established on a variety of complex, multicomponent schedules of reinforcement. This is an initial step in the systematic investigation of stimulus control as a basic

process in drug abuse that we anticipate will be developed further by other investigators as well. To assist others in producing such stimulus control, a tutorial style was incorporated in describing procedures and results. This should help us achieve our ultimate objective: a more complete understanding of the control of drug abuse.

REFERENCES

Ahmed, S. H., & Koob, G. F. (1999). Long-lasting increase in the set point for cocaine self-administration after escalation in rats. *Psychopharmacology, 146,* 303–312.

Arroyo, M., Markou, A., Robbins, T. W., & Everitt, B. J. (1998). Acquisition, maintenance and reinstatement of intravenous cocaine self-administration under a second-order schedule of reinforcement in rats: Effects of conditioned cues and continuous access to cocaine. *Psychopharmacology, 140,* 331–344.

Balster, R. L., & Schuster, C. R. (1973). Fixed-interval schedule of cocaine reinforcement: Effect of dose and infusion duration. *Journal of the Experimental Analysis of Behavior, 20,* 119–129.

Barbieri, E. J., Ferko, A. P., DiGregorio, G. C., & Ruch, E. K. (1992). The presence of cocaine and benzoylecgonine in rat cerebrospinal fluid after the intravenous administration of cocaine. *Life Sciences, 51,* 1739–1746.

Bickel, W. K., & Kelly, T. H. (1988). The relationship of stimulus control to the treatment of substance abuse. *NIDA Research Monograph, 84,* 122–140.

Bickel, W. K., & Kelly, T. H. (1997). Stimulus control processes in drug taking: Implications for treatment. In D. M. Baer & E. M. Pinkston (Eds.), *Environment and behavior* (pp. 185–193). Boulder, CO: Westview Press.

Bindra, D. A. (1972). A unified account of classical conditioning and operant training. In M. A. Black & W. F. Prokasy (Eds.), *Classical Conditioning: Vol. 2. Current research and theory* (pp. 453–481). New York: Appleton-Century-Crofts.

Caine, S. B., & Koob, G. F. (1994a). Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. *Journal of Pharmacology & Experimental Therapeutics, 270,* 209–218.

Caine, S. B., & Koob, G. F. (1994b). Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food. *Journal of the Experimental Analysis of Behavior, 61,* 213–221.

Childress, A. R., McLellan, A. T., Ehrman, R., & O'Brien, C. P. (1987). Extinction of conditioned responses in abstinent cocaine or opioid users. *NIDA Research Monograph Series, 76,* 189–195.

Dinsmoor, J. A. (1995a). Stimulus control: Part 1. *The Behavior Analyst, 18,* 51–68.

Dinsmoor, J. A. (1995b). Stimulus control: Part 2. *The Behavior Analyst, 18,* 253–269.

Dougherty, J., & Pickens, R. (1973). Fixed-interval schedules of intravenous cocaine presentation in rats. *Journal of the Experimental Analysis of Behavior, 20,* 111–118.

Ehrman, R. N., Robbins, S. J., Childress, A. R., & O'Brien, C. P. (1992). Conditioned responses to cocaine-related stimuli in cocaine abuse patients. *Psychopharmacology, 107,* 523–529.

Eninger, M. U. (1952). Habit summation in a selective learning problem. *Journal of Comparative and Physiological Psychology, 45,* 604–608.

Everitt, B. J., & Robbins, T. W. (2000). Second-order schedules of drug reinforcement in rats and monkeys: Measurement of reinforcing efficacy and drug-seeking behaviour. *Psychopharmacology, 153,* 17–30.

Ferster, C. B., & Skinner, B. F. (1957). *Schedules of reinforcement.* Englewood Cliffs, NJ: Prentice-Hall.

Gibbon, J. (1977). Scalar expectancy theory and Weber's law in animal timing. *Psychological Review, 84,* 279–325.

Gibbon, J., & Balsam, P. (1981). Spreading association in time. In C. M. Locurto, H. S. Terrace, & J. Gibbon (Eds.), *Autoshaping and conditioning theory* (pp. 219–253). New York: Academic Press.

Goeders, N. E., & Guerin, G. F. (1994). Non-contingent electric shock facilitates the acquisition of intravenous cocaine self-administration. *Psychopharmacology, 114,* 63–70.

Goeders, N. E., McNulty, M. A., & Guerin, G. F. (1993). Effects of alprazolam on intravenous cocaine self-administration in rats. *Pharmacology, Biochemistry & Behavior, 44,* 471–474.

Goldberg, S. R. (1973). Comparable behavior maintained under fixed-ratio and second-order schedules of food presentation, cocaine injection, or d-amphetamine injection in the squirrel monkey. *Journal of Pharmacology and Experimental Therapeutics, 186,* 18–30.

Goldberg, S. R., & Kelleher, R. T. (1976). Behavior controlled by scheduled injections of cocaine in squirrel and rhesus monkeys. *Journal of the Experimental Analysis of Behavior, 25,* 93–104.

Goldberg, S. R., Schindler, C. W., & Lamb, R. J. (1990). Second-order schedules and the analysis of human drug-seeking behavior. *Drug Development Research, 20,* 217–229.

