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On the nature of directed behavior to drug-associated light cues in rhesus monkeys (*Macaca mulatta*)

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Abstract

The present study investigated the role of drug-paired stimuli in controlling the behavior of rhesus monkeys. Systematic observations were made with nine monkeys who had a history of drug self-administration; they had been lever pressing to produce intravenous infusions of various drugs. These observations revealed that the stimulus light co-occurring with drug infusion produced robust and cue-directed behavior such as orienting, touching and biting. Experiment 1 showed that this light-directed behavior would occur in naïve monkeys exposed to a Pavlovian pairing procedure. Four monkeys were given response-independent injections of cocaine. In two monkeys, a red light preceded cocaine injections by 5 s, and a green light co-occurred with the 5-s cocaine injections. In the other two monkeys, the light presentations and cocaine injections occurred independently. Light-directed behavior occurred in all four monkeys within the first couple of trials and at high levels but decreased across sessions. The cocaine-paired stimulus maintained behavior longer and at higher levels than the uncorrelated stimuli. Furthermore, light-directed behavior was not maintained when cocaine was replaced with saline. Light-directed behavior did not occur in the absence of the lights. When these monkeys were subsequently trained to lever press for cocaine, light-directed behavior increased to levels higher than previously observed. Behavior directed towards drug-paired stimuli is robust, reliable and multiply determined; the mechanisms underlying this activity likely include Pavlovian conditioning, stimulus novelty, habituation and operant conditioning.

Keywords

sign tracking; Pavlovian conditioning; cocaine; drug self-administration; rhesus monkeys

Drug self-administration procedures provide a context to investigate antecedent stimulus control because stimuli typically precede or co-occur with drug administration. It was in this context at the University of Michigan self-administration laboratory that monkeys were observed directing a substantial amount of behavior such as touching and licking toward stimulus lights associated with intravenous drug infusion. Like most casual observations,

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The study was conducted at the University of Michigan.

however, the conditions necessary and/or sufficient for the observed phenomenon have not been specified.

We decided to formalize the observations of this behavior. Nine adult rhesus monkeys (*Macaca mulatta*), each participating in an ongoing research project involving drug self-administration, were employed in the present study. Each of the monkeys had a history of drug self-administration and had been self-administering various compounds under the current conditions for various periods of time. The conditions in effect at the time of our observations varied across monkeys as did the drugs and doses that were self-administered (the details are presented in Table 1). The drugs self-administered included cocaine (0.003, 0.01 & 0.03 mg/kg/infusion), methohexital (0.1 mg/kg/infusion), alfentanil (0.0003 & 0.01 mg/kg/infusion), alfentanil with morphine pretreatment, and two experimental drugs, PNU101017 (0.1 mg/kg/infusion) and CPDD-46 (0.3 mg/kg/infusion). Monkeys self-administered these drugs under fixed-ratio (FR) 10 or 30 schedules that included timeouts 45 to 600 s following drug delivery. Monkeys M3029 and M3575 self-administered under a chained fixed-interval 10-min FR 20 schedule of reinforcement. During the timeout, stimulus lights were extinguished and lever presses had no effect. The duration of the drug injection was 5 s, and a transilluminated disc located on the center of the work panel was illuminated green during the 5-s drug injection.

Sessions were recorded with a video camera, situated approximately 4 feet in front of the monkey's cage prior to the beginning of each session. Sessions were scored by the 2nd author and occasionally by the 1st to ensure consistency. Scoring involved transcribing the number of mouthing, touching and orienting responses that occurred during the green light on standardized score sheets. Mouthing was defined as contacting the lighted disc with any part of the face (lips, tongue, teeth, nose, etc.); touching was defined as contacting the lighted disc with hand(s) or finger(s); and orienting was defined as looking at the lighted disc for more than 1 s without touching or mouthing. Several sessions had long timeouts (10 minutes) resulting in a small number of trials, therefore only the first ten trials were scored.

All nine monkeys were observed directing behavior toward the green light (Table 1). Five of the nine monkeys directed behavior toward the green light on 100% of the observed trials. This behavior only occurred during light presentations. Mouthing was the most prevalent response. Mouthing was the only light-directed response observed in the two sessions for M3577, and it occurred at a rate of approximately four responses per trial. Monkey M3575, on the other hand, only touched the light and at an average of 2.75 responses per trial. Monkeys M2181 and M3678 had the smallest number of light-directed responses at 1.2 responses per trial and 1 response per trial, respectively. Methohexital was least effective in producing mouthing and in getting a response to occur on every trial relative to the other drugs.

