CONDITIONED SUPPRESSION OF AN OPERANT RESPONSE USING DRUGS AS CONDITIONED STIMULI

A Dissertation

Presented to

the Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

Evelyn G. Turner

August, 1975

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ABSTRACT

The possible use of a drug state as a conditioned stimulus in a classical conditioning paradigm was investigated in a series of four experiments. Suppression of an operant response served as an index of a classically conditioned response (conditioned suppression). In all the experiments drug injections were paired with a series of unavoidable shocks. Subsequently, effects of the shock-paired drug on operant response rate were compared to effects obtained in control subjects which received unpaired drug-shock experience. These experiments demonstrated that d-amphetamine (0.8mg/kg) served as a CS for conditioned suppression of a one-lever task (VI-60sec). Stimulus generalization from the shock-paired drug to cocaine (7.5mg/kg) also occurred. Reduction of external apparatus cues, by administering shocks in the operant chamber instead of a separate apparatus, produced a more durable suppression effect. Response totals recovered to a maximum of 80% of baseline responding after twelve days of testing. In one experiment animals were trained on a d-amphetamine vs. cocaine discrimination prior to shocks paired with one of the two drugs. It was hypothesized that during retraining of the operant discrimination, suppression would be observed for sessions involving the shock-paired drug. Since the suppression obtained was not cue-specific, the difficulty of the d-amphetamine vs. cocaine discrimination may have minimized transfer between the operant and classical

components of the study. The prior discrimination training did not reduce the generalization of suppression from d-amphetamine to cocaine. In a final experiment d-amphetamine vs. saline discrimination training preceded the drug-shock sessions in which either d-amphetamine or saline were shock-paired for each individual subject. Although discrimination was readily acquired, no cue-specific suppression occurred. The results of this experiment suggest that a saline injection cannot serve as a CS in the absence of explicit differentiation procedures. Further research is required for clarification of this interpretation.

The results of the four studies suggest that, with further development, the conditioned suppression paradigm may be a useful alternative to operant discrimination in the study of drug stimulus control. Advantages of the paradigm are discussed. Two general conclusions of this series of investigations were (1) that drug states, as possible representatives of other internal stimuli, may acquire behavioral properties through classical conditioning procedures, and (2) that generalization can occur between similar internal stimuli. Results were discussed in the context of possible applications to behavioral problems such as drug abuse and psychosomatic symptoms.

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ABSTRACT

Although a large number of studies have investigated the use of internal events as stimuli serving as learned cues, the similarities between stimulus properties of internal and external events is largely ignored. Generally, investigators of internal stimuli limit themselves to conclusions about the particular internal event that they study, without application to the area of internal stimulus control. A large number of studies from different research areas, involving acquired stimulus functions of internal events is reviewed here. Similarities between internal and external stimuli are emphasized. Practical implications of internal stimulus control are also discussed.

American psychology, for much of its development, has attempted to understand, predict, and control the behavior of living organisms by studying the interactions of environmental stimuli with behavior. Analysis of external stimulus variables within stimulus control paradigms has been a major research area of experimental psychology (Watson, 1968). Such a trend can be attributed to the influence of behavioral scientists who stressed the objective study of observable events rather than unobservable mental functions (Watson, 1930).

Traditional distinctions between afferent functions of the autonomic and skeletal systems have erroneously influenced views of the stimulus functions of the viscera. Previously, psychological thought was dominated by the assumption that organs under efferent control in the autonomic nervous system did not have afferent connections with the central nervous system (Ruch and Patton, 1965; Grossman, 1967). Such assumptions, in addition to the behaviorist stress on observable events resulted in a neglect of the possible stimulus functions of internal events.

Although the interaction of external stimuli with behavior has been explored and described in great detail (Skinner, 1938; Ferster and Skinner, 1957), no attempt has been made to apply extensively the same type of analysis to stimulus functions of internal events. Internal stimuli have been investigated and discussed in a limited context, mostly in the area of drug stimulus control.

A number of reviews are available concerning certain types of interoceptive stimuli (Bykov, 1943; Razran, 1961; Adam, 1967) and drug stimuli (Schuster and Balster, 1975). While these reviews note the similarities between particular internal stimuli and external stimuli, no review which includes several types of internal control is presently available.

Definition of Stimuli

In order to be considered a stimulus, an event should exert one or more of the following stimulus functions: (1) Unconditioned stimuli (US)--those capable of eliciting an unconditioned response; (2) Conditioned stimuli (CS)--those which acquire the ability to elicit a conditioned response through repeated pairing with an unconditioned stimulus; (3) Reinforcing stimuli--those which when presented (positive) or removed (negative) increase the probability of the response which they follow; (4) Discriminative stimuli (SD)--those which covary with the availability or nonavailability of a reinforcing stimulus or with the type of response required for presentation of a reinforcing stimulus. Schuster and Balster (1975) noted that the stimulus function of an event is defined by its interaction with behavior rather than by its physical attributes. These authors maintain that understanding the mechanisms of transduction is unnecessary for analysis of stimulus-response parameters.

STIMULUS FUNCTIONS OF INTEROCEPTIVE EVENTS

In 1928 Bykov and Ivanova demonstrated that an interoceptive stimulus could serve as the basis for formation of a classically conditioned response (Bykov, 1943). They repeatedly infused normal saline into a dog's stomach, via a gastric fistula, producing diuresis. Extraneous external stimuli were minimized and infusions were controlled by the experimenter from a separate room. After twenty-five infusions a sham infusion, in which the solution was infused into the stomach and immediately aspirated, produced diuresis despite the fact that no real increase in gastric fluid occurred. Since earlier studies (Bykov, 1943) indicated that conditioned responses could be formed only if the stimulus reached the cerebral cortex, Bykov concluded that the gastric mucosa must possess interoceptors whose impulses reach the cortex. He reached this conclusion prior to existence of anatomical evidence for autonomic projections to the central nervous system. Bykov and other members of his laboratory then initiated a series of experiments using interoceptive stimuli to obtain conditioned responses (CRs). Demonstrating the generality of the gastric CS for experimental tasks, they successfully used gastric irrigation as a CR for a leg flexion response and for a salivary response. Intestinal stimulation produced by inflation of a balloon inserted into an intestinal fistula, also effectively served as a CS for the leg flexion and salivary responses (Bykov, 1967).

Subsequently, a large number of classical conditioning studies, using several types of interoceptive stimulation have extended the early experiments of Bykov (Razran, 1961). Examples of other types of stimulation employed as CSs for salivation and leg flexion are fluid distension of the renal pelvis (Adam, 1967) and intrauterine irrigation (Fel'berbaum, 1952).

Vassilevskaya (1940) provided evidence that conditioning was mediated by receptors of the specific organs stimulated (Bykov, 1943). Gastric infusions of procaine suppressed responding to the gastric CS for a 45-minute period during which responding to an exteroceptive CS (metronome) was unaffected. He concluded that the procaine inactivated intestinal receptors. Fel'berbaum (1952) obtained similar suppressed responding to intrauterine stimulation after irrigation of the endometrium with a tetracaine solution.

Razran (1961) proposed three categories of interoceptive conditioning, based on the nature of the CS and US: (a) intero-interoceptive conditioning--the CS and US are both interoceptive; (b) intero-exteroceptive conditioning--the CS is interoceptive and the US is exteroceptive; (c) extero-interoceptive conditioning--the CS is exteroceptive and the US is exteroceptive. Razran regarded the first two categories as being more important because they involve acquisition of signalling properties by internal events. He proposed that the built-in nature of such events cause interoceptive

conditioning to be a frequent occurrence in the daily routine of the organism. Cases of instrumental or operant conditioning in which interoceptive stimuli serve as discriminative cues have also been considered examples of interoceptive conditioning (Adam, 1967). Standard classical conditioning experiments in which both CS (bell) and US (meatpowder) are exteroceptive may be categorized as extero-exteroceptive conditioning.

The basic instances of intero-exteroceptive conditioning were provided by Bykov (1943) with use of gastric infusion and intestinal pressure as CSs for salivation and leg flexion. Pogrebkova (1950, 1952a, b) illustrated rapid intero-interoceptive conditioning of hypercapnic respiratory responses, induced by respiration of 10% carbon dioxide. Rhythmic distentions of the intestinal mucosa elicited responses after 3-6 trials, and stabilized after 5-10 trials. Introduction of an auditory CS (tone) was used to compare exteroceptive and interoceptive conditioning. In both cases conditioning was rapid and highly resistant to extinction. Pogrebkova attributed his results to the unusual arousal nature of the respiratory stimulus which included marked changes in the organism's vital functions.

Differential responding to two stimuli is produced by consistently reinforcing one stimulus (CS+) and consistently omitting reinforcement of a similar stimulus (CS-). Airapetyantz (1940) obtained differential responding between

infusions of 36°C and 28°C, with the former stimulus producing salivation but not the latter (Bykov, 1943). Vassilevskaya (1940) obtained differentiation between water and hydrochloric acid intestinal irrigations administered at the same temperature, and between water irrigations at different temperatures (Bykov, 1943). The results of the studies provided evidence of thermoreceptors and chemoreceptors by establishing a control for mechanical stimulation in the first case and for temperature in the second. Such techniques are now standard in interoceptive conditioning studies (Razran, 1961).

Response differentiation may be used to investigate interactions of various types of stimuli. Airapetyantz (1940) established differentiation of a leg flexion response to infusions of two water temperatures (Bykov, 1943). The response was also conditioned to a metronome and a bell so that any of the three positive CSs elicited the response. Presentation of the negative CS suppressed responding to any of the positive CSs until reinforcement had occurred several times. Exteroceptive stimuli affected responses to interoceptive stimuli in a similar manner. Airapetyantz invoked Pavlov's concept of induction to explain the effects he obtained.

The differentiation technique provides a sensitive measure of spatial and temporal "discrimination" thresholds for interoceptive stimuli (discrimination would be considered subliminal). In a representative study of interoceptive

differentiation of responding, Adam (1967) obtained generalization of a salivary response to stimulation of the ureter 5 cm below the renal pelvis where the CS had been initially established. Stimulation of the contraleteral pelvis as a test stimulus also resulted in generalization of the response. Differentiation between renal stimulation and the generalized stimulus was obtained with training for ipsilateral ureteral stimulation but not for contralateral stimulation of the pelvis. Such studies suggest that pathways having certain functional relationships may not be easily modified by experience.

Moiseeva (1952) reported a spatial differentiation threshold for intestinal stimulation of only a few centimeters for a salivary response. Adam (1967) supported these findings using EEG activation as the measure of differentiation. He obtained unconditioned differentiation of intestinal stimulations separated by 7 cm. Stimuli separated by 5 cm or less produced generalization. In humans Makarov (1965) determined temporal thresholds for gastric pressure, and examined interactions of temporal and spatial parameters for subjective thresholds.

Adam (1967) established rhythmic carotid stimulation (30 oscillations/min) as a discriminative stimulus (SD) for an instrumental response of lifting the cover of a revolving dispenser for food reward. The internally elicited response had a longer and more variable latency and required more

training trials than the same response trained to an auditory stimulus.

Adam (1967) conducted an experiment using standard operant conditioning techniques in order to obtain information on the time of perception of the stimulus. He used onset of intestinal stimulation as an SD signalling availability of reinforcement with offset of stimulation serving as the S signalling nonavailability of reinforcement. After training, fixed-ratio (FR) responding began within one second of stimulus onset but continued approximately 5 seconds beyond stimulus offset, although the functional roles of onset and offset had been changed. Adam (1967) noted that the typical operant response composed of quickly repeated movements, may cease abruptly and thus can be affected more promptly by environmental (internal) stimuli than can classical responses which typically have more inertia. Therefore, operant technique provides a better index of the time of stimulus perception. The longer latency of cessation of responding after termination of the stimulus suggests that offset of interoceptive stimulation is not perceived as quickly as onset.

The study of interoceptive conditioning is based on the assumption that the principles of organization for internal and somatic nervous systems are the same, an assumption supported by the observation of organized representation of visceral input at each level of the nervous system, and of integration of regulation of internal organs with somatic functions (Dell, 1952). Interest in the attempt to condition

the EEG activation response was based on the observation that cortical desynchronization results from increased reticular activity influenced, in turn, by inputs from sensory pathways (Moruzzi and Magoun, 1949). Adam hypothesized that reticular activity could also be stimulated by visceral afferents as well as by somatic afferents. If that were true, the reticular formation was a structure where interaction of somatic sensory and visceral inputs could most easily be assumed. Adam conducted a series of studies to investigate the influence of interoceptively stimulated reticular activity, as reflected by EEG activation. In spite of some unconditioned desynchronization properties of the stimuli, Adam established renal, carotid, and intestinal stimuli as CSs for a habituated EEG activation. Since the auditory stimulus used as the US actually disinhibited the habituated desynchrony, the conditioned response was actually a case of conditioned disinhibition. The results suggested that the activity of visceral afferents increases reticular activity, the activation being similar to that exercised by classical sensory afferents.

To test the possibility that conditioned desynchronization was actually conditioned reticular activation, Adam then employed direct electrical reticular stimulation as the US. In most subjects one reinforcement trial resulted in conditioned desynchronization, indicating that for conditioned desynchronization, direct reticular stimulation is more effective as a US than exteroceptive stimuli. Furthermore, he

hypothesized that reticular activation might easily be conditioned to visceral stimuli. His hypothesis was supported by conditioning of reticular activity to exteroceptive stimuli (Segundo, Roig, and Sommer-Smith, 1959).

Adam implicitly assumed that the interoceptive stimuli used in his studies were unconscious. Since the stimuli often elicited unconditional EEG desynchronization, which has typically been considered an index of attention and arousal, his basic assumption was questionable. He effectively used psychophysical methods to study awareness of internal stimuli in human subjects. At the desynchronization threshold, seventy per cent of the subjects were unaware of duodenal pressure produced by means of a swallowed balloon. In a second experiment subjects swallowed two balloons. After habituation of desynchronization to inflation of balloon A, balloon B (approx. 20 cm distal to A) was inflated. Appearance of desynchronization indicated that higher centers discriminated between the two points of stimulation, although none of the subjects reported subjective sensation, indicating that the mechanisms of cortical arousal are not identical with the mechanisms of conscious sensation.

Adam then obtained awareness of previously subliminal stimulation. After the subjective threshold was established, intestinal pressure was lowered in successive steps. By advising the subjects when the stimuli were being applied, subjects learned to be aware of stimulations much below

initial subjective thresholds, in some cases nearly as low as the desynchronization threshold.

Adam proposed that such learning may occur quite often in routine behaviors such as training children to become aware of bladder and rectal impulses and to bring previously reflexive responses under voluntary control. His hypothesis is supported by successful treatment of patients for nocturnal enuresis by Airapetyantz (1952) who established conditioned awareness of artificial filling of the bladder by associating it with verbal reinforcement. Conditioning of bladder sensations was also obtained so that sham manometer readings controlled subjective sensations in the absence of corresponding bladder stimulation. Stronger support for routine interoceptive conditioning is provided by cases of "natural" extero-interoceptive conditioning. Dogs having lost the micturition reflex (leg lifting) through surgical procedures showed an almost completely restored micturition pattern after observing other dogs exhibit the pattern (Airapetyantz, 1952). Other examples of natural conditioning include clinical reports of human patients (Bykov, 1943). Okhnyanskaya (1953) reported natural conditioning of an inhalation-produced vasomotor response to the word "inhale."

Airapetyantz summarized several years of research in a 1952 review paper recounting his demonstrations of the Pavlovian phenomena of differentiation, extinction and other forms of inhibition, and induction, all of which characterize

interoceptive conditioned reflexes as well as exteroceptive conditioned reflexes.

Razran (1961) reviewed studies demonstrating second order conditioning between interoceptive and exteroceptive stimuli, with both types of stimuli serving as the initial CS (Vassilevskaya, 1948, 1950; Pauperova, 1952). Sensory preconditioning between interoceptive stimuli was also demonstrated (Goncharova, 1955).