Gollub, L. R. (1977). Conditioned reinforcement: Schedule effects. In W. K. Honig and J. E. R. Staddon (Eds.), *Handbook of operant behavior* (pp. 432–480). Englewood Cliffs, NJ: Prentice Hall.

Harrison, J. M. (1991). Stimulus control. In I. H. Iverson & K. A. Lattal (Eds.), *Experimental Analysis of Behavior* (Part 1, pp. 251–299). Amsterdam: Elsevier.

Katz, J. L. (1989). Drugs as reinforcers: Pharmacological and behavioural factors. In J. M. Liebman & S. J. Cooper (Eds.), *The neuropharmacological basis of reward* (pp. 164–213). New York: Oxford University Press.

Kelleher, R. T. (1966). Chaining and conditioned reinforcement. In W. K. Honig (Ed.), *Operant behavior: Areas of research and application* (pp. 160–212). New York: Appleton-Century-Crofts.

Kelleher, R. T., & Gollub, L. R. (1962). A review of conditioned reinforcement. *Journal of the Experimental Analysis of Behavior, 5,* 543–597.

Kirby, K. C., Lamb, R. J., & Iguchi, M. Y. (1997). Stimulus control of drug abuse. In D. M. Baer & E. M. Pinkston (Eds.), *Environment and behavior* (pp. 173–184). Boulder, CO: Westview Press.

Lau, C. E., & Sun, L. (2002). The pharmacokinetic determinants of the frequency and pattern of intravenous cocaine self-administration in rats by pharmacokinetic modeling. *Drug metabolism and disposition, 30,* 254–261.

Lynch, W. J., & Carroll, M. E. (2001). Regulation of drug

intake. *Experimental and Clinical Psychopharmacology, 9,* 131–143.

Lynch, W. J., LaBounty, L. P., & Carroll, M. E. (1998). A novel paradigm to investigate regulation of drug intake in rats self-administering cocaine or heroin intravenously. *Experimental and Clinical Psychopharmacology, 6,* 22–31.

Markou, A., Weiss, F., Gold, L. H., Caine, B., Schulties, G., & Koob, G. F. (1993). Animal models of drug craving. *Psychopharmacology, 112,* 163–182.

Nicola S. M., & Deadwyler, S. A. (2000). Firing rate of nucleus accumbens neurons is dopamine-dependent and reflects the timing of cocaine-seeking behavior in rats on a progressive ratio schedule of reinforcement. *Journal of Neuroscience, 20,* 5526–5537.

Norman, A. B., Norman, M. K., Hall, J. F., & Tsibulsky, V. L. (1999). Priming threshold: A novel quantitative measure of the reinstatement of cocaine self-administration. *Brain Research, 831,* 165–174.

O'Brien, C. P., Childress, A. R., McLellan, A. T., & Ehrman, R. (1990). Integrating systematic cue exposure with standard treatment in recovering drug dependent patients. *Addictive Behaviors, 15,* 355–365.

Panlilio, L. V., Goldberg, S. R., Gilman, J. P., Jufer, R., Cone, E. J., & Schindler, C. W. (1998). Effects of delivery rate and non-contingent infusion of cocaine on cocaine self-administration in rhesus monkeys. *Psychopharmacology, 137,* 253–258.

Panlilio, L. V., Katz, J. L., Pickens, R. W., & Schindler, C. W. (2000, June). *A formal analysis of the regularity of drug self administration in rats.* Paper presented at the meeting of the College on Problems of Drug Dependence, San Juan, PR.

Panlilio, L. V., Weiss, S. J., & Schindler, C. W. (1996). Cocaine self-administration increased by compounding discriminative stimuli. *Psychopharmacology, 125,* 202–208.

Panlilio, L. V., Weiss, S. J., & Schindler, C. W. (2000). Effects of compounding drug-related stimuli: Escalation of heroin self-administration. *Journal of the Experimental Analysis of Behavior, 73,* 211–224.

Pert, A. (1994). Neurobiological mechanisms underlying the acquisition and expression of incentive motivation by cocaine-associated stimuli: Relationship to craving. In L. Erinoff (Ed.), Neurobiological models of drug addiction, *NIDA Research Monographs* (pp. 163–190). Washington, DC: US Government Printing Office.

Pettit, H. O., & Justice, J. B. (1989). Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. *Pharmacology, Biochemistry & Behavior, 34,* 899–904.

Pettit, H. O., & Justice, J. B. (1991). Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. *Brain Research, 539,* 94–102.

Pickens, R., & Thompson, R. (1968). Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. *Journal of Pharmacology and Experimental Therapeutics, 161,* 122–129.

Rescorla, R. A., & Solomon, R. L. (1967). Two-process learning theory: Relationship between Pavlovan conditioning and instrumental learning. *Psychological Review, 74,* 151–182.

Rilling, M. (1977). Stimulus control and inhibitory processes. In W. K. Honig & J. E. R. Staddon (Eds.), *Handbook of operant behavior* (pp. 432–480). Englewood Cliffs, NJ: Prentice Hall.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Review, 18,* 247–291.