Our observations confirmed that this light-directed behavior is indeed robust and general, however they provided little advancement of our understanding of the behavior in terms of its ontogeny, function and organization. Therefore, an experiment was conducted to determine if we could produce this light-directed behavior in the absence of a response-reinforcer contingency with Pavlovian conditioning procedures.

Antecedent stimuli that reliably precede an unconditional stimulus eventually will exert control over behavior. Such Pavlovian conditioning can even enlist movements involving the skeletal system. Brown and Jenkins (1968), for example, exposed food-deprived pigeons to trials in which a translucent key was illuminated for a brief period of time and was followed by access to food. Trials were separated with intertrial intervals in which the experimental chamber was darkened. Following such exposure to light-food pairings, pigeons began to peck the transilluminated response keys. Autoshaping, as it came to be called, because behavior is shaped automatically, also has been demonstrated in rats (Peterson, Ackil, Frommer & Hearst, 1972), squirrel monkeys (Gamzu & Schwam, 1974) and rhesus monkeys (Likely, 1974; Sidman & Fletcher, 1968). Hearst and Jenkins (1974) introduced the term “sign-tracking” to cover a broader class of directed action such as orientation, approach and contact that also comes under the control of conditional stimuli via Pavlovian conditioning processes.

The goals of the present experiment were to determine if the behavior directed toward a drug-paired stimulus observed in self-administering monkeys could be generated in the absence of a response-reinforcer contingency and to assess the role of Pavlovian conditioning in producing this behavior. Terry Robinson and colleagues established that signals paired with cocaine elicited sign tracking in rats (Flagel, Akil, & Robinson, 2009; Flagel, Watson, Akil, & Robinson, 2008; Uslaner et al., 2006), so it would be expected that this same phenomenon would be observed in naive monkeys. To that end, four monkeys were exposed to trials that arranged explicit pairings between stimulus lights and cocaine (correlated group) or trials that presented the lights and cocaine independently of each other (uncorrelated group). Only cocaine was investigated because it reliably produced light-directed behavior and is ubiquitous in self-administration research. As an additional control, saline was also tested in the correlated group to determine the role of cocaine in maintaining this behavior.

If light-directed behavior occurs in either group, then self-administration of drug is not a necessary condition for the genesis of this behavior. Moreover if light-directed behavior is a form of sign tracking generated by Pavlovian conditioning with cocaine as the unconditional stimulus, then light-directed behavior should occur at higher levels in the correlated condition and should not be maintained when saline is substituted for cocaine.

Method

Subjects

Four naïve adult rhesus monkeys (*Macaca mulatta*) were employed in the present study. Two (M2484, male and M2083, female) were assigned to the correlated group and two (M2087, male and M4393, female) were assigned to the uncorrelated group. They were previously implanted with indwelling catheters (see Winger, Palmer, & Woods, 1989) and were given 100 response-independent cocaine infusions to acclimate them to the drug delivery. The monkeys had no history of operant training nor were they ever exposed to the stimulus lights which were located on the work panel which was installed exclusively for the present experiment. The monkeys were fed approximately 10 pieces of Purina Monkey Chow® in the morning and 10 in the afternoon and had continuous access to water. The monkeys were

housed individually in a colony with other monkeys; enabling social, visual, auditory and other forms of stimulation.

Apparatus

Sessions were conducted in the monkeys' home chambers, which measured 83.3 cm by 76.2 cm by 91.4 cm. The chambers were adapted with a work panel that contained three translucent discs that were spaced 2.5 cm apart and were positioned 30 cm above the floor. The discs could be transilluminated with 5-W red and green Christmas-tree bulbs. A water spout was located on the opposite side of the cage from the work panel. Each monkey was fitted with a jacket that connected a tether to the cage. The catheter passed from the monkey through the tether and outside the cage, where it attached to a roller infusion pump (Watson and Marlow CO., Model MHRK 55). The pumps were calibrated to deliver 0.2 mL/s. Experimental contingencies were programmed and data recorded using IBM compatible computers and MED-PC[®] interface and programming language (Med Associates Inc.). In a subsequent condition two levers were added to the panel (model 121-07, BRS/LVE); they were spaced 5 cm apart and centered below the left and right discs and could be operated with a force of about 0.10 N.