The large number of interoceptive conditioning studies lead to several conclusions comprising the present state of knowledge of the field:

1. Interoceptive conditioning seems to follow the same principles as exteroceptive Pavlovian conditioning, exhibiting the same phenomena such as induction and differentiation.
2. Interoceptive conditioning, while readily obtained, generally requires more training to establish and is more stable than exteroceptive conditioning.
3. Interoceptive stimuli are largely unconscious, although strong conditioning of awareness can be established easily.
4. When interactions are examined, interoceptively-produced reactions tend to dominate exteroceptive ones.
5. Due to the in-built nature and relatively constant presence of the stimuli, interoceptive conditioning

may be pervasive and recurrent in an organism's history.

6. The unconscious nature of most conditioned interoceptive stimuli tends to negate the view that classical conditioning in humans may be cognitively mediated.

DRIVE STIMULI AS DISCRIMINATIVE CUES

Initially drive stimuli were used as cues to study drive state, but an additional effect was the focusing of attention on properties of internal cues in general. Three main views concerning the functions of drive states have been: (a) drives as activators or energizers without directional properties, (b) drives as incentives or rewards, and (c) drives as cues having directional properties. While the conflict between these concepts remains unresolved, it is likely that drive stimuli constitute a significant part of the stimulus complex to which the organism responds.

Hull (1933) produced an early example of the use of drive conditions as cues in learning. In a two-choice maze, rats learned to make choices appropriate to the drive state induced by deprivation, although several hundred trials were required for the discrimination. Other investigators obtained discriminations with fewer trials (Leeper, 1935; Kendler and Mencher, 1948; Seeman and Williams, 1952). In addition, different levels of the same drive have served as discriminative

stimuli (Bloomberg and Webb, 1949; Jenkins and Hanratty, 1949).

Kendler (1946) found that rats could discriminate between hunger and thirst drives when both drives had been present simultaneously during training. During discrimination testing, when only one drive state was present, subjects responded appropriately. Kendler proposed a "selective association hypothesis" that only those drive stimuli which are themselves reduced become connected to a rewarded response.

Amsel (1949) obtained a T-maze discrimination, using hunger and thirst as cues for shock escape. Levine (1953) obtained differential responses for light avoidance on the basis of either hunger or thirst drives. Since neither drive was reduced by shock or light avoidance, these studies refuted Kendler's proposal that only reduced drives become associated with a response.

Using a T-maze paradigm, Miller, DiCara, and Wolf (1968) injected rats with an antidiuretic hormone (ADH) if they chose one arm of the maze and saline if they chose the other. Subjects preloaded with water by stomach intubation avoided the arm associated with ADH injection. In a second experiment they used subjects having a renal disorder which caused inefficient salt excretion. After intubation of concentrated salt solution, the rats learned to choose rather than avoid the arm paired with ADH injection. Lewis (1968) found that parathyroidectomized and adrenalectomized rats acquired a

two-bar operant discrimination task in which NaCl was associated with one bar and calcium lactate with the other when training was preceded by the appropriate dietary deficiency.

The selective association hypothesis is contradicted further by operant learning studies in which presence or absence of a drug state is the discriminative stimulus (Thompson and Pickens, 1971). In such studies, correct responses resulted in reduction of the drive which motivated performance but do not directly affect the drug stimulus which directs or cues the appropriate behavior. Drug discrimination studies suggest that drive stimuli need not be reduced by a response to become associated with that response.

Webb (1955) noted that even in situations where external stimuli were used as discriminative stimuli, the internal stimuli arising from drive states could also be conditioned.

Experiments such as Webb's raise the question of the relative importance in conditioning of drive stimulus-response components and of environmental stimulus-response components. Disruptions observed when drive levels differ between the training and testing situations (Heathers and Arakelian, 1942; Yamaguchi, 1952), suggest the importance of drive stimulus-response components. Switching drive state from training to testing also results in a discrimination decrement (Webb, 1949; Kendler, Levine, Alchek, and Peters, 1952; Woodbury and Wilder, 1954). An alternative to the selective association hypothesis is that drive stimuli are part of a stimulus

complex and increase in salience when systematic external cues become less available (Webb, 1952). For example, people generally eat at a particular time of day. In the absence of information about time, however, they eat when hungry.

STIMULUS PROPERTIES OF ELECTRICAL CNS STIMULATION

Brain Stimulation as US

Baer (1905) found that classical conditioning could be obtained using electrical stimulation as both CS and US. He paired stimulation of the visual and of the motor cortex, and found that visual cortex stimulation alone would elicit the same movement as motor cortex stimulation, although the movement was less vigorous and less consistent. Loucks (1935-1936) failed to form CRs to an auditory CS with stimulation of the motor cortex as the US. However, conditioning was readily established when each CS-US pairing was immediately followed by food presentation. Loucks concluded that simple Pavlovian pairing was insufficient to establish CRs with brain stimulation USs and that an additional motivational factor was required.

Kriayev (1938) reported formation of a CR after five or six pairings of a tone with stimulation of the motor cortex as US. Using cerebellar stimulation as the US, Brogden and Gantt (1942) obtained conditioned responses in about the same number of trials as Kriayev. Giurgea (1953, 1957) demonstrated that stimulation of the motor cortex could be used as

the US, employing stimulation of other cortical loci as the CS, although persistent pairing of the stimuli for several days was required. Use of the motor cortex as a locus for an electrical US has been reported by several subsequent investigators (Doty, 1961; Doty and Giurgea, 1961; Nikolaeva, 1955; Tchilingaryan, 1963; Wagner, Thomas, and Norton, 1967). Radio-transmitted stimulation in freely moving dogs has also been used as a US (Michel, 1965). Doty (1969) reported conditioning of movements or autonomic effects evoked as URs by stimulation of thalamus (Arias, Ross, and Pineyrua, 1966), hypothalamus (Affani, Marchiafavia, and Zernicki, 1962), septal area (Malmo, 1951), mesencephalic reticular formation (Segundo, Roig, and Sommer-Smith, 1959), limbic areas (Yoshii and Yamaguchi, 1963), central gray substance and stratum profundum of superior colliculus (Ross, Pineyrua, Prieto, Arias, Stirner, and Galeano, 1965).

Brain Stimulation as CS

With the apparent exception of the cerebellum (Donhoffer, 1966), it is possible to use excitation any place in the brain as a CS in chickens, cats, rats, rabbits, guinea pigs, dogs, or monkeys (Doty, 1969). Stimulation of muscle afferents is ineffective as a CS at frequencies from 4/sec to 100/sec, although the former frequency elicits a high-amplitude response in sensorimotor cortex (Swett and Bourassa, 1967). Doty (1969) suggested that the muscle spindle afferents do not connect with systems mediating conditioned reflexes.

Since the muscle spindle afferents project to the cerebellum, these data are consistent with failure of cerebellar stimulation to evoke CRs (Donhoffer, 1966). The dentate nucleus and ventrolateral nucleus of the thalamus are also relatively ineffective as the basis for electrical CSs (Donhoffer, 1966; Swett and Bourassa, 1967). The reader is referred to Doty (1969) for a more comprehensive review.

Generalization and Discrimination of Brain Stimulation CSs

Stimulation of a particular locus with frequencies differing from the original stimulus may or may not be as effective in eliciting CRs. Instances in which animals respond equally well to several frequencies (Doty, 1965a, b; Freeman, 1962) contradict instances in which the response fails to generalize to other frequencies (Nielson, 1962; Schuckman, 1966).

Spatial generalization is not noted unless the different points stimulated lie close together in the same functional system (Doty, 1961, 1965a, b, 1967; Leiman, 1962; Loucks, 1961; Nieder and Neff, 1961; Nielson, Knight, and Porter, 1962; Schuckman, 1966; Stutz, 1968). Generalization does occur within the visual system. After training of an aversive CR to one locus in Brodman area 17, macaques made unhesitating responses to stimulation of any locus in area 17 of either hemisphere, and frequently emitted CRs to stimulation of area 18 but never to area 19 (Doty, 1969).

Although temporal and spatial arrangement of excitation

and inhibition is extremely complex, it is theoretically possible to produce crude experience of an externally applied stimulus by means of a central electrical stimulus. With cats as subjects, Nieder and Neff (1961), obtained generalization of an aversive CR between presentation of clicks at 100/sec and stimulation of the inferior colliculus at the same frequency. While avoidance could have been due to some noxious nature of collicular stimulation, the finding of generalization from collicular stimulation to click tends to negate the above explanation. Comparable experiments using the visual system have been negative (Leiman, 1967; Nielson, Knight, and Porter, 1962).

Frequency discrimination has been demonstrated in macaques, chickens, rats, and cats (Doty, 1969). Some of the experiments failed to control for total amount of current so that discrimination was probably not based on frequency alone.

Spatial discrimination studies indicate that macaques can discriminate between CS stimulation at points 1 to 3 cm apart in Brodman areas 17, 18, 19, 9, and 20 when frequency (2 to 100/sec) and intensity of stimulation (four to tenfold range of current) are randomly varied (Doty, 1965a, b, 1967). Spatial discrimination has been demonstrated in rabbits (Iordanis, 1964) and cats (Doty, Rutledge, and Larsen, 1956).

Woody and Yarowsky (1972) provided an example of discrimination of closely located brain loci, in addition to analysis of the conduction latencies occurring during

acquisition of a classical response. They obtained classical conditioning of an EMG response to a 20ua electrical CS delivered to the coronal precruciate area in cats. The CR was acquired at about the same rate as that formed to a click CS (Woody and Brozek, 1969). Stimulation of any combination of three of six brain loci could serve as the CS and were discriminated from stimulation of three other loci situated as little as 1.5 cm away. Reversing the order of CS-US presentation for sensitization and pseudoconditioning control, resulted in extinction of the response. The authors assumed that the latency of the motor response (12 msec) included the conduction time from the coronal precruciate area to the periphery, which is 7-8 msec (Woody, 1970; Woody, Vassilevsky, and Engel, 1970). The remaining 4 msec thus provided an experimental estimate of the time required for access to the learned information after a stimulus reaches the cortex. The stored information was assumed to be a basic component of the sensorimotor integration producing selective activation of motor efferents which project to the muscle groups responsible for the specific motor response (Woody and Engel, 1972).

Although the major purpose of research using electrical stimulation in a conditioning context has been to investigate functional properties of the nervous system in learning, an adventitious benefit has been the finding that activity within numerous loci in the nervous system can participate in conditioned behaviors and essentially all loci tested have

access to the pathways serving as a substrate for learning.

CELLULAR CONCOMITANTS AND ANALOGS OF LEARNING

There are two major approaches to cellular learning phenomena, the measurement of cellular concomitants of learning and establishment of cellular analogs of learning. The first approach involves recording activity of single cells at different phases of the conditioning process. As expected, cells in several areas of the nervous system have displayed altered firing patterns during the course of learning (Jasper, Ricci, and Doane, 1958; Yoshii and Ogura, 1960; Bures, 1965; Olds, 1969). Investigators have also reported operant conditioning of single cell responding, by means of nerve stimulation (Adam, 1967), or electrical brain stimulation (Olds, 1965a, b). Since it is impossible to determine the input to individual cells, it is more valid to consider such changes in cellular responses as an index of the occurrence of conditioning in the absence of behavioral measures. For example, cells in the lateral geniculate, unaffected by overall illumination of the visual field, can be trained to respond differentially to patterned illumination (Lindsley, Chow, and Gollender, 1967). In such an instance, it is not clear whether the procedure produced conditioning of single cells or unconditioned participation in entire systems.

Within the second major cellular approach, the classical and operant paradigms are applied to single cells as stimulus

sequences, using electrical instead of natural stimuli (Kandel, 1967). The development of such cellular analogs of learning is relatively new in the science of conditioning, possibly due to two factors: (a) Cellular neurophysiological morphological, and biochemical techniques for such study are only recently developed (b) Interpretation of cellular studies depends on anatomical and physiological knowledge of connections for groups of cells in the nervous system. Such knowledge has not been completely detailed for any function of the central nervous system (Kandel, 1967). For this reason the most suitable preparations for cellular analogs of learning are those which are most simple, and which exhibit conditioning of "alpha conditioning"--a change in the efficacy of a preexisting reflex (Kreps, 1925; Sergeyev, 1962, 1964; Razran, 1961). Invertebrate species, such as the sea slug Aplysia depilans, possessing numerically smaller nervous systems with large neurons accessible to microelectrode and biochemical investigation, have been among the most satisfactory preparations to date.

Kandel and Tauc (1964, 1965a, b) conducted classical conditioning experiments on the isolated abdominal ganglion of Aplysia. While taking intracellular recordings, they delivered stimuli to each cell by means of two separate afferent nerves. Parameters of the stimuli were adjusted so that stimulus A (analog of the CS) produced a relatively small EPSP, and stimulus B (analog of the US) which was usually a

train of stimuli, produced a burst of spikes. As a result of pairings every ten seconds for at least one minute, with a CS-US interval of 300 msec, the EPSP to stimulus A was augmented so that, at peak facilitation, it triggered an action potential. They concluded that intermittent stimulation of one nerve with a strong stimulus increased the response to a weaker stimulus applied to another nerve. They labelled this effect "heterosynaptic facilitation" which they considered an instance of alpha conditioning, an early phase of classical conditioning.

Operant conditioning analogs have been developed by Hoyle (1965) who used the locust, S.gregoria, for his preparation. Intracellular recordings were taken from leg muscle cells, rather than neural tissue. During operant avoidance conditioning, the leg was shocked when frequency fell below a criterion level of spontaneous activity for a designated epoch. After 10 to 12 shocks a change in spontaneous activity appeared and was maintained in some cells for hours. The demand level could then be increased and maintained repeatedly until a point was reached at which further attempts resulted in a decrement.

Frazier, Waziri, Pinsker, and Kandel (1965) examined effects of contingent and noncontingent nerve stimulation in Aplysia. The cells they studied exhibited an endogenous rhythm which was readily modified selectively producing two behaviors, bursts or quiet periods. Pinsker and Kandel

(Kandel, 1967) refined the stimulation technique by using a monosynaptic IPSP produced by intracellular stimulation of an identified neuron. The contingent effects obtained were more reliable than those found with nerve stimulation.

More recent work using cellular analogs examined properties of habituation in Aplysia. Carew, Castellucci, and Kandel (1971) found that dishabituation of a previously habituated response was not merely reversal of the habituation process but appeared to be a facilitatory process related to sensitization. Carew, Pinsker, and Kandel (1972) developed a procedure for producing long-term habituation to serve as a model for long-term memory. They found that cells trained with spaced-trial procedures exhibited more habituation than the cells trained with massed trials, when retention was tested one day, and one week after training. The finding that the habituation response follows the same principles as associatively learned behavior in vertebrates (Woodworth and Schlosberg, 1954), suggests the usefulness of the model.

During conditioning of vertebrates the behavior of both central and peripheral cells may be modified, resulting in a virtually unlimited number of possible sequences of stimulus-response modification in learned behavioral responses. Therefore, the cellular model is usually too limited to be of use. Such models promise, however, to be useful in describing the pathways involved in particular learning procedures. The findings indicate that learned responses of single cells are

capable of serving as stimuli for responses further along some afferent pathway.

INTERNAL ACTIVITY--STIMULUS OR RESPONSE?

Rosenfeld and Fox (1971, 1972a, b) found a high correlation between a stereotyped, voluntary reaching movement in the cat and an EEG potential in the contralateral sensorimotor cortex. This "associated movement potential" (MEP) is an averaged potential similar to sensory evoked potentials (Rosenfeld and Fox, 1972a, b). The motor response was measured precisely by means of a photographic technique which allowed the pathway of a given point on a limb to be plotted, averaged, and then treated similar to a response waveform. A correlation analysis was performed for particular variables of the movement (e.g., vertical displacement) and EEG (e.g., amplitude) measures. A correlation matrix was produced for several movement and several waveform variables, for specified segments (28 msec) during limb displacement. The analysis indicated that during the excursion of the limb, the sequential instantaneous values of limb displacement covary systematically with sequential values of movement evoked potential amplitude. In other experiments the amplitude of selected MEP segments was modified operantly (Fox and Rudell, 1968, 1970; Rosenfeld, Rudell, and Fox, 1969). The cat was rewarded only when the waveform amplitude, at a specified latency, exceeded a specified criterion. The conditioning of

the movement potential resulted in predictable, finely detailed alteration in the associated movement. Bidirectional conditioning of the amplitude of movement potential components produced predictable bidirectional and finely detailed changes in movement.