Schindler, C. W., Katz, J. L., & Goldberg, S. R. (1988). The use of second-order schedules to study the influence of environmental stimuli on drug-seeking behavior. In B. Ray (Ed.), *Learning factors in substance abuse,* National Institute on Drug Abuse Research Monograph 84 (DHHS No. ADM) 88-1576, (pp. 180–195). Washington, DC: United States Government Printing Office.

Schindler, C. W., Panlilio, L. V., & Goldberg, S. R. (2002). Second-order schedules of drug self-administration in animals. *Psychopharmacology, 163,* 327–344.

Shoaib, M., Swanner, L. S., Beyer, C. E., Goldberg, S. R., & Schindler, C. W. (1998). The GABA-sub(B) agonist baclofen modifies cocaine self-administration in rats. *Behavioural Pharmacology, 9,* 195–206.

Shulman, G. D. (1989). Experience with the cocaine trigger inventory. *Advances in alcohol & substance abuse, 8,* 71–85.

Terrace, H. S. (1966). Stimulus control. In W. K. Honig (Ed.), *Operant behavior: Areas of research and application* (pp. 271–344). New York: Appleton-Century-Crofts.

Tsai, S. Y., & Weiss, S. J. (1977). A further test of composite-stimulus control in additive summation. *Bulletin of the Psychonomic Society, 9,* 169–172.

Tsibulsky, V. L., & Norman, A. B. (1999). Satiety threshold: A quantitative model of maintained cocaine self-administration. *Brain Research, 839,* 85–93.

Wallace, B. C. (1989). Psychological and environmental determinants of relapse in crack cocaine smokers. *Journal of Substance Abuse Treatment, 6,* 95–106.

Weiss, S. J. (1964). Summation of response strengths instrumentally conditioned along a composite stimulus continuum during free-operant summation. *Journal of the Experimental Analysis of Behavior, 68,* 151–155.

Weiss, S. J. (1969) Attentional processes along a composite stimulus continuum during free-operant summation. *Journal of Experimental Psychology, 82,* 22–27.

Weiss, S. J. (1970). An effective and economical sound-attenuation chamber. *Journal of the Experimental Analysis of Behavior, 13,* 37–39.

Weiss, S. J. (1971). Discrimination training and stimulus compounding: Consideration of nonreinforcement and response differentiation consequences of S^{Δ}. *Journal of the Experimental Analysis of Behavior, 15,* 387–402.

Weiss, S. J. (1972). Stimulus compounding in free-operant and classical conditioning: A review and analysis. *Psychological Bulletin, 78,* 189–208.

Weiss, S. J. (1978). Discriminated response and incentive processes in operant conditioning: A two-factor model of stimulus control. *Journal of the Experimental Analysis of Behavior, 30,* 361–381.

Weiss, S. J., & Emurian, H. (1970). Stimulus control during the summation of conditioned suppression. *Journal of Experimental Psychology, 85,* 204–209.

Weiss, S. J., & Panlilio, L. V. (1999). Blocking a selective association in pigeons. *Journal of the Experimental Analysis of Behavior, 71,* 13–24.

Weiss, S. J., Panlilio, L. V., & Schindler, C. W. (1993a). Selective associations produced solely with appetitive contingencies: The stimulus-reinforcer interaction re-

visited. *Journal of the Experimental Analysis of Behavior, 59,* 309–322.

Weiss, S. J., Panlilio, L. V., & Schindler, C. W. (1993b). Single-incentive selective associations produced solely as a function of compound-stimulus conditioning context. *Journal of Experimental Psychology: Animal Behavior Processes, 19,* 284–294.

Weiss, S. J., & Schindler, C. W. (1987). The composite-stimulus analysis and the quantal nature of stimulus control: Response and incentive factors. *Psychological Record, 37,* 177–191.

Weiss, S. J., & Schindler, C. W. (1989). Integrating control generated by positive and negative reinforcement on an operant baseline: Appetitive-aversive interactions. *Animal Learning and Behavior, 17,* 433–446.

Weiss, S. J., Thomas, D. A., & Weissman, R. D. (1996). Combining operant-baseline-derived conditioned excitors and inhibitors from the same and different incentive classes: An investigation of appetitive-aversive interactions. *Quarterly Journal of Experimental Psychology: Section B. Comparative & Physiological Psychology, 49,* 357–381.

Weiss, S. J., & Van Ost, S. L. (1974). Response discriminative and reinforcement factors in stimulus control of performance on multiple and chained schedules of reinforcement. *Learning and Motivation, 5,* 459–472.

Weissenborn, R., Yackey, M., Koob, G. F., & Weiss, F. (1995). Measures of cocaine-seeking behavior using a multiple schedule of food and drug self-administration in rats. *Drug & Alcohol Dependence, 38,* 237–246.

Wise, R. A. (1999). Cognitive factors in addiction and nucleus accumbens function: Some hints from rodent models. *Psychobiology, 27,* 300–310.

Wise, R. A., Newton, P., Leeb, K., Burnette, B., Pocock, D., & Justice, J. B., Jr. (1995). Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology, 120,* 10–20.

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