Procedure

Correlated—Each trial began with an intertrial interval that was programmed according to a variable-time (VT) 60-s schedule (range 20-120 s). Following the intertrial interval, the right-side disc was transilluminated red for 5 s, after which it extinguished, the center disc was illuminated green, and the infusion pump was operated for 5 s. Following this 5 s, the green light was extinguished, the pump was stopped, and the next intertrial interval commenced. Two conditions were investigated in an A-B-A-B reversal design: cocaine hydrochloride 0.01 mg/kg/infusion (A) and physiologic saline (B). Monkey M2484 was not exposed to the second saline condition.

Uncorrelated—The lights and pump operated independently of one another in the uncorrelated procedure. Both the lights and the pump were programmed to operate according to two independent VT 60-s (range 20-120) schedules, one for the lights and one for the pump. After an average of 60 s, the right disc was transilluminated red for 5 s after which it extinguished, and the center disc was transilluminated green for 5 s. The pump was programmed to deliver injections independently of the lights according to a VT 60-s schedule. According to this VT schedule, the pump was operated for 5 s during which time 0.01 mg/kg/injection of cocaine was delivered. Following the 5 s, the pump stopped, and another interval commenced. When light-directed responding was not maintained, the monkeys were exposed to the correlated procedure described above.

Each condition was in effect until there was no trend in the % of trials with CR as judged by visual inspection. Each session consisted of 60 cocaine injections. Sessions were conducted twice daily (10:00 am and 4:00 p.m.) five days per week. Each session was recorded with a video camera, and the sessions were scored for touching, mouthing and orienting that were directed to the red and green lights.

Results

Table 2 shows the number of sessions under each condition. Figure 1 shows the percentage of trials with a response (i.e., those containing at least one mouthing, touching or orienting response; percent response hereafter) during the red and green lights and across the first and last four sessions of each condition for M2083 (top panel) and M2484 (bottom panel). This percentage was calculated by dividing the total number of trials with a response by 60 and multiplying by 100. As can be seen for both monkeys, light-directed activity occurred at a high level in the first session. There was some variability in percent response across sessions, but it eventually decreased and stabilized at approximately 30% under the green and red lights for M2484 and approximately 45% under the green light and 30% under the red light for M2083. When saline was substituted for cocaine, percent response fell to around 10% for both monkeys. Percent response decreased to near zero during M2484's second exposure to cocaine. However, after about 7 sessions, it increased to 20%. In M2083's second cocaine exposure, percent response gradually increased to around 50-70% with slightly more responding during the red light (a reversal of the pattern seen under the first cocaine condition). The second saline exposure for M2083 resulted in a rapid decrease in percent response, and the decrease was faster than the first saline exposure.

Figure 2 shows percent response for M4393 (upper panel) and M2087 (lower panel). During the uncorrelated procedure, percent response fell from about 90% to 0% in M4393 and from about 50% to around 10% for M2087 over 23 and 12 sessions, respectively. When the lights and cocaine were correlated, percent response initially increased but eventually decreased to zero or near zero for both monkeys.

Figure 3 shows the total number of mouthing, touching, and orienting responses that occurred in the last four sessions of each condition for M2083 (top panel) and M2484 (bottom panel). For both monkeys, touching was by far the most prevalent response followed by mouthing. M2083 emitted more mouthing responses than M2484. Also, the total number of responses tended to be higher in the cocaine condition. Overall, M2083 had more than 3 times as many responses during cocaine than saline, and M2484 had 7 times as many responses during cocaine. This analysis was not done for M4393 and M2087 as there was no light-directed behavior.

Monkeys M2484 (correlated group), M4393 and M2087 (uncorrelated group) usually were situated opposite the work panel and were facing away from it. It is not surprising therefore, that conditioning failed to occur given that the monkeys were not facing the stimulus lights. Locurto, Travers, Terrace, & Gibbon (1980) showed that restraining pigeons in front of the stimulus increased the speed of conditioning. Logistically, we could not restrain the monkeys in front of the stimulus panel; however, we could make cocaine delivery contingent upon lever pressing in an attempt to promote visual contact with the lights. In the next condition levers were installed and the three monkeys were shaped to lever press via differential reinforcement of successive approximations for 0.01 mg/kg/injections of cocaine in an attempt to reinstate the light-directed behavior. The cocaine was delivered over a 5-s period and was accompanied by green illumination of the center disc. Following this 5 s, the green light was extinguished, the pump was stopped, and the monkey could begin

responding again for cocaine. Shaping continued until lever pressing occurred reliably. The response requirement was increased in steps 2, 3, and 5 until 10 was reached. An FR 10 was in effect for 13-15 sessions. Sessions were videotaped, and the behavior was scored subsequently for the occurrence of mouthing, touching and orienting.