Using a similar analysis of sensory evoked potentials, Rosenfeld and Hetzler (1973a, b) rewarded rats for signalling large and small components with appropriate barpresses. Most subjects learned to operantly generate one type of component and remain on one bar. Approximately 20 per cent of the subjects displayed discrimination in the absence of operant production of particular wave types. As performance of the animals evolved, components of the evoked response served as a discriminative stimulus for some subjects and as an operantly modified response for others.

Biofeedback

The finding that modification of a movement associated potential results in correlated modified behavior suggests that in some cases the distinction between stimulus and response is unclear. The double function of the electrical event obtained by Rosenfeld and Hetzler (1973a, b) further supports this concept. The possibility that modified internal responses have the potential to act as stimuli was of little import as long as little evidence was available that internal responses can be modified through experience. However, the operant conditioning of internal events renders the

stimulus role of internal events much more important in that such a process may be acting routinely in daily behavior.

Two early publications (Mowrer, 1938; Skinner, 1938) reported failure to operantly condition autonomic responses. Subsequently, the belief was established that visceral responses could be modified only by classical conditioning. Miller (1969) noted that such an idea coincided nicely with the concept that classical conditioning was more primitive than operant learning. Thus, primitive responses were modified by primitive learning. The prevalent nature of the belief was reflected by Kimble (1961) in his statement that experimental evidence demonstrates that autonomically mediated behavior can be modified by classical, but not instrumental training methods.

Miller (1969) hypothesized that the two types of learning phenomena were simply different manifestations of the same underlying process. He demonstrated that instrumental procedures could produce learning of a visceral response. As a result of his success, the area of biofeedback, in which autonomic responses are modified by operant techniques, now receives wide attention and promises to be useful in the area of applications. Examples of responses obtained using operant techniques are: changes in heart rate (Hnatiow and Lang, 1965; Hothersall and Biener, 1969); blood pressure and vasomotor responses (DiCara and Miller, 1968; Snyder and Noble, 1968); electrodermal activity (Crider, Shapiro, and Tursky,

1968); salivary responses (Miller and Carmona, 1967); urine formation (Miller and DiCara, 1968); and electroencephalographic rhythms (Kamiya, 1969; Mulholland, 1968; Wyrwicka and Sterman, 1968).

STIMULUS PROPERTIES OF DRUGS

Drugs can be interpreted as stimulus events since they produce alteration in the internal environment which result in carrying of information through afferent pathways. Some drugs also cause changes in the response of traditional sensory systems altering the perception or coding of stimuli. Overton (1971) proposed the existence of drug receptors which utilize the systems allowing sensory control of behavior. By whatever mechanism drugs can act as stimuli with conditioned as well as unconditioned properties.

Drugs as Unconditioned Stimuli

Drugs have been used successfully as unconditioned stimuli (USs) in a variety of classical conditioning paradigms. The CS has been paired in different instances with (a) drug administration (b) onset of drug unconditioned responses (UR) (c) time of peak UR intensity. Examples of responses obtained are: induced anorexia (Russek and Pina, 1962); salivation and pupil dilation (Korol, Sletten, and Brown, 1969); increased activity wheel measures (Pickens and Dougherty, 1969); nalorphine-induced withdrawal symptoms (Goldberg and Schuster, 1967); and morphine facilitation and promethazine

inhibition of aggressive behavior in male Siamese fighting fish (Braud and Weibel, 1969). Poison and taste aversion studies can also be considered an example of classical conditioning, even though the effective parameters of the response (number of trials, inter-stimulus interval, etc.) do not fit neatly with data accumulated in more traditional experiments (Cappell and LaBlanc, 1971; Carey, 1973; Kalat and Rozin, 1971, 1973; LaBlanc and Cappell, 1975).

Drugs as Reinforcing Stimuli

The technique of drug self-administration has been an important approach in the study of drugs as reinforcers. In this model the amount of drug in the animal's body is contingent on an operant response. Administration of the drug is accomplished in several ways: oral (Harris, Claghorn, and Schoolar, 1967), intravenous (Thompson and Schuster, 1964), intracerebral (Olds and Olds, 1958), intragastric (Altshuler, Weaver, Phillips, and Burch, 1975), and inhalation (Jarvik, 1967). Self-administration behavior is readily obtained with rats (Davis, 1966; Pickens, 1967; Weeks, 1962, 1963) and with monkeys (Deneau, Yanagita, and Seevers, 1968; Schuster and Thompson, 1963). Some drugs which have been found to produce self-administration are: morphine (Nichols, 1968; Weeks and Collins, 1968); amobarbital (Davis, Lulenski, and Miller, 1968); pentobarbital and phenobarbital (Deneau, Yanagita, and Seevers, 1969); ethanol (Woods, Ikomi, and Winger, 1971); cocaine (Woods and Schuster, 1968); and amphetamine (Pickens and Harris, 1968).

Implicit in self-administration studies is the concept that responding at rates greater than baseline indicates reinforcing properties of the drug. This assumption is supported by the fact that drug reinforcement properties are affected by variation of magnitude of reward, although the direction of effect is opposite to that of most reinforcers (Pickens, 1968; Schuster, 1968). Further evidence for a reinforcing effect of the drug is maintenance of high fixed-ratio schedules with drug infusion as reinforcement (Pickens and Thompson, 1968) and appearance of the reinforced behavior only in the presence of a positive discriminative stimulus (Schuster, 1968). Such data are consistent with motivational notions of reinforcing stimuli.

Drugs as Conditioned Stimuli

One of the least common applications of drugs as stimuli is in the role of conditioned stimulus. Cook, Davidson, Davis, and Kelleher (1960) used intravenously administered l-epinephrine, l-norephinephrine, and acetylcholine as CSs for leg flexion avoidance. When monitored physiological responses were maximal (30 sec after start of injection), the US (shock) was delivered. Leg flexions emitted before this time prevented shock delivery. An external CS (tone) and an internal CS (jejunal pressure) were also used as CSs. The order in which the stimuli gained complete effectiveness was: tone, acetylcholine, l-norepinephrine, jejunal pressure, l-epinephrine. Saline or glucose never elicited the response,

while lower doses of the drugs used in training did elicit the response.

Turner, Broussard, and Braud (1974) employed a conditioned aggression paradigm (Vernon and Ullrich, 1966) with d-amphetamine (0.5, 1.0, or 3.0 mg/kg; i.p.) as the CS for shock-elicited aggression. Subsequent experiments with the same subjects indicated that (a) animals with a drug-shock history avoided amphetamine and water in a T-maze paradigm while control animals showed no preference and (b) animals with a drug-shock history decreased rate of responding on a VI-30" operant task, typical of a conditioned suppression pattern (Estes and Skinner, 1941) when given amphetamine; control animals increased response rate after amphetamine injections. An advantage of the study was that the first and third experiments minimize possible instrumental avoidance properties such as those involved in the study of Cook et al. (1960).

Drugs as Discriminative Stimuli

Two of the earliest demonstrations of drug discriminative control were provided by studies conducted for other reasons. The results of Griden and Culler (1937) can be interpreted to indicate that an animal can learn to perform two responses to the same CS under different drug conditions (curarized and noncurarized). Conger (1951) investigated the effects of ethanol on approach-avoidance conflict. Following ethanol injections, animals could obtain food in the goal box

of a straight alley; water injections indicated shock in the same goal box. Another group was given the opposite contingencies. Discrimination was obtained in both groups. Since that time the generality of drug discriminative control has been demonstrated for a variety of tasks such as position in a T-maze (Bindra and Reichert, 1967; Overton, 1964), shuttle-box avoidance (Sachs, Weingarten, and Klein, 1966), conditioned freezing (Bindra, Nyman, and Wise, 1965), and conditioned barpress suppression (Barry, Etheredge, and Miller, 1965). The phenomenon has also been demonstrated in a large number of species including man (Overton, 1964; Griden and Culler, 1937; Ryback, 1969; and Bustamante and Rosello, 1968; Bustamante, Jordan, Vila, Gonzalez, and Insua, 1970), and with a continuum of control exercised by many different drug classes (Overton, 1973a).

Such research has certain methodological problems. Overton (1973b) used a T-maze avoidance task employing high levels of continuous shock and high doses of drug. He used nominal scale measurements (correct or incorrect) for the first two trials only, after which escape from continuous shock served as a salient reinforcer directing behavior during subsequent trials. While such studies demonstrate acquisition of drug stimulus control, the measurement operations do not easily lend themselves to investigation of generalization between different doses of the same drug or generalization between different drugs. The nominal scale measurement

obtained for only two trials cannot answer questions of degree. In addition, performance decrements resulting from the large doses of drugs required for stimulus control interfere with comparison of different drugs unless performance deficits could be equated. An additional problem is the high degree of noxious stimulation needed to motivate behavior under such drugged conditions.

An alternative design was systematically investigated and reported by Harris and Balster (1971). In their experiments one of two drug states (drug vs. nondrug, or high vs. low dose) either signalled which bar was operative in a two-bar discrimination task or signalled which of two schedules was in effect for a single bar operant. Such a design is useful for the study of generalization gradients. They reported drug-state gradients not unlike those obtained with traditionally employed external cues such as sound frequency (Catania, 1971). The benefits of such a design and the apparent sensitivity of operant control have produced a number of research possibilities:

a. Measurement of generalizations occurring between different doses of the same drug (Harris and Balster, 1971).
b. Reduced performance decrements due to low doses required for discriminative control.
c. The control capability of interoceptive drug-produced cues as compared to that of external cues is striking when the minimal amount of drug required for discriminative

control is considered. This observation is relevant not only to pharmacology, and study of interoceptive control, but also to the more traditional study of acquired exteroceptive control. The differential acquisition rates of certain exteroceptive cues (colored lights acquire control more rapidly than auditory stimuli) was commonly explained in terms of "organism familiarity." Since extensive drug experience prior to the experimental situation is unlikely, differential acquisition rates for external cues should be reevaluated in terms other than familiarity or experience, perhaps on a continuum of salience.

d. Measurement of generalizations between the training drug and a novel drug condition, allowing behavioral comparison of different drugs, and estimation of dose equivalence of different drugs.

e. Biochemical manipulations, via injections of amine blocking agents, result in response patterning suggestive of detection or nondetection of the training drug. The technique appears promising for researchers interested in the mechanism of drug action, because no extensive biochemical analysis or large scale sacrifice of experimental animals is required.

Operant techniques in drug research have added sensitivity to the areas of drug action, discriminative control of behavior, and the regulatory role of interoceptive cues. Yet

the research strategy employed currently has some methodological problems. When a one-bar, multiple-schedule task is used, the dependent variable is usually a cumulative recording. Although such recording illustrate changes in behavior as a result of drug manipulation, the data are not easily quantifiable. The alternative solution is to employ a two-bar operant task and use percent correct scores obtained during extinction sessions or extinction probes (short periods of extinction preceding reinforced practice). Data obtained with this technique are usually expressed as a percent score (appropriate bar-responses divided by total responses). The underlying assumption in this design is that if no stimulus control has developed, the expected value for correct responses will be approximately that expected with random responding, that is, approximately 50 per cent. Deviations from the expected value indicate the degree of stimulus control exercised by the drug state. A differential reinforcement of low rate (DRL) schedule (Ferster and Skinner, 1957) is typically employed in such research. Although the DRL schedule has several advantages (Harris and Balster, 1971), it is frequently overlooked that bursts of trial-and-error searching behavior occurs during extinction even with well trained animals. Since the DRL schedules result in a low total number of responses, each inappropriate response may be heavily weighted in determining accuracy of discrimination. Schedules producing higher rates of responding (e.g., VI) may

allow more sensitive measurement of stimulus control. Furthermore, recent research indicates that data obtained from food-motivated animals during extinction sessions may be subject to artifact resulting from the organism's deprivation conditions (Broussard and Dobbins, 1974). An alternate design for assessing the strength of drug-state stimulus control would be of great value.

DISCUSSION

The studies reviewed here indicate that internal events, regardless of how they originate, can serve as stimuli in ways paralleling external cues. Although most models of stimulus control concern external stimuli, information from a number of research areas suggests similarities between internal and external stimulus parameters.

Bykov (1943) noted that visceral activity accompanied overt behavioral change. He suggested that changes in visceral activity could effect the behavior of organisms. After establishing visceral conditioning, Bykov suggested that there was no functional difference between stimuli originating from the internal and external milieus. He felt that although internal impulses seldom reached consciousness, such a difference was unimportant and that an effort to determine common functional principles might be more parsimonious and fruitful. Airapetyantz (1952) suggested exteroceptive reflexes interact and form a "mobile functional organization"

in which the two systems precondition one another in forming higher nervous activity.

When the observations of researchers in the several research areas reviewed are integrated, several similarities between internal and external stimuli are notable:

1. The Ability to be Conditioned. Interoceptive cues can be readily conditioned using a large variety of stimulus sources. The types of stimulation which have been studied most extensively are interoceptive (visceral) stimuli (Bykov, 1943; Razran, 1961; Adam, 1967) and drug stimuli (Thompson and Pickens, 1971).

2. Conditioning Paradigms. Most types of internal stimuli have been studied in classical (Bykov, 1943; Doty, 1969) and operant (Adam, 1967; Overton, 1971; Rosenfeld and Hetzler, 1973a, b) conditioning paradigms.

3. Basic Pavlovian Phenomena. Several investigators have obtained Pavlovian phenomena commonly obtained in interoceptive conditioning studies. Airapetyantz (1952) reported demonstrations of differentiation, extinction, generalization, and induction. Adam (1967) also obtained these phenomena.

4. Complex Conditioning Phenomena. Second-order conditioning (Vassilevskaya, 1948, 1950; Pauperova, 1952) and sensory preconditioning (Goncharova, 1955) have been demonstrated for interoceptive stimuli. Appearance of such phenomena is particularly striking because they suggest that the complexity of interoceptive conditioning may be similar to that involved in exteroceptive conditioning.

5. Generalization. Generalization occurs between similarly perceived internal cues (Adam, 1967; Harris and Balster, 1971) as it does to similarly perceived external cues and may be used as an index of perceived similarity (Kimble, 1961).

6. Discrimination. Internal cues are easily discriminated. This conclusion is suggested by extremely fine differentiation of responding to conditioned internal cues. Organisms can discriminate extremely small differences in cue intensity (Harris and Balster, 1971) or cue location (Adam, 1967; Woody and Yarowski, 1972).

7. Sensitivity. Organisms seem to be very sensitive to internal states. Sensitivity is amply demonstrated by the ease of conditioning to small amounts of stimuli (Harris and Balster, 1971), and to small component changes in EEG evoked potentials.

8. Once modified by conditioning procedures, internal events may then acquire cue properties for other responses (Rosenfeld and Hetzler, 1973a, b).

In addition to the large number of similarities between interoceptive and exteroceptive stimuli, a number of dissimilarities have been demonstrated. The differences listed below do not consistently occur with interoceptive stimuli, but do occur in a notable percentage of cases:

1. In some cases conditioning with internal cues requires more trials to establish stable responding (Bykov, 1943; Razran, 1961). Conditioning of drug cues, on the other

hand, may proceed more rapidly than conditioning of external cues (Balster, 1970).

2. Interoceptively conditioned responses can be more resistant to extinction than exteroceptively based responses (Bykov, 1943; Razran, 1961).

3. Interoceptively produced responses tend to dominate exteroceptively conditioned ones, when interactions are examined (Razran, 1961; Airapetyantz, 1940).

4. Most interoceptive stimuli are not consciously perceived by the subject. However, awareness is easily obtained with training (Adam, 1967).

The similarities between internal and external stimuli, along with several findings of this review, suggest that increased attention to the stimulus role of internal events may prove useful. The tendency of internal events to dominate exteroceptively conditioned responses under laboratory conditions (Airapetyantz, 1952), implies that such interactions may routinely occur outside of the laboratory situation (Razran, 1961; Adam, 1967). Therefore, explanations of behavior, treating only exteroceptive stimuli are likely to be inadequate (Razran, 1961).