Adding a response requirement for cocaine increased light-directed behavior in all three monkeys (see Figure 4), even for the two monkeys (M2087 and M4393) that had previously stopped responding to the lights. Touching the light was the predominant response topography, although mouthing accounted for about half the responses. Thus, the response-cocaine contingency resulted in patterns of behavior not unlike those seen in our initial observations. The contingency ensured that the monkeys were situated near the work panel, and this may have contributed to the return of the light-directed behavior. However it remains unknown if the response-drug contingency simply allowed the light-directed behavior to come under the control of a drug-paired CS or if the light-directed behavior occurred for some alternative reason related to the operant contingency.

General Discussion

The current study was undertaken to better understand the control exerted by drug-correlated antecedent and co-occurrent stimuli in rhesus monkeys. Our initial formal observations established the generality of this light-directed behavior. Light-directed behavior was observed in all nine monkeys self-administering drug under various conditions including different schedules of drug reinforcement, different drugs and different doses of drug. We next showed that a response-drug contingency was unnecessary for the occurrence of this light-directed behavior. To our surprise, light-directed behavior occurred in the initial sessions of both the correlated and uncorrelated procedures. However the behavior was maintained longer and at higher levels under the correlated procedure. The introduction of the light-cocaine correlation in monkeys first exposed to the uncorrelated procedure failed to produce light-directed behavior. Cocaine injections elicited more light-directed behavior than saline. Adding the response-cocaine contingency increased light-directed behavior in all monkeys including the two that previously ceased responding to the lights. Mouthing was the predominant response in conditions where lever pressing was required for drug delivery; whereas touching was predominant during the Pavlovian conditioning procedure.

The main finding was that light-directed behavior in monkeys can occur in the absence of a response-drug contingency. Monkeys with no experience self-administering a drug directed behavior towards lighted discs. The light-directed behavior occurred immediately and at high levels within the first session but decreased across subsequent sessions. This light-directed behavior was maintained at a higher level under the correlated procedure (excluding the monkeys first exposed to the uncorrelated procedure) and was maintained at a higher level in the presence of cocaine versus saline. Touching of the lighted discs was the predominant response topography. Light-directed behavior was undifferentiated between the stimuli that preceded (red light) and accompanied (green light) cocaine injection. Finally, the cocaine injections did not elicit responding in the absence of the lights.

The light-directed behavior maintained in the correlated condition was likely due to Pavlovian conditioning because the lights did not control as much light-directed behavior in the absence of such a correlation. These results are consistent with other studies that show that Pavlovian conditioning does not develop unless there is a positive CS-US correlation (Gamzu & Williams, 1973). The final levels of percent response in the two monkeys first exposed to the correlated procedure were similar to the levels reported in an autoshaping experiment using squirrel monkeys by Sidman and Fletcher (1968). Curiously, light-directed behavior was not observed when the light-cocaine presentations were correlated in the monkeys first exposed to the uncorrelated procedure. This finding replicates Gamzu and Schwam (1974) who showed that squirrel monkeys first exposed to an uncorrelated procedure never acquired key pressing when a positive CS-US correlation was introduced. It is possible that other stimuli in the environment more predictive of cocaine delivery such as the noise and the vibration of the infusion pump could have blocked the emergence of the lights as CS.

The results support a multiprocess explanation of the light-directed behavior. The high level of light-directed behavior seen in the initial trials of the correlated and uncorrelated procedures was unrelated to the light-cocaine pairings and was probably due to the novelty of the lights. The data were not typical of acquisition curves produced by Pavlovian conditioning. The maintenance of light-directed behavior, on the other hand, appeared to be related to factors that govern Pavlovian conditioning. The results were consistent with studies that show that sign tracking does not develop unless there is a positive CS-US correlation. Light-directed behavior was maintained to a lesser degree in the absence of a light-cocaine correlation or if saline was substituted for cocaine suggesting that the behavior was critically linked to the light-cocaine pairings and thus was controlled via Pavlovian conditioning. An alternative explanation was that cocaine directly elicited the behavior. This was unlikely because the behavior was not observed in the absence of the lights and was not maintained during the uncorrelated procedure even though cocaine was administered. Finally, although self-administration of cocaine was not necessary for the light-directed behavior to occur, the behavior was maintained at higher levels when the operant contingency was introduced. The response-drug contingency may further increase the probability of light-directed behavior because it ensured contact with the light-drug pairings (Locurto et al., 1980) or because of some alternative explanation related to the operant contingency (i.e., schedule induction).

If antecedent stimuli acquire an eliciting function due to pairing with unconditional stimuli, they are called conditional stimuli; if they acquire a response-strengthening function, they are called conditioned reinforcers. This process also occurs with stimuli paired with drugs (Cunningham, 1993; Davis & Smith, 1976; Panlilio & Schindler, 1997; Siegel, 1975; Schuster & Woods, 1968). Stimuli paired with cocaine, for example, can elicit locomotor activity (Bridger, Schiff, Cooper, Paredes, & Barr, 1982), and rats will work to observe stimuli paired with ethanol reinforcement (Shahan, 2003). Given the control and ubiquity of stimuli that precede drug administration, it is of considerable interest to understand the mechanisms by which drugs extend control to antecedent stimuli.

The topographies of mouthing and touching observed and the fact that they differed between experiments was puzzling. Evidence of mouthing the CS can be traced as far back as Pavlov (1928); he reported that dogs would often lick the apparatus following conditioning trials. Jenkins and Moore (1973) showed that the topography of keypecking in pigeons was related to the type of US; conditioned stimuli that were paired with water versus food elicited distinct pecking topographies that were related to the consumption of the US. Cocaine however is different from traditional US in that it is delivered intravenously and thus requires no consummatory behavior. Electrical brain stimulation (EBS) is similar to cocaine in that it does not require a consummatory response. Peterson et al. (1972) compared food and EBS as the US in rats and found that both resulted in conditioning. However the topographies were related to the US type; the food-paired CS elicited mouthing and gnawing, but the one paired with EBS did not. It remains unknown why stimuli paired with cocaine elicited mouthing and touching in the present study. One thing is clear; the CR was different in structure than the UR elicited by cocaine. Mouthing, orienting and touching did not occur to cocaine alone in the absence of the lights.

The lights exerted control over behavior quite rapidly, within the first couple of trials even before the first light-cocaine pairing. This differs from Gamzu & Schwam (1974) in which their monkeys took approximately ten sessions to acquire key pressing in a similar procedure but with food as the unconditioned stimulus. It was likely that novelty accounted for the initial occurrence of light-directed behavior, especially the responding that occurred in the early trials of the first session. The decrease in percent response could have resulted from habituation to the novelty. There are other possible explanations for the rapid acquisition of light-directed behavior. Before the conditioning trials began, the monkeys had approximately 100 response-independent cocaine injections, and these could have influenced the speed of acquisition. Downing and Neuringer (1976) have shown that 100 prior food presentations produced the fastest speed of acquisition of pigeons' key pecking in an autoshaping procedure relative to 0, 1, or 10 prior exposures. Also the general nature of the response class could have increased the speed of acquisition. In Gamzu and Schwam (1974) the dependent measure was key pressing whereas the present experiment involved a broader response class: mouthing, touching and orienting. It is possible that the monkeys in Gamzu and Schwam's study also oriented toward or touched the stimulus as quickly as the monkeys in the present study. Indeed acquisition of the conditioned orienting response can be quite rapid (Buzsáki, 1982).

In retrospect the uncorrelated procedure was probably not the best control procedure for Pavlovian conditioning given that it does not prohibit accidental CS-US (i.e., light-cocaine) pairings. This is even more important with drug a US because the drug as an interceptive stimulus lingers for longer periods of time than say a food pellet or a puff of air. An explicitly unpaired procedure would have ensured no accidental pairing and would be expected to have resulted in less light-directed behavior than what was observed in our uncorrelated procedure.