When the data indicating the double function of internal events (as stimuli or as responses) is considered, an integration is possible. DiCara (1970) suggested that instrumental learning of autonomic responses, rather than being a mere curiosity, could serve an adaptive purpose. Since most

"natural" learning is coincidental, some conditioning may be maladaptive and learned autonomic responses may result in "psychosomatic symptoms" which then in turn serve as cues for behavior. Such a pattern approximates the vicious circle of feedback occurring in exteroceptively controlled behavior. Bykov (1943) suggested that if stimulation of particular interoceptors were repeatedly paired with external stress stimuli or maladaptive behavior, the latter could readily be evoked due to the associations formed. Considering the reinforcing nature of internal cues (Thompson and Schuster, 1964), a concept of reinforcement for neurotic maladaptive behaviors also seems plausible. Due to the pervasiveness of internal states and the ease of conditioning some particular states, occasional maladaptive internal cue functioning seems almost a certainty.

Such formulations may be most useful for clinical application since deconditioning or counterconditioning of maladaptive cues is a therapeutic possibility. Using available biofeedback techniques, a new adaptive response to internal stimuli may be conditioned. Relaxation of muscle tension has been shown to correlate with "pleasant states" and is useful for the treatment of chronic stress reactions (Jacobsen, 1938) and for treatment of hyperactivity in children (Braud, 1974). Even the mere training of consciousness to internal cues may have therapeutic value. Although the issue of consciousness once retarded the study of interoception, Adam's work has

made this objection untenable. Successful training of awareness of duodenal pressure indicated that, with training, interoceptive cues can be consciously detected. The distinction between unconscious and consciousness then is not one of interoceptive versus exteroceptive, as was previously assumed, but rather training or no training.

Stoyva and Kamiya (1968) proposed that awareness and its physiological concomitants are to some extent identical. When a person is generating the alpha frequency, in the EEG (10-13 Hz) the "alpha state" is strongly predisposing to certain subjective sensations and feelings. Such a view suggests the availability of additional dependent variables for research, i.e., subjective report.

Another interesting research and theoretical view has been suggested by Ezios (1971). He suggested that biofeedback be used as a tool to sharpen skills of discrimination, control, and verbal description of internal events. Once accomplished in these skills, a well-trained subject could then be used in research using standard psychophysical scaling techniques to investigate thresholds and just noticeable differences (jnd's) of physiological processes.

Once theoretical biases and conventions are weakened, the investigation of interoceptive stimulus control has wide research and therapeutic possibilities. It seems likely that although most interoceptive impulses influence behavior without awareness, the contribution of such stimuli to behavioral

control is enormous. The assumption that an internal realm of behavior has a memory (an ability to be modified by experience) is not unwarranted considering visceral cueing and learning. It is probable that conditioned visceral reflexes are continuously established, modified, and extinguished. Consequently, a complete elucidation of human "psychological" functioning cannot be attained without an understanding of interoceptive systems. Razran (1968) aptly noted: "After all, our viscera are with us all the time, you can't get rid of them, and they keep on learning, whereas the Lord has not provided us with levers to pull or buttons to push or even peck at."

SUMMARY AND CONCLUSIONS

The initial experimental analysis of interoceptively conditioned responses suggests that interoceptive and exteroceptive cue functions are basically the same. For this reason, an adequate explanation of behavior requires consideration of interoceptive control as well as exteroceptive control. Further experimental analysis is required for development of such formulations. Clarification of interoceptive stimulus functions currently promises to be extremely useful in the area of clinical application to psychosomatic symptoms. Some theorists (Razran, 1961; DiCara, 1970) suggest that the study of consciousness is a second area which may benefit from the study of interoceptive cues.

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CHAPTER II

FOUR EXPERIMENTS: CONDITIONED SUPPRESSION OF AN OPERANT RESPONSE USING DRUGS AS CONDITIONED STIMULI

ABSTRACT

The possible use of a drug state as a conditioned stimulus for conditioned suppression was investigated in a series of four experiments. In all the experiments drug injections were paired with a series of unavoidable shocks. Subsequently, effects of the shock-paired drug on operant response rate were compared to effects obtained in control subjects which received unpaired drug-shock experience. These experiments demonstrated that d-amphetamine (0.8mg/kg) served as a CS for conditioned suppression of a one-lever task (VI-60sec). Stimulus generalization from the shock-paired drug to cocaine (7.5mg/kg) also occurred. Reduction of external apparatus cues, by administering shocks in the operant chamber instead of a separate apparatus, produced a more durable suppression effect. It was hypothesized that following d-amphetamine vs. cocaine discrimination, suppression would be observed for retraining sessions involving the shock-paired drug. Since the suppression obtained was not cue-specific, the difficulty of the d-amphetamine vs. cocaine discrimination may have minimized transfer between the operant and classical components of the study. In a final experiment d-amphetamine vs. saline discrimination training preceded drug-shock sessions in which either d-amphetamine or saline were shock-paired for each individual subject. No cue-specific suppression occurred. The results of this experiment suggest that a saline injection cannot serve as a CS in the absence of explicit differentiation procedures.

Since the early 1950's, it has been well established that drug states can serve as cues for a number of behavioral tasks (Overton, 1971) in a number of species (Overton, 1964; Griden and Culler, 1937; Ryback, 1969; and Bustamante, Rosello, Jordan, Pradera, and Insua, 1968) with varying degrees of control exercised by different drug classes (Overton, 1973a). Such research, however, has some methodological problems (Overton, in press). Overton (1971) used a T-maze avoidance design, high levels of continuous shock, and high drug doses. He used nominal scale measurements (correct or incorrect) for the first two trials. While such studies demonstrate acquisition of drug stimulus control, the nominal scale measures do not easily lend themselves to investigation of generalization between different doses of the same drug or generalization between different drugs.

An alternative design for investigation of drug discrimination was studied by Harris and Balster (1971). In their experiments one of two drug states either signalled which bar was operative in a two-bar discrimination task or which of two schedules was in effect for a single bar operant. Such a paradigm has advantages since these authors report drug generalization gradients similar to gradients produced by external cue control (Catania, 1971). In addition, such an operant discrimination paradigm has produced a number of other research possibilities. Very small doses of a drug can acquire discriminative control, and thus reduce performance

decrements associated with experiments using high dosages (Harris and Balster, 1970). Comparison of drug discriminative control with external stimulus control indicates that even small amounts of drug seem to acquire stronger discriminative control than salient external cues (Balster, 1970). Until the sensitivity of drug stimulus control was established, the differential acquisition rates of different external cues was attributed to organism familiarity. Since drug experience prior to the experimental situation is unlikely, differential behavioral control with external cues should be re-evaluated, perhaps in terms of species specific "preparedness" for different types of stimuli (Seligman, 1970).

Operant techniques in drug research have added sensitivity to the study of drug action, discriminative control of behavior, and the regulatory role of interoceptive cues. However, these techniques have some associated problems. When a one-bar, multiple-schedule task is used, the dependent variable is usually a cumulative recording. Although such analog recordings illustrate changes in behavior as a result of drug manipulation, the data are not easily quantifiable. The alternative solution is to employ a two-bar operant task and use percent correct scores obtained during extinction sessions or extinction probes (short periods of extinction preceding reinforced practice). Data obtained with this technique are usually expressed as a percent score (appropriate bar-responses divided by total responses). The underlying

assumption in this design is that if no stimulus control has developed, the expected value for correct responses will be similar to random responding: approximately 50 per cent correct bar responses. Deviations from the expected value indicate the degree of stimulus control exercised by the drug state. A differential reinforcement of low rate (DRL) schedule (Ferster and Skinner, 1957) is typically employed in such research. Although the DRL schedule has several advantages (Harris and Balster, 1971), it has disadvantages as well. Bursts of trial-and-error searching behavior occur during extinction even with well trained animals (Waters, Richards, and Harris, 1973), and DRL schedules produce a low total number of responses, causing inappropriate responses to be heavily weighted in determining accuracy of discrimination. Schedules producing higher rates of responding (e.g., VI) may allow more sensitive measurement of stimulus control. Furthermore, recent research indicates that data obtained from food-motivated animals during extinction sessions may be subject to artifact resulting from the organism's deprivation conditions (Broussard and Dobbins, 1974). An alternate design for assessing the strength of drug-state stimulus control would be of great value.

Turner, Broussard, and Braud (1974) employed a conditioned aggression paradigm (Vernon and Ullrich, 1966) with d-amphetamine as the CS for shock-elicited aggression. In subsequent experiments with the same animals those subjects

with a drug-shock history decreased their rate of responding on a VI-30" operant task when given d-amphetamine. Such a decrement is similar to a conditioned suppression pattern (Estes and Skinner, 1941). They concluded that use of a drug CS in a conditioned suppression paradigm might be a useful tool in studies of drug states as interoceptive stimuli.

The present study was designed to explore the possibilities of using a conditioned suppression paradigm (CER) for drug stimulus investigations. A number of studies have investigated the effects of drugs on a CER response (Heistad, 1957, 1958; Heistad and Torres, 1959; Barry, Etheredge, and Miller, 1965; Cecala and Hartley, 1967; Kanzler, 1967; Sherman, 1967). No research is available however about the use of drugs as conditioned stimuli in a conditioned suppression design.

EXPERIMENT I

The purpose of this experiment was to determine if 1) a drug state would serve as a conditioned stimulus for bar-press suppression and 2) if animals would generalize suppression to a drug different from the one originally paired with shock. The design of this experiment and of the three subsequent studies involved four treatment phases: 1) training to an operant bar-press task with rate used as baseline; 2) paired and unpaired drug shock presentation for classical conditioning of a drug CS; 3) retraining period for the operant task and 4) testing acquired response suppression to the drug.

METHOD

Subjects

Twenty adult male Fisher rats (200-250g) were obtained from Simonsen Laboratories and allowed free access to food for approximately two weeks after their arrival. Animals were housed individually and handled daily. Following this two week period, subjects were placed on a food-cycling schedule and fed small rations of food until their weights were 80% of free-feeding weight. During the experiment, subjects were maintained at 80% free-feeding weight and allowed free access to water. The animals were fed immediately after each experimental session for the duration of the experiment.

Apparatus

Operant Training Apparatus. All operant training and testing occurred in five identical plexiglass chambers (Scientific Prototype, Model A-100) enclosed in sound-attenuating cubicles (Scientific Prototype, Model SPC-300). Each cubicle was equipped with a small fan to maintain fresh air circulation and a two-inch speaker for white noise transmission. Two levers (Scientific Prototype, Model PLS-100) were mounted three inches apart on the front wall of each chamber and one inch above the grid floor. A brass food tray was centrally located between the levers and was used to dispense food reinforcement (45 mg Noyes pellet) delivered by a pellet dispenser (Foringer, Model PDC) located behind the front panel. A 7 watt house light provided a constant low level of illumination. Cue lights located above the response levers were not used during any part of the experiment. All behavioral programming was accomplished by solid state circuitry (Grason-Stadler 1200 series) located in the same room. Data was collected by response counters and cumulative recorders.

Shock Apparatus. Unavoidable footshock was administered in two plexiglass chambers (10"x12"x10") each equipped with a grid floor. The shock source (LVE 1671) and scrambler (BRS/LVE, SC 902) were located in a separate room and programmed for automatic presentation of each series of scrambled shocks. No response measures were taken in this apparatus.

Drugs

The drug solutions used were prepared by dissolving the chemicals in a 0.9% saline solution (Travenol Laboratories). Fresh solutions of 0.8 mg/ml d-amphetamine sulfate (Sigma Chemicals) and 7.5 mg/ml cocaine hydrochloride (Mallinckrodt) were prepared at least once a week.

PROCEDURE

Training. All subjects were trained to barpress on a variable interval, 60 seconds (VI-60) schedule of reinforcement. Preliminary training consisted of a concomitant CRF--magazine VI-60 second schedule resulting in an automatically dispensed food pellet on the average of every 60 seconds in the absence of bar presses. For each animal, one lever was arbitrarily assigned as the correct lever. Initially, responses on that lever were reinforced on a CRF schedule. For some animals, one session of hand shaping was required to obtain CRF performance. Preliminary training was terminated following stable CRF performance.

Animals were then shaped to a VI-60 second schedule by gradually increasing the average interval between reinforcements. A VI-60 second schedule of reinforcement was the training and testing schedule in effect for the duration of the experiment. All animals were given 30 days of 30 minute reinforcement sessions prior to shock training. Total number of responses per session were recorded.

Drug-Shock Presentation. Following initial training and response stabilization, drug-shock pairing was instituted. Operant sessions were suspended during this period. Each of 15 days of shock presentation was considered one conditioning trial. Subjects were randomly assigned to two groups of ten subjects, which differed only in that d-amphetamine and shock were paired or unpaired.

A modified Rescorla procedure (Rescorla, 1967) was used to control for sensitization and pseudoconditioning effects. The paired group (PG) was given a 0.8 mg/kg intraperitoneal injection of d-amphetamine 15 minutes prior to receiving 200 unavoidable shocks (1.0 mA, 0.5 sec, 4.5 sec intershock interval). The unpaired group (UP) received the shock procedure at the same time of day as the PG animals. UP animals received saline injections 15 minutes prior to shock and daily amphetamine injections at times randomly selected from designated times within a twenty-four hour day. PG animals received saline injections at the time selected for drug administration to UP animals. This control procedure resulted in within-trial randomization of CS-US order for the UP group and consistent CS-US pairing for the PG animals while equalizing drug experience for all animals. Randomization resulted in one actual pairing of drug and shock for the UP animals. No response measures were taken during this phase of the experiment.

Retraining. Following the 15 days of drug and shock

presentation, all animals were retrained on the operant task for six days.

Generalization and Suppression Testing. Following the six days of retraining, animals were tested for suppression of operant responding resulting from amphetamine administration or for generalization of suppression to administration of cocaine. PG and UP groups were randomly subdivided into two groups. Half of the animals in each group received intraperitoneal injections of 0.8 mg/kg d-amphetamine (AP,AU) and half received 7.5 mg/kg cocaine hydrochloride (CP,CU) 15 minutes prior to operant sessions. These drug doses were selected since generalization of a two-bar discrimination task has been reported for these doses (Huang and Ho, 1974). Suppression testing was conducted over six half-hour sessions. Number of responses per session and cumulative recordings were taken each day. Table 1 presents the design matrix resulting from division of the Paired and Unpaired groups.

RESULTS

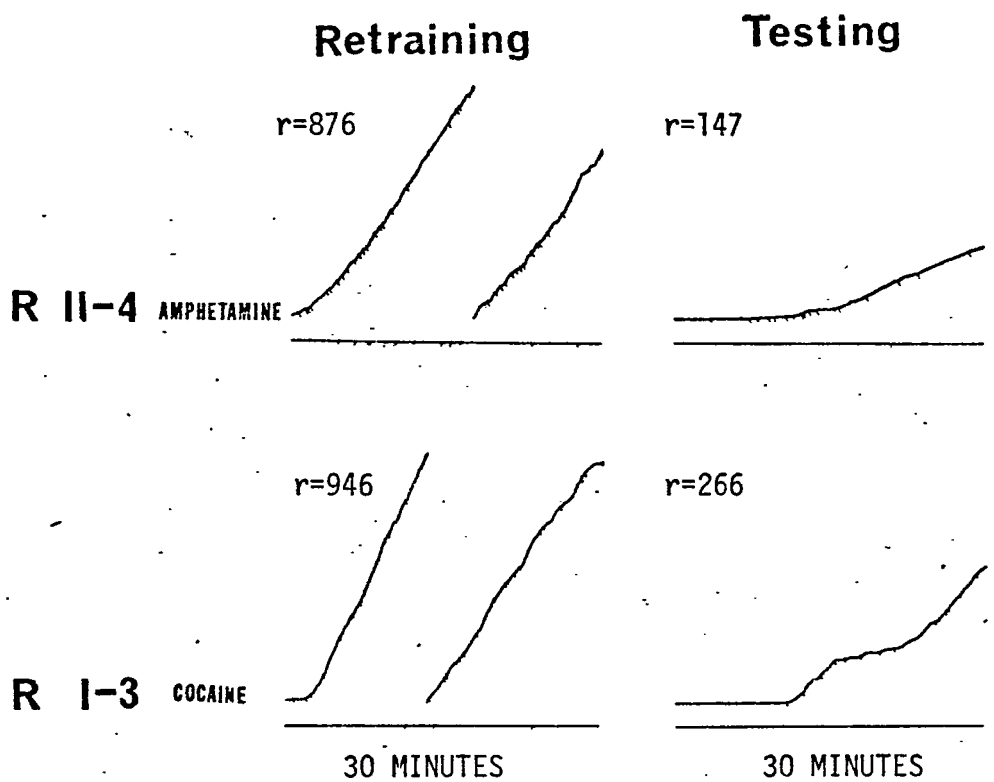
Representative changes in response rate for the Paired and Unpaired groups are presented as cumulative records in Figures 1 and 2. Those subjects which had received d-amphetamine injections paired with shock reduced their response rate when given d-amphetamine or cocaine after the retraining period (Figure 1). Subjects which had received unpaired d-amphetamine and shock experiences increased their rate of

TABLE 1

Design matrix for two shock conditions (Paired or Unpaired) and two test drugs (d-amphetamine or cocaine).(Experiment I).

DRUG-SHOCK PRESENTATIONS		Abbreviations
Paired	d-amphetamine n=5	PA
	cocaine	PC
Unpaired	d-amphetamine	UA
	cocaine	UC

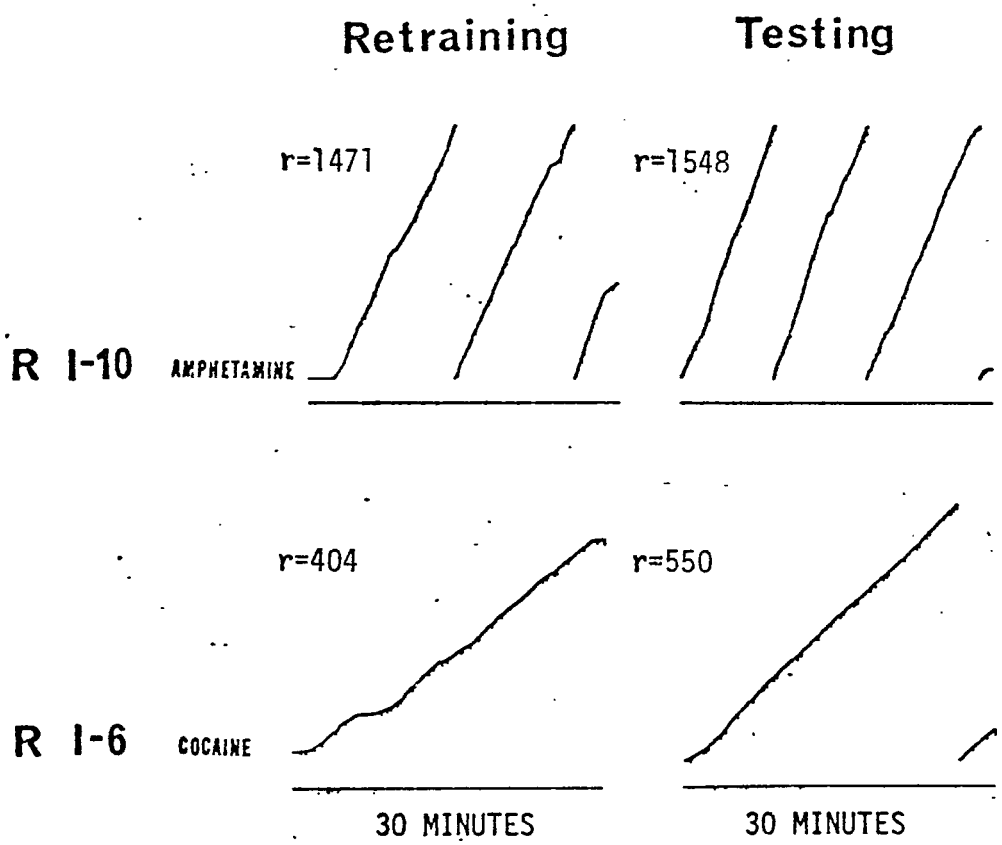
PAIRED



Consecutive cumulative records of two PAIRED subjects from the last day of Training and the first day of Suppression Testing

FIGURE 1

UNPAIRED



Consecutive cumulative records of two UNPAIRED subjects from the last day of Training and the first day of Suppression Testing

FIGURE 2

responding when given d-amphetamine after retraining (Figure 2).

For analysis purposes, the last six days of training were selected as asymptotic performance levels and used as baseline for the training phase. Mean total number of responses per session for each group (PA, PC, UA, and UC) for six days of each of the three phases (Training, Retraining, and Suppression Testing) are presented in Table 2 and are graphically represented in Figure 3.

A baseline score for each group was obtained by calculating the mean for the six training days. Baseline change scores for retraining and suppression testing were calculated by subtracting the mean response score for each session from the training mean. Table 3 presents response change scores for six days of retraining and six days of suppression testing. Figure 4 shows group means for change from baseline for retraining and suppression testing days. There are no obvious differences among the groups during retraining. During suppression testing, Paired subjects tested under cocaine suppressed response rate almost as much as Paired subjects tested under amphetamine. Cocaine-tested animals recovered response rate faster than did amphetamine animals. When Figure 3 is compared with Figure 4, differences between the two unpaired groups are less pronounced in the second figure. Both unpaired groups slightly increased response rate during suppression testing as compared to baseline or retraining.

TABLE 2

GROUP MEANS FOR RESPONSES PER SESSION FOR SIX DAYS OF TRAINING, RETRAINING AND SUPPRESSION TESTING

	PA	PC	UA	UC
TRAINING				
1	640.0	632.2	614.4	854.8
2	696.8	650.2	478.4	804.0
3	758.8	891.2	634.6	873.8
4	801.0	811.2	630.0	970.2
5	913.4	693.2	521.0	773.4
6	838.0	941.2	718.2	874.8
RETRAINING				
1	605.8	474.2	330.2	725.6
2	389.4	605.0	430.4	697.4
3	667.0	387.4	548.6	732.6
4	655.0	652.4	535.4	693.2
5	608.2	535.2	438.6	668.8
6	926.2	616.2	533.4	1010.0
SUPPRESSION TESTING				
1	308.6	269.4	605.6	944.0
2	159.6	236.0	634.8	910.4
3	235.0	278.8	611.6	958.0
4	260.6	299.0	653.0	949.4
5	371.0	521.4	623.6	1066.0
6	375.4	540.2	589.6	1079.4

GROUP MEANS FOR RESPONSES PER SESSION FOR SIX DAYS OF TRAINING, RETRAINING AND SUPPRESSION TESTING

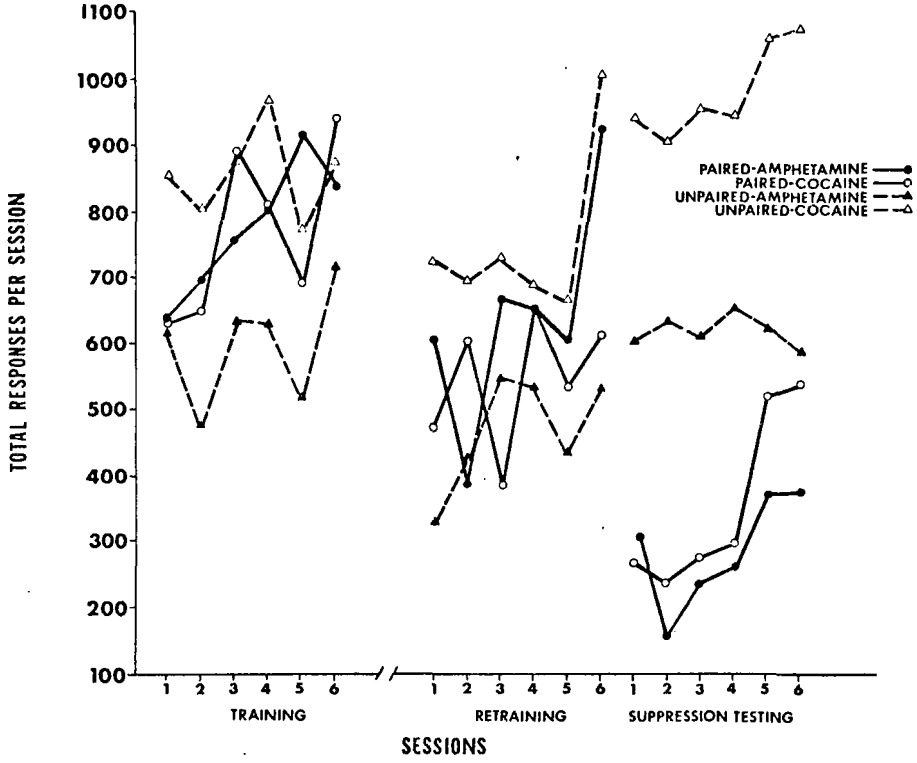


FIGURE 3

TABLE 3

GROUP MEANS FOR RESPONSE CHANGE SCORES (DIFFERENCE FROM TRAINING MEAN) FOR RETRAINING AND SUPPRESSION TESTING (EXPERIMENT I)

	PA	PC	UA	UC
RETRAINING				
1	-168.9	-295.7	-269.6	-132.9
2	-385.3	-164.9	-169.4	-161.1
3	-107.7	-382.5	-51.2	-125.9
4	-119.7	-117.5	-64.4	-165.3
5	-166.5	-234.7	-161.2	-189.7
6	151.0	-153.6	-66.4	151.5
SUPPRESSION TESTING				
1	-466.1	-500.5	5.8	85.5
2	-615.1	-533.9	35.0	51.9
3	-539.7	-491.1	11.8	99.5
4	-514.1	-470.9	53.2	90.9
5	-403.7	-248.5	23.8	207.5
6	-399.3	-229.7	-10.2	220.9

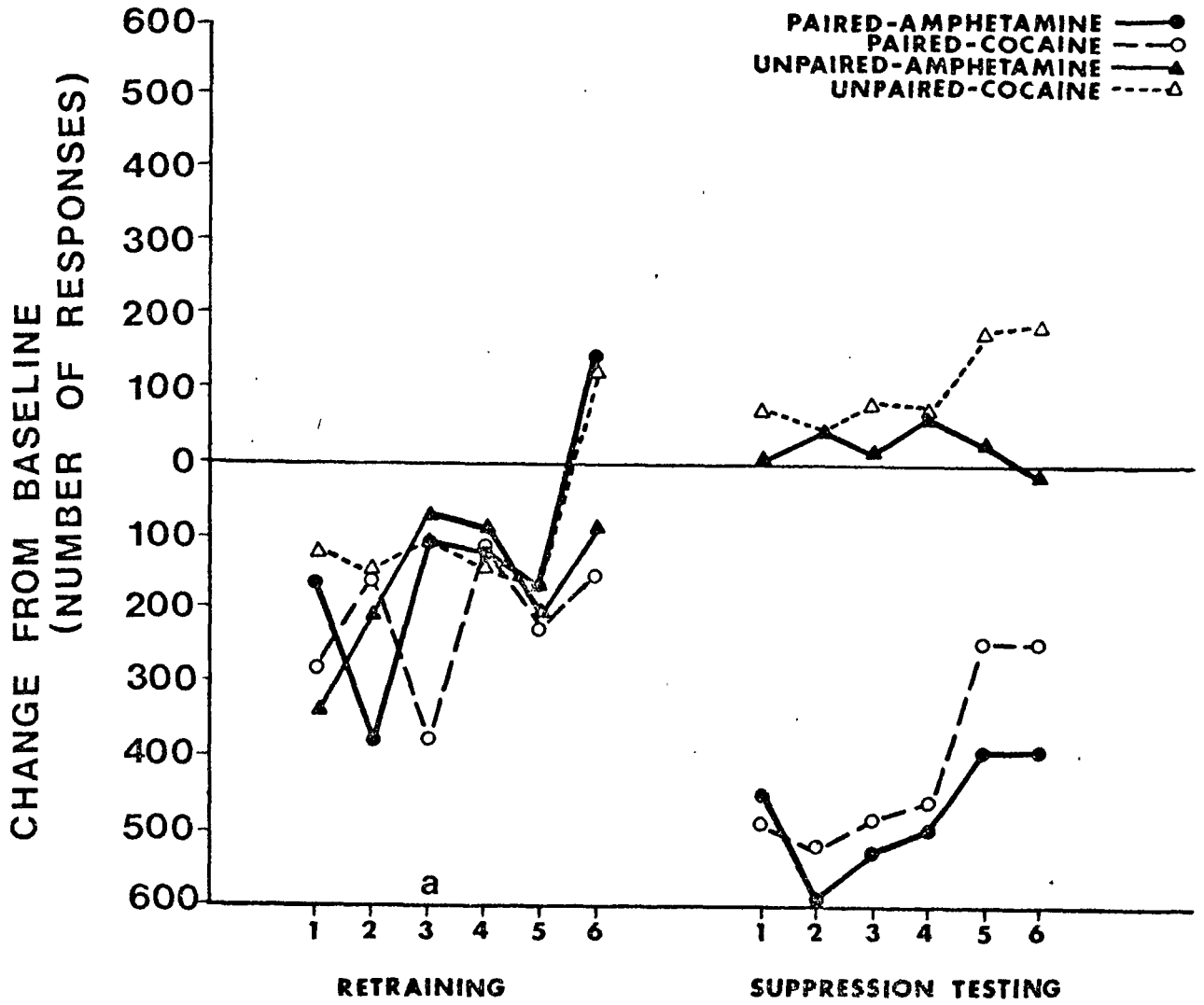

PAIRED-AMPHETAMINE
PAIRED-COCAINE
UNPAIRED-AMPHETAMINE
UNPAIRED-COCAINE
CHANGE FROM BASELINE
(NUMBER OF RESPONSES)
600
500
400
300
200
100
0
100
200
300
400
500
600
a
1 2 3 4 5 6
1 2 3 4 5 6
RETRAINING
SUPPRESSION TESTING

FIGURE 4

Response change scores for the retraining and suppression phases were subjected to separate analysis of variance procedures, with each six day phase serving as one "Block." Results of the analyses are shown in Tables 4 and 5. "Pair" refers to scores grouped by shock condition (Paired or Unpaired) and "Test" refers to scores grouped by experimental session. Treatment sums of squares for response change scores were tested by Hartley's test for homogeneity of variance (Winer, 1962). None of the Fmax scores were significant.

Analysis of variance data in Table 4 indicate no difference in response rate during retraining between drug-paired and unpaired groups. Both groups initially suppressed responding but eventually recovered to baseline level. This is indicated by the significant "Test" score in Table 4 ($p<.001$). The data of Table 5, however, indicate that a difference was obtained in number of responses between paired and unpaired animals during suppression testing. The "Pair" score of Table 5 indicates a significant difference between drug-paired and unpaired animals ($p<.001$) for suppression testing. Although a difference between amphetamine-tested and cocaine-tested animals appears in both Figures 3 and 4, analysis of variance did not show this difference to be significant.

TABLE 4

ANALYSIS OF VARIANCE TABLE FOR RESPONSE CHANGE FROM BASELINE SCORES DURING RETRAINING

Source	ss	df	F
Between Subjects			
Pair	114144.9	1	0.391
Drug	32242.4	1	0.111
Pair x Drug	105198.	1	0.361
Within Subjects			
Test	826836.3	5	5.340**
Pair x Test	86371.1	5	0.558
Drug x Test	219306.8	5	1.416
Pair x Drug x Test	444994.4	5	2.874*
$Error_1$	4668201.0	16	
$Error_2$	2477606.0	80	

*$p < .05$

**$p < .001$

TABLE 5

ANALYSIS OF VARIANCE TABLE FOR RESPONSE CHANGE FROM BASELINE SCORES DURING SUPPRESSION TESTING

Source	ss	df	F
Between Subjects			
Pair	8238305.0	1	41.36***
Drug	252266.3	1	1.3
Pair x Drug	6220.8	1	0.03
Within Subjects			
Test	460252.5	5	6.787***
Pair x Test	151606.7	5	2.236
Drug x Test	138089.8	5	2.036
Pair x Drug x Test	22869.4	5	0.337
$Error_1$	3186931.0	16	
$Error_2$	1085002.0	80	

***$p < .001$

EXPERIMENT II

A second experiment was conducted to determine whether suppression would be more resistant to extinction if paired or unpaired shock were administered in the same apparatus used for reinforced responding.