The present study extends the literature on sign tracking by demonstrating that cocaine can extend control to visual stimuli that precede or accompany cocaine injections in naïve rhesus monkeys. The results are generally consistent with previous research on sign tracking to

cocaine-paired stimuli in rats (Flagel, Akil, & Robinson, 2009; Flagel, Watson, Akil, & Robinson, 2008; Uslaner et al., 2006). Future research will have to determine how light-directed behavior relates to drug type, dose and the intertrial interval. Now that we have a better understanding of the necessary and sufficient conditions for this behavior, what can sign-tracking of drug-paired stimuli tell us about drug reinforcement? One attractive possibility is that it is predictive of a drug's reinforcing effectiveness (see Davis and Smith, 1987). This is after all the rationale behind using drugs in conditioned place preference (CPP) procedures. An advantage of this sign-tracking behavior over CPP is that there is considerably more behavior produced by the former. Direct comparisons of these two procedures might be worth pursuing further. The stimuli associated with drug self-administration are behaviorally important events, and an understanding of how those stimuli acquire control over behavior as conditional stimuli or conditioned reinforcers is fundamental to stimulus control in general and drug taking in particular.

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Figure 1.

The percentage of trials containing at least one mouthing, touching or orienting response during the red (filled circles) and green (open circles) lights across the first and last four sessions of the cocaine and saline conditions each condition across for M2083 (top panel) and M2484 (bottom panel). The saline and cocaine conditions are labeled and separated by solid vertical lines.

Figure 2.

The percentage of trials containing at least one mouthing, touching or orienting response during the red (filled circles) and green (open circles) lights across the first and last four sessions of the correlated and uncorrelated conditions for M2087 (top panel) and M4393 (bottom panel). The uncorrelated and correlated conditions are labeled and separated by solid vertical lines.

Figure 3.

The total number of mouthing, touching and orienting responses that occurred in the last five sessions of each condition for M2082 (top panel) and M2484 (bottom panel). The labels C and S on the abscissa refer to the cocaine and saline conditions, respectively. The first series in each graph represents responding during the red light, and the second series represents responding during the green light. Note the breaks in the axes.

Figure 4.

The percentage of trials containing at least one mouthing, touching or orienting response across consecutive sessions for M4393, M2087 and M2484.

Table 1

Total Number of Mouthing, Orienting and Touching Responses, Percent of Trials with a Response, and Total Numbers of Reinforcers for Nine Rhesus Monkeys in Selected Sessions of i.v. Self-Administration of Different Drugs.

Monkey	Drug/dose (mg/kg)	Schedule ^a	Mouthing	Orienting	Touching	% Trials w/ a Response	Total # of Reinforcers
M3347	Alfentanil 0.0003	FR 30 TO 45"	14	2	5	70	10
M2181	Methohexital 0.1	FR 30 TO 600"	9	5	0	90	10
	Methohexital 0.1	FR 30 TO 600"	5	4	0	70	10
	Methohexital 0.1	FR 30 TO 600"	11	2	0	70	10
	PNU101017 0.1	FR 30 TO 600"	27	0	6	100	10
M3589	Cocaine 0.03	FR 30 TO 600"	27	0	0	100	10
	Cocaine 0.03	FR 30 TO 600"	28	0	0	100	10
M3577	Cocaine 0.03	FR 30 TO 600"	39	0	0	100	10
	CPDD-46 0.3	FR 30 TO 600"	40	0	0	100	10
M3678	Methohexital 0.1	FR 10 TO 10"	0	8	3	90	10
	Methohexital 0.1	FR 10 TO 10"	3	5	1	60	10
	Methohexital 0.1	FR 10 TO 10"	2	7	1	80	10
M3029	Alfentanil 0.01	Chained FI 10' FR 30	20	0	0	100	5
	Alfentanil 0.01	Chained FI 10' FR 30	37	0	0	100	6
	Alfentanil 0.01	Chained FI 10' FR 30	27	0	0	100	6
	Alfentanil 0.01	Chained FI 10' FR 30	25	1	0	100	6
M3575	Cocaine 0.01	Chained FI 10' FR 30	0	0	11	100	4
M3579	Methohexital 0.1	FR 30 TO 600"	0	0	14	40	10
M14422	Cocaine 0.003	FR 30 TO 45"	27	1	84	100	10
	Cocaine 0.003	FR 30 TO 45"	10	1	39	100	6

^aFR, fixed-ratio; TO, timeout; FI, fixed-interval; Chained, response requirement leads to next component with a stimulus change, in this case, drug was delivered in the FR component.

Table 2

Total Number of Sessions in Each Condition for Monkeys.

Monkey	Condition			
	Cocaine	Saline	Uncorrelated	Correlated
M2083				
1st exposure	18	9		
2nd exposure	19	4		
M2484				
1st exposure	25	8		
2nd exposure	16			
M2087				
1st exposure			12	11
M4393				
1st exposure			23	21