METHOD

Subjects

Twenty male Fisher rats (200-250g) served as subjects. Deprivation conditions were the same as in Experiment I.

Apparatus

The operant chambers described in Experiment I were used but were wired for shock presentation. The shock programming source was the same as used in Experiment I.

Procedure

Animals were trained in four phases. The training, retraining and testing phases were identical to those described in Experiment I. The drug-shock phase differed, however, in that shock presentation was conducted within the operant chambers. On shock days, PG animals received d-amphetamine injections 15 minutes before being placed in the operant chambers, and UP animals were given saline. Time of drug injections for UP animals was randomly determined. All animals received 200 unavoidable shocks per day (0.25 mA, 0.5 sec, 4.5 sec intershock interval). Suppression testing was extended to twelve days in this study.

RESULTS

The means for total number of responses for twelve days of retraining and suppression testing are presented in Table 6 and presented graphically in Figure 5.

As in Experiment I, the last six days of training were used for analysis of baseline performance compared to retraining and suppression-testing performance. Baseline scores and baseline change scores for each group were obtained using the method described in Experiment I. Table 7 presents response change scores for twelve days of retraining and suppression testing; Figure 6 shows group means for response change scores for retraining and suppression testing. Both Figure 5 and Figure 6 indicate that animals given amphetamine-shock pairings and tested under cocaine suppressed response rate almost as much as animals paired and tested under amphetamine. Drug-paired animals suppressed responding from baseline performance while unpaired animals showed a slight increase in responding.

Response change scores for the retraining and suppression testing phases were subjected to separate analysis of variance procedures, with each twelve day phase serving as a "Block." Results of the analyses are presented in Tables 8 and 9. Treatment sums of squares were tested by Hartley's test for homogeneity of variance (Winer, 1962) and resulted in non-significant Fmax scores for independent variances.

TABLE 6

MEAN NUMBER OF RESPONSES FOR ALL GROUPS OVER TWELVE DAYS OF RETRAINING AND SUPPRESSION TESTING

Days	RETRAINING Group PA	PC	UA	UC
1	556.3	408.8	584.4	525.0
2	427.6	450.6	462.2	669.8
3	457.4	546.0	562.4	617.2
4	530.6	538.0	554.2	523.4
5	658.4	458.0	698.2	594.2
6	655.8	542.3	767.8	730.4
7	672.8	576.4	661.6	718.6
8	708.6	676.2	742.9	824.4
9	603.0	787.4	793.8	766.3
10	690.4	740.3	817.4	752.6
11	713.3	696.8	911.8	879.3
12	787.0	752.3	844.4	770.4
	SUPPRESSION TESTING			
1	193.4	344.2	789.5	823.7
2	198.2	360.4	808.1	795.1
3	168.6	304.0	863.8	839.8
4	214.1	329.3	842.4	794.6
5	266.1	398.2	818.6	794.6
6	278.1	394.3	892.0	890.0
7	366.2	409.2	891.8	878.4
8	378.1	384.2	799.8	833.3
9	419.3	559.6	849.6	984.9
10	579.6	573.9	863.9	952.1
11	592.6	664.3	822.8	948.3
12	628.6	544.3	943.8	878.4

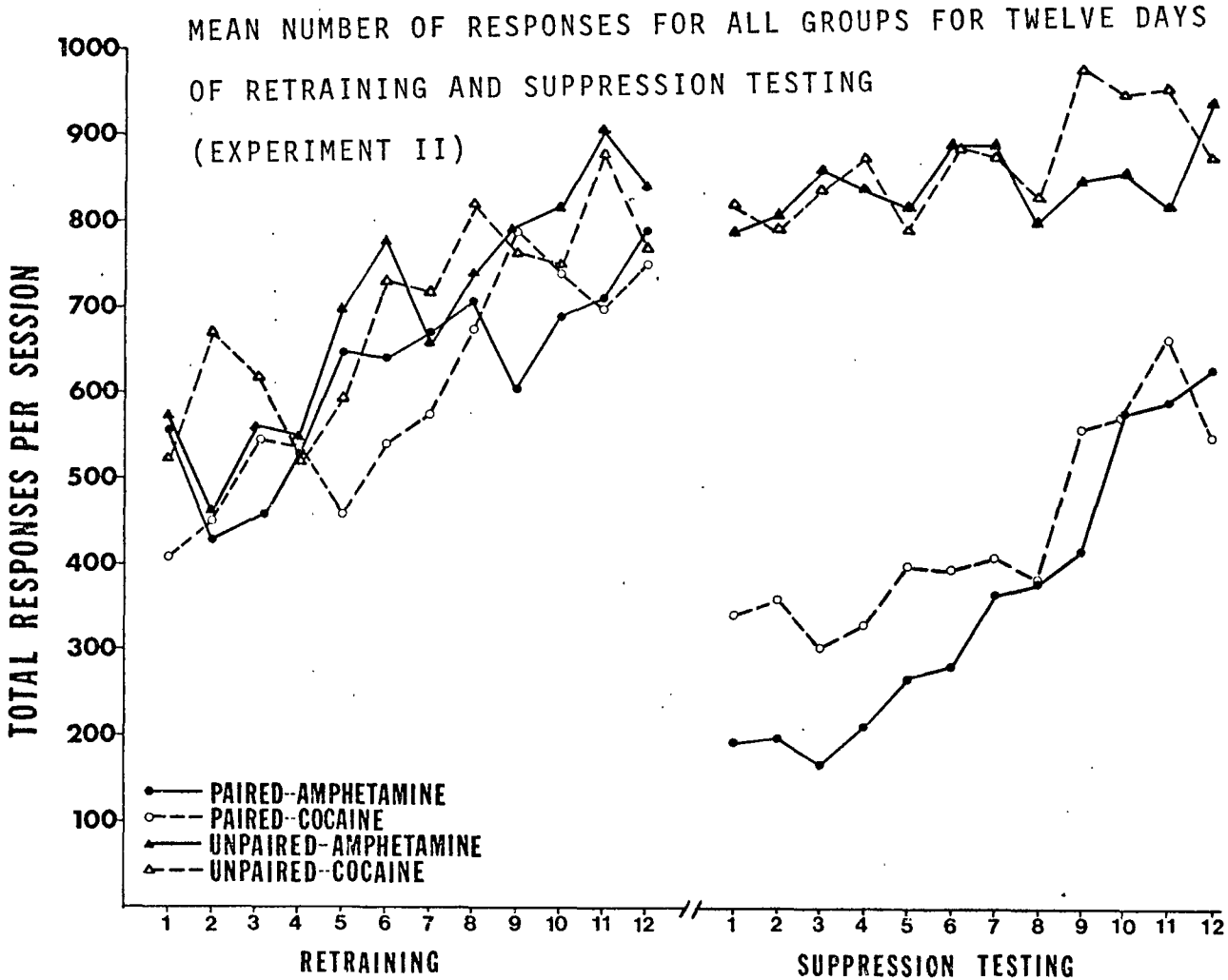

MEAN NUMBER OF RESPONSES FOR ALL GROUPS FOR TWELVE DAYS
OF RETRAINING AND SUPPRESSION TESTING
(EXPERIMENT II)
TOTAL RESPONSES PER SESSION
1000
900
800
700
600
500
400
300
200
100
PAIRED--AMPHETAMINE
PAIRED--COCAINE
UNPAIRED-AMPHETAMINE
UNPAIRED--COCAINE
1 2 3 4 5 6 7 8 9 10 11 12
RETRAINING
1 2 3 4 5 6 7 8 9 10 11 12
SUPPRESSION TESTING

FIGURE 5

TABLE 7

MEAN CHANGE FROM BASELINE SCORES (NUMBER OF RESPONSES) FOR RETRAINING AND SUPPRESSION TESTING (EXPERIMENT II)

Days	RETRAINING Group PA	PC	UA	UC
Training Means	792.2	764.2	793.8	819.4
1	-235.9	-355.4	-209.4	-294.4
2	-364.6	-313.6	-331.6	-149.6
3	-334.8	-218.2	-231.4	-202.2
4	-261.6	-226.2	-239.6	-296.0
5	-133.4	-306.2	-95.6	-225.2
6	-136.4	-222.2	-26.0	-89.2
7	-119.0	-187.8	-132.2	-100.8
8	-83.6	-88.0	-51.0	+5.0
9	-189.2	+23.2	-0.2	-53.1
10	-102.8	-24.2	+23.6	-66.2
11	-79.0	67.4	+118.0	+60.0
12	-5.2	-12.0	+50.6	-49.0
	SUPPRESSION TESTING			
1	-598.8	-420.0	-4.3	+4.3
2	-593.4	-403.8	+14.3	-24.3
3	-624.6	-460.2	+70.0	+20.4
4	-578.1	-434.9	+48.6	+57.8
5	-526.1	-366.0	+24.8	-24.8
6	-514.1	-369.9	+99.2	+70.6
7	-426.0	-355.0	+99.0	+59.0
8	-414.1	-380.0	+6.2	+13.9
9	-373.9	-204.6	+56.8	+165.5
10	-212.6	-190.6	+69.6	+132.7
11	-199.4	-99.9	+29.0	+138.9
12	-163.6	-219.9	+150.0	+59.0

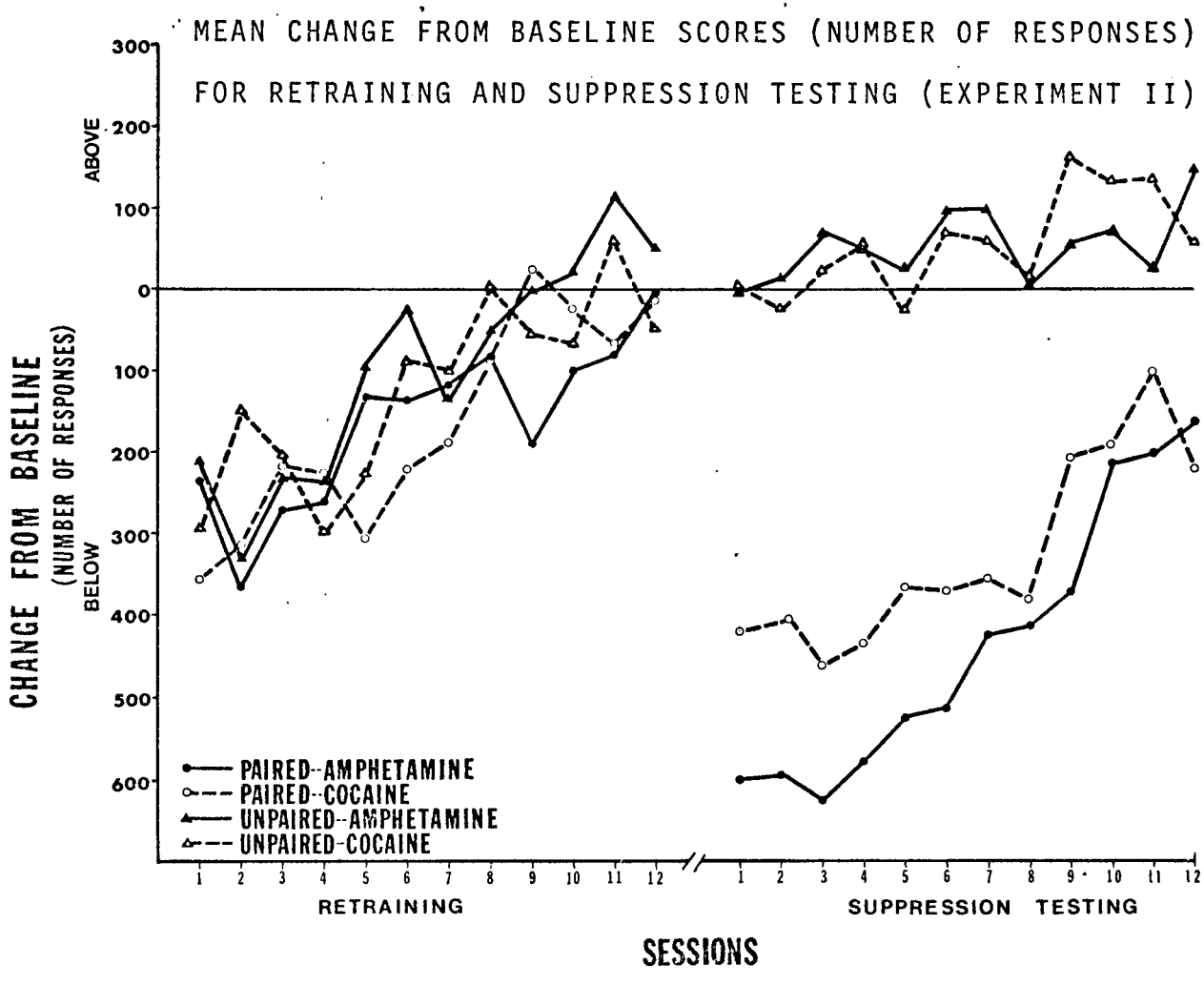

MEAN CHANGE FROM BASELINE SCORES (NUMBER OF RESPONSES)
FOR RETRAINING AND SUPPRESSION TESTING (EXPERIMENT II)
CHANGE FROM BASELINE
(NUMBER OF RESPONSES)
ABOVE
BELOW
300
200
100
0
100
200
300
400
500
600
PAIRED--AMPHETAMINE
PAIRED--COCAINE
UNPAIRED--AMPHETAMINE
UNPAIRED--COCAINE
1 2 3 4 5 6 7 8 9 10 11 12
RETRAINING
1 2 3 4 5 6 7 8 9 10 11 12
SUPPRESSION TESTING
SESSIONS

FIGURE 6

TABLE 8

ANALYSIS OF VARIANCE TABLE FOR RESPONSE CHANGE FROM BASELINE SCORES DURING RETRAINING

Source	ss	df	F
Between Subjects			
Pair	963425.0	1	0.413
Drug	173880.4	1	0.128
Pair x Drug	183706.1	1	0.135
Within Subjects			
Test	7045410.0	11	2.058*
Pair x Test	3229672.0	11	0.943
Drug x Test	4196415.0	11	1.226
Pair x Drug x Test	2308808.0	11	0.674
$Error_1$	21729168.0	16	
$Error_2$	54770432.0	176	

*$p < .05$

TABLE 9

ANALYSIS OF VARIANCE TABLE FOR RESPONSE CHANGE FROM BASELINE SCORES DURING SUPPRESSION TESTING

Source	ss	df	F
Between Subjects			
Pair	11773575.0	1	33.8**
Drug	214260.6	1	0.608
Pair x Drug	150347.7	1	0.426
Within Subjects			
Test	1553426.0	11	141220.5**
Pair x Test	720370.0	11	65488.9**
Drug x Test	179460.4	11	16314.8*
Pair x Drug x Test	111733.5	11	10157.6
$Error_1$	5642070.0	16	
$Error_2$	1536583.0	176	

*$p < .05$

**$p < .001$

Analysis of variance data in Table 8 indicate no difference in responding during retraining between drug-paired and unpaired groups. Both groups initially suppressed responding but later recovered to baseline performance. The initial suppression is reflected in the significant "Test" score in Table 8 ($p<.001$). Table 9, however, indicates a strong effect between paired and unpaired animals during suppression testing. The "Pair" score of Table 9 indicates a significant difference between drug-paired and unpaired animals ($p<.001$) during suppression-testing. Differences between amphetamine-tested and cocaine-tested animals (Figures 5 and 6) were not significant.

EXPERIMENT III

This experiment examined the effects of operant discrimination training on the generalization of classically conditioned suppression from d-amphetamine to cocaine hydrochloride. It was hypothesized that extended discrimination training would decrease generalization effects.

Subjects

Forty adult male Fisher rats of the type described in Experiment I were used. They were maintained at 80% of the freefeeding weight throughout the experiment and allowed free access to water.

Apparatus

Five operant chambers and programming equipment previously described were used in this study.

Procedure

Design. The design was a 2x2x2 factorial design in which the variables examined were: 1) type of training during acquisition (Discrimination or Nondiscrimination); 2) drug-shock relationship during classical conditioning phase (Paired or Unpaired); and 3) drug which was paired with shock (d-amphetamine or cocaine). Animals were randomly assigned to discrimination or nondiscrimination groups for the training phase of the experiment. Following training, the two groups were then subdivided into eight shock-pairing treatment groups. Table10 shows the eight groups resulting from the

TABLE 10

Design matrix for initial training groups and subsequent division into eight shock treatment groups (Experiment III).

TRAINING	DRUG-SHOCK PRESENTATIONS		Abbreviations
Discrimination (d-amphetamine vs. saline)	Paired	d-amphetamine n=5	DPA
		cocaine	DPC
	Unpaired	d-amphetamine	DUA
		cocaine	DUC
Nondiscrimination	Paired	d-amphetamine	NPA
		cocaine	NPC
	Unpaired	d-amphetamine	NUA
		cocaine	NUC

factorial design.

Training. All animals were given several days of initial training to obtain stable CRF performance. Animals were then shaped to a VI-60 second schedule. Performance on this schedule was maintained for 15 daily sessions of 25 minutes duration with the operative lever randomly assigned daily. For discrimination training, each drug (0.8 mg/kg d-amphetamine or 7.5 mg/kg cocaine hydrochloride) provided the cue for the operative lever for the Discrimination group and was randomly associated with the operative lever for the Nondiscrimination group. Within-block counterbalancing was used to determine order of drug administration during training with 4 sessions serving as one block.

During discrimination training, food reinforcement was available on the operative lever on a VI-60 second schedule. Responses on the incorrect lever before completion of an interval cancelled reinforcement and reset the interval if reinforcement was due. On Day 7 and every fourth day after, a 10 minute extinction probe was conducted, followed by 15 minutes of reinforced practice. Measures taken were cumulative records, response totals, number of responses on correct and incorrect levers, and percent correct responses. Discrimination training was conducted for a total of 85 sessions.

Drug-Shock Administration. Following discrimination training, operant sessions were suspended for sixteen sessions of shock administration. Each of the Discrimination and

Nondiscrimination groups was subdivided into four groups according to drug-shock condition (Paired or Unpaired) and the drug used (d-amphetamine or cocaine). For drug-paired animals, one of the drug conditions was always associated with presentation of 200 unavoidable shocks (0.25 mA, 0.5 sec, 4.5 sec intershock interval). For unpaired animals, the drug was administered at a time randomly selected each day. Shock was administered to the Unpaired animals at the same time of day as the Paired animals. Saline control procedures were used as in Experiment I.

Retraining. Following shock sessions, all animals were given fourteen days of reinforced practice. Each day animals in the Discrimination groups received either cocaine or d-amphetamine with the appropriate lever being operative. Nondiscrimination groups were given the same drug treatment, except that drug-lever associations were randomized. On the second day and every fourth day after, a 10 minute extinction probe was conducted and followed by 15 minutes of reinforced practice. The experiment was terminated at this point because of the illness or death of a number of subjects. These procedures resulted in four extinction probes, two of which were conducted with d-amphetamine and two of which were conducted with cocaine. Cumulative recordings, total number of responses, and percent correct responses were recorded. No separate suppression tests were required since drug was administered immediately upon reinstatement of operant sessions.

RESULTS

The data from the training and retraining phases were subdivided for purposes of analysis into two types of sessions (reinforced practice and extinction probes) resulting in four groups of scores: (1) Training--reinforced practice sessions; (2) Training Probes--10 minute extinction tests; (3) Retraining --reinforced practice following the drug-shock phase; and (4) Retraining Probes--10 minute extinction tests.

Two response measures, mean total responses per session and percent correct responses were obtained for each of the four groupings mentioned above. The arcsin transformation was used to normalize the distribution of percent correct scores for analysis.

Loss of subjects due to illness or death resulted in cell sizes too small for use of analysis of variance procedures. The data were analyzed by means of multiple t-tests selected on the basis of the experimental design (Winer, 1962; Bruning and Klintz, 1968). All t-tests for mean total response scores are presented in Appendix A. The individual comparisons which were made, the obtained differences between means, number of df, and the t-scores with associated probabilities are presented. T-tests for arcsin percent correct scores are presented in Appendix B.

Training

Total response means during Training sessions are presented in Figure 7 for the Discrimination training groups and

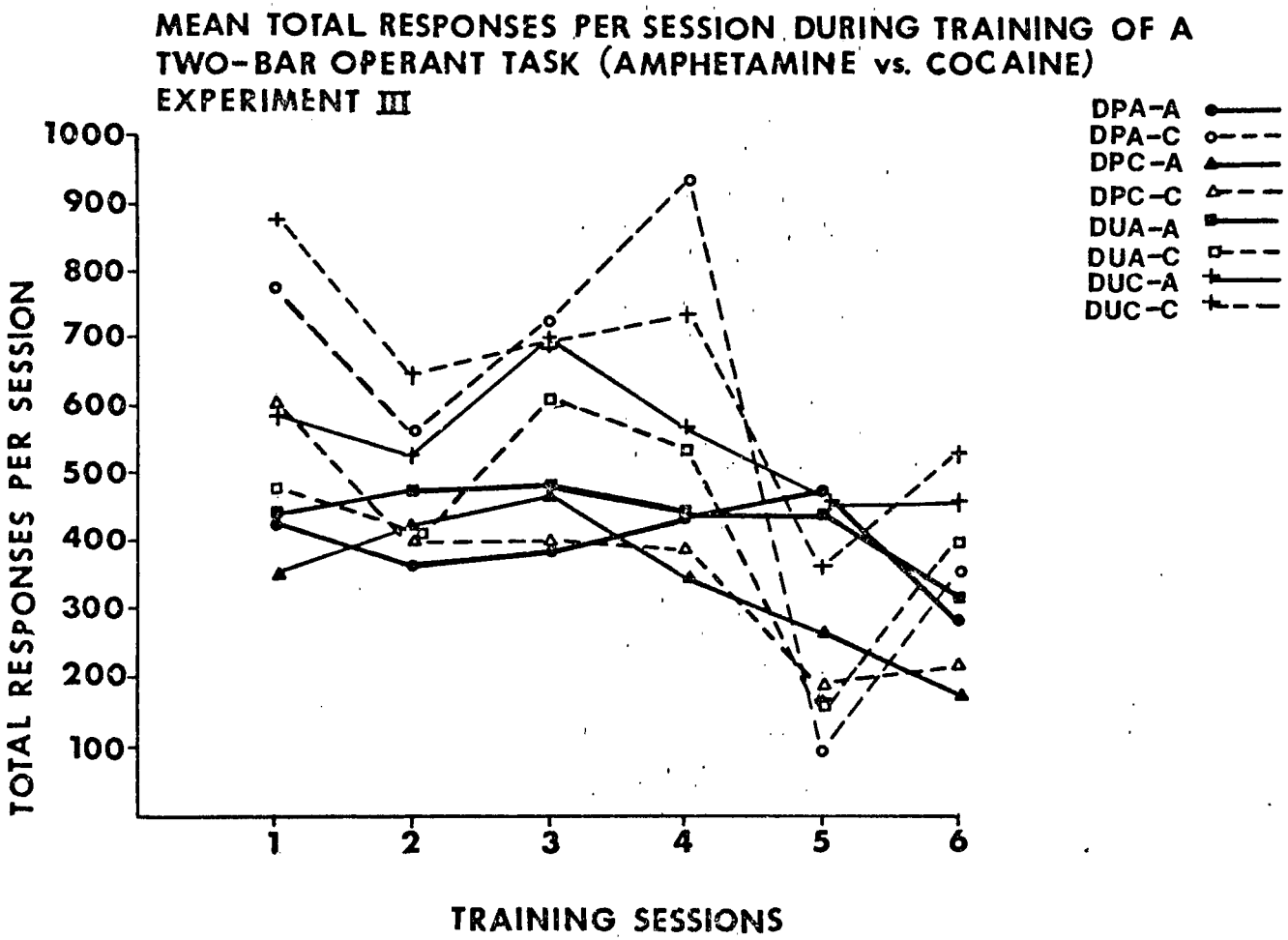

MEAN TOTAL RESPONSES PER SESSION DURING TRAINING OF A TWO-BAR OPERANT TASK (AMPHETAMINE vs. COCAINE)
EXPERIMENT III
DPA-A
DPA-C
DPC-A
DPC-C
DUA-A
DUA-C
DUC-A
DUC-C
TOTAL RESPONSES PER SESSION
1000
900
800
700
600
500
400
300
200
100
1
2
3
4
5
6
TRAINING SESSIONS

FIGURE 7

in Figure 8 for the Nondiscrimination control groups. Scores are represented separately for the last six d-amphetamine sessions and for the last six cocaine sessions during Training. The Discrimination-Nondiscrimination factor did not significantly affect total responses during training (t=-1.235, n.s.). Comparisons made using correlated t-tests between amphetamine sessions and cocaine sessions for each group resulted in only one significant score (DPA-A vs DPA-C, t=-7.74, df=3, p=.004).

Mean percent correct scores during Training are presented in Figure 9. The Discrimination-Nondiscrimination factor resulted in a significant difference between the two combined groups during reinforced practice (t=2.648, df=32, p=.011). Comparisons between the amphetamine sessions and cocaine sessions for each group resulted in no significant differences.

Training Probes

Mean total responses during Training Probes for all Discrimination groups and all Nondiscrimination control groups are presented in Figures 10 and 11. All between-group comparisons of the groups represented in those figures produced nonsignificant scores. Correlated t-tests between amphetamine sessions and cocaine sessions produced only one significant score (DUC-A vs DUC-C, t=3.96*, df=4, p=.017). The Discrimination-Nondiscrimination comparison did not indicate a significant effect on total responses (t=-1.286, df=33, p=.203).

Mean percent correct scores during Training Probes for

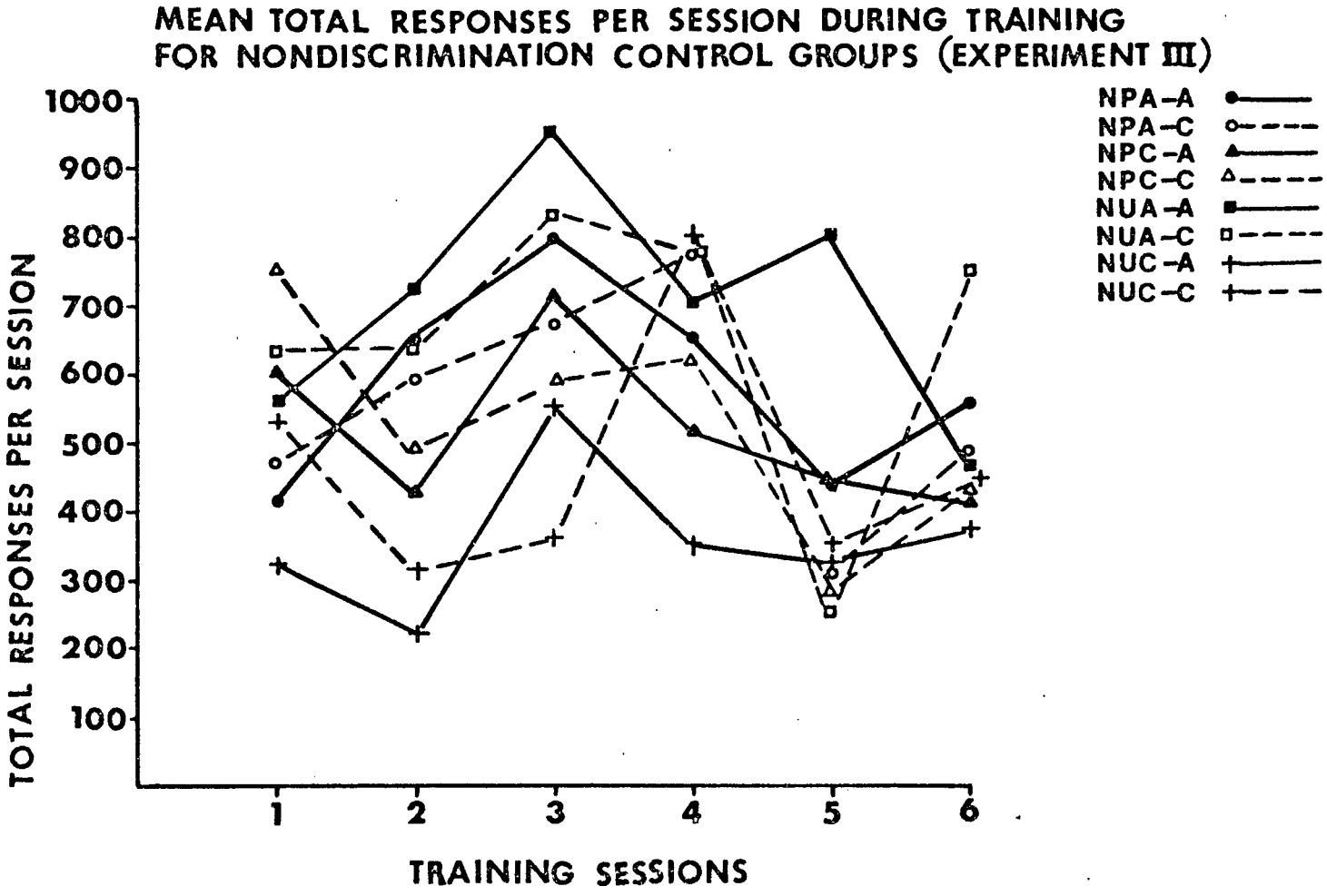

MEAN TOTAL RESPONSES PER SESSION DURING TRAINING
FOR NONDISCRIMINATION CONTROL GROUPS (EXPERIMENT III)
TOTAL RESPONSES PER SESSION
1000
900
800
700
600
500
400
300
200
100
1
2
3
4
5
6
TRAINING SESSIONS
NPA-A
NPA-C
NPC-A
NPC-C
NUA-A
NUA-C
NUC-A
NUC-C

FIGURE 8

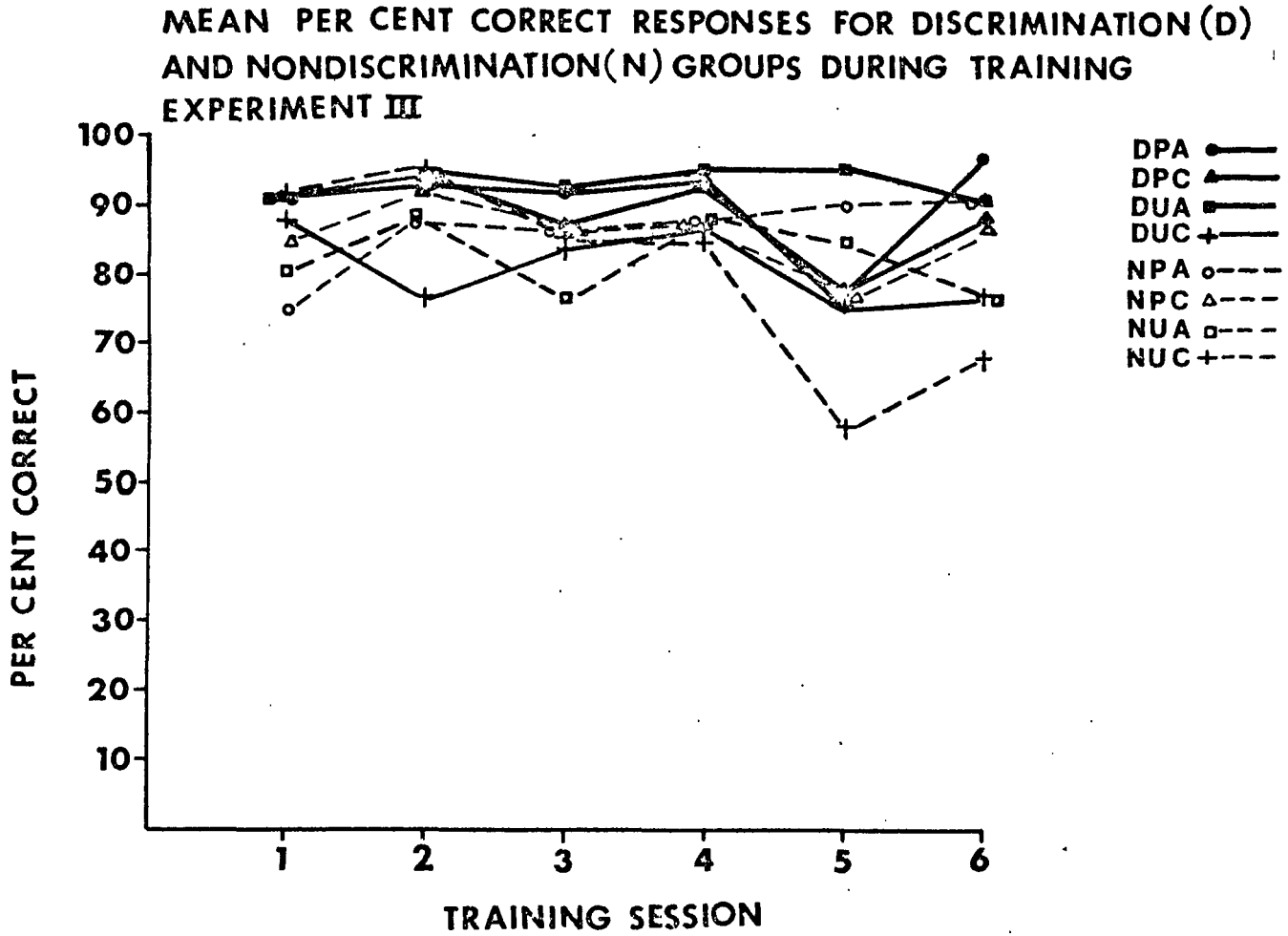

MEAN PER CENT CORRECT RESPONSES FOR DISCRIMINATION (D) AND NONDISCRIMINATION (N) GROUPS DURING TRAINING EXPERIMENT III
PER CENT CORRECT
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
TRAINING SESSION
DPA
DPC
DUA
DUC
NPA
NPC
NUA
NUC

FIGURE 9

TOTAL RESPONSES PER SESSION FOR SUBJECTS TRAINED ON A TWO BAR OPERANT DISCRIMINATION TASK (AMPHETAMINE vs. COCAINE) EXPERIMENT III

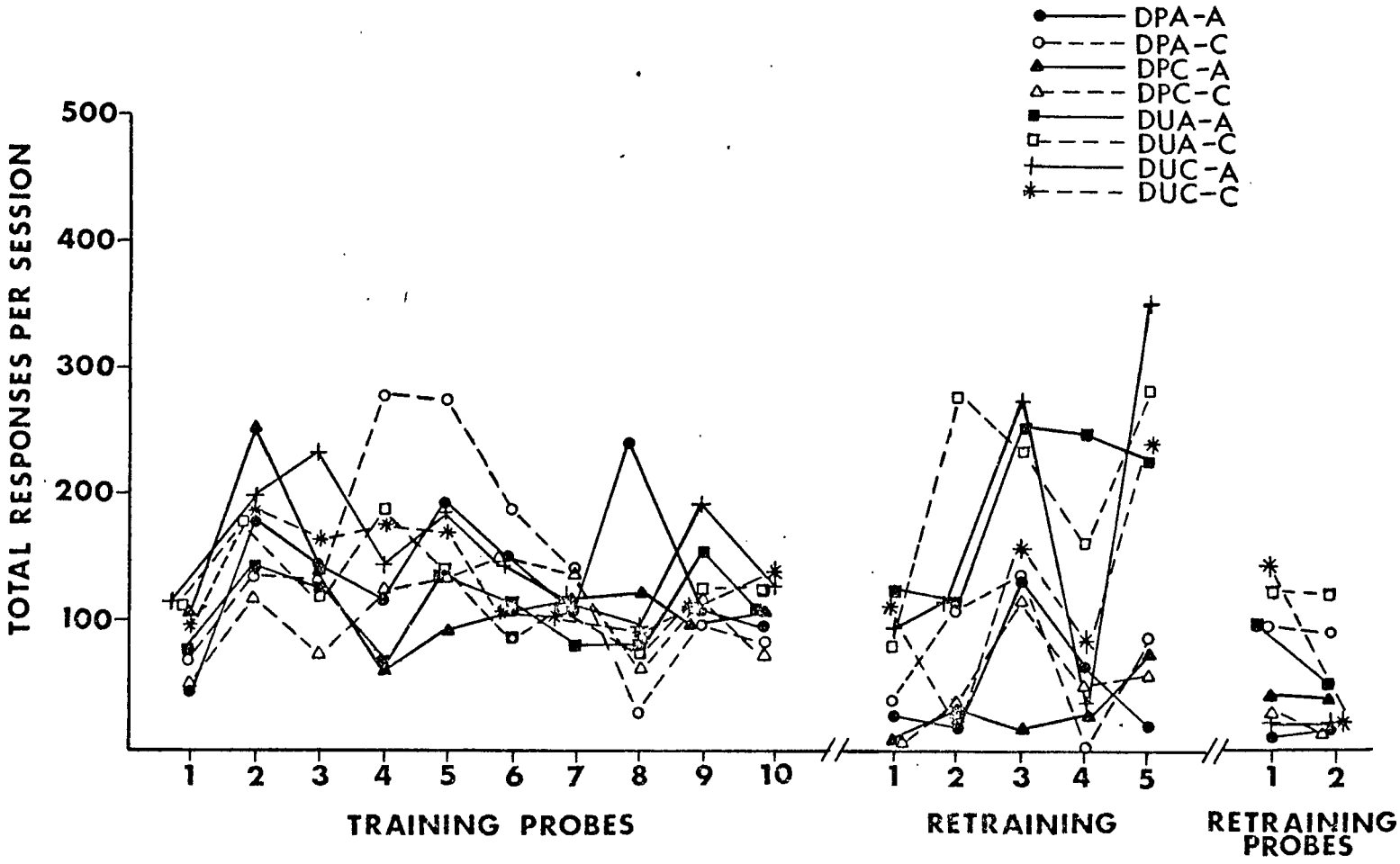


FIGURE 10

TOTAL RESPONSES PER SESSION FOR DISCRIMINATION CONTROL SUBJECTS (NONDISCRIMINATION) EXPERIMENT III

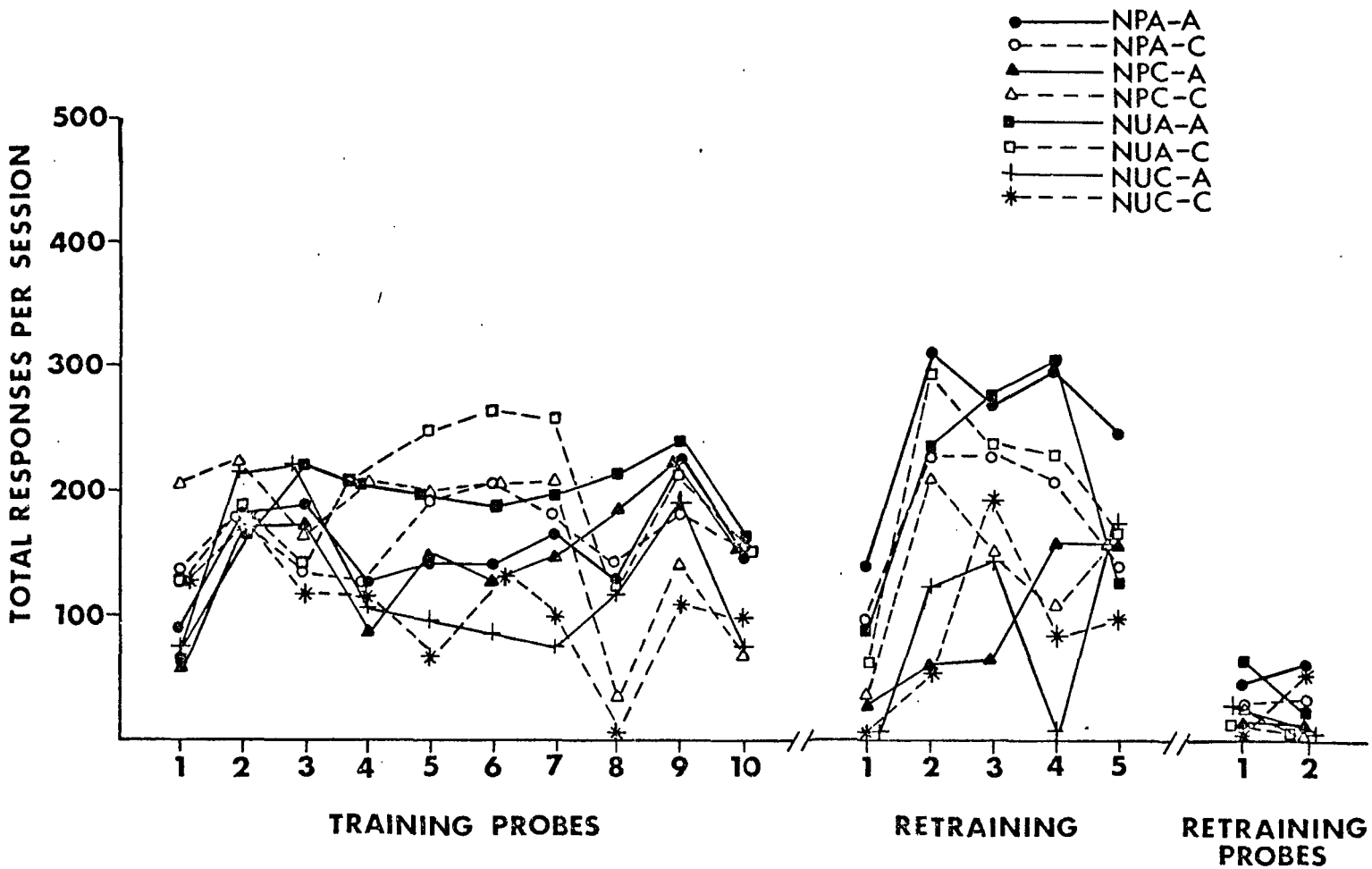


FIGURE 11

all Discrimination groups and all Nondiscrimination control groups are presented graphically in Figures 12 and 13. All between-group comparisons of the individual groups represented produced nonsignificant scores.

Figure 14 graphically presents mean percent correct scores combined for d-amphetamine sessions and for cocaine sessions for all Discrimination and Nondiscrimination groups. The Discrimination groups (solid lines) tend to have higher percent correct scores for extinction tests during Training than do Nondiscrimination groups (broken lines).

The Discrimination-Nondiscrimination comparison indicated a significant difference between the mean arcsin percent correct scores of the combined Discrimination and combined Nondiscrimination groups ($t=4.044^{***}$, $df=32$, $p<.001$). This finding is supported by significant scores for comparisons of subgroups (DP vs NP, $t=2.477^{*}$, $df=16$, $p=.019$; DU vs NU, $t=3.148^{**}$, $df=15$, $p=.004$). The positive sign of the t-score indicates that the Discrimination groups produced significantly higher percent correct scores than did the Nondiscrimination groups.

Retraining

Mean total responses during reinforced practice in Retraining, for Discrimination and Nondiscrimination groups are represented in Figures 10 and 11. All between-group comparisons of individual groups produced nonsignificant scores. Correlated t-tests between d-amphetamine sessions and cocaine

PER CENT CORRECT RESPONSES FOR SUBJECTS TRAINED ON A TWO BAR OPERANT DISCRIMINATION TASK (AMPHETAMINE vs. COCAINE) EXPERIMENT III

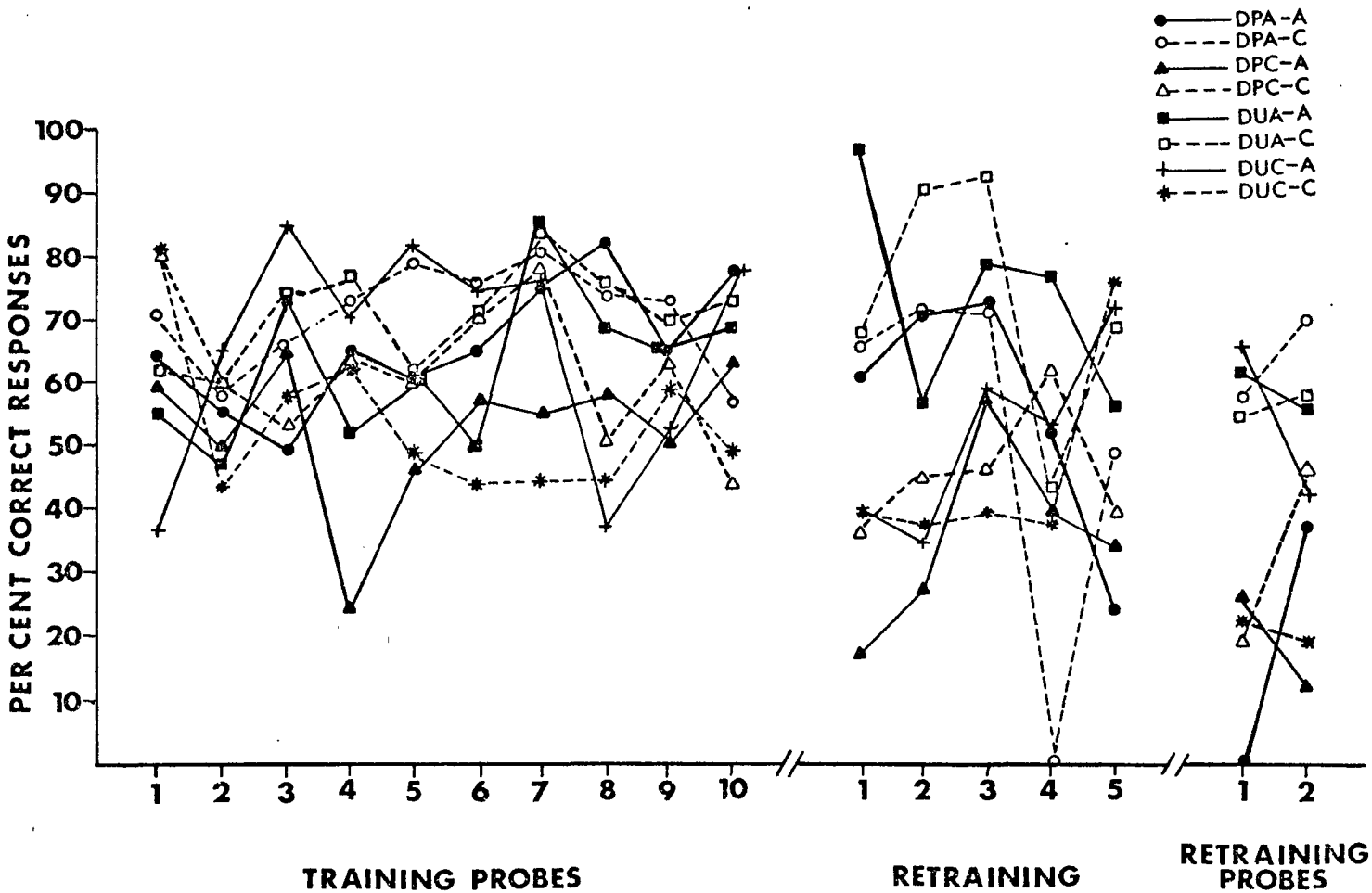


FIGURE 12

PER CENT CORRECT RESPONSES FOR DISCRIMINATION CONTROL SUBJECTS (NONDISCRIMINATION) EXPERIMENT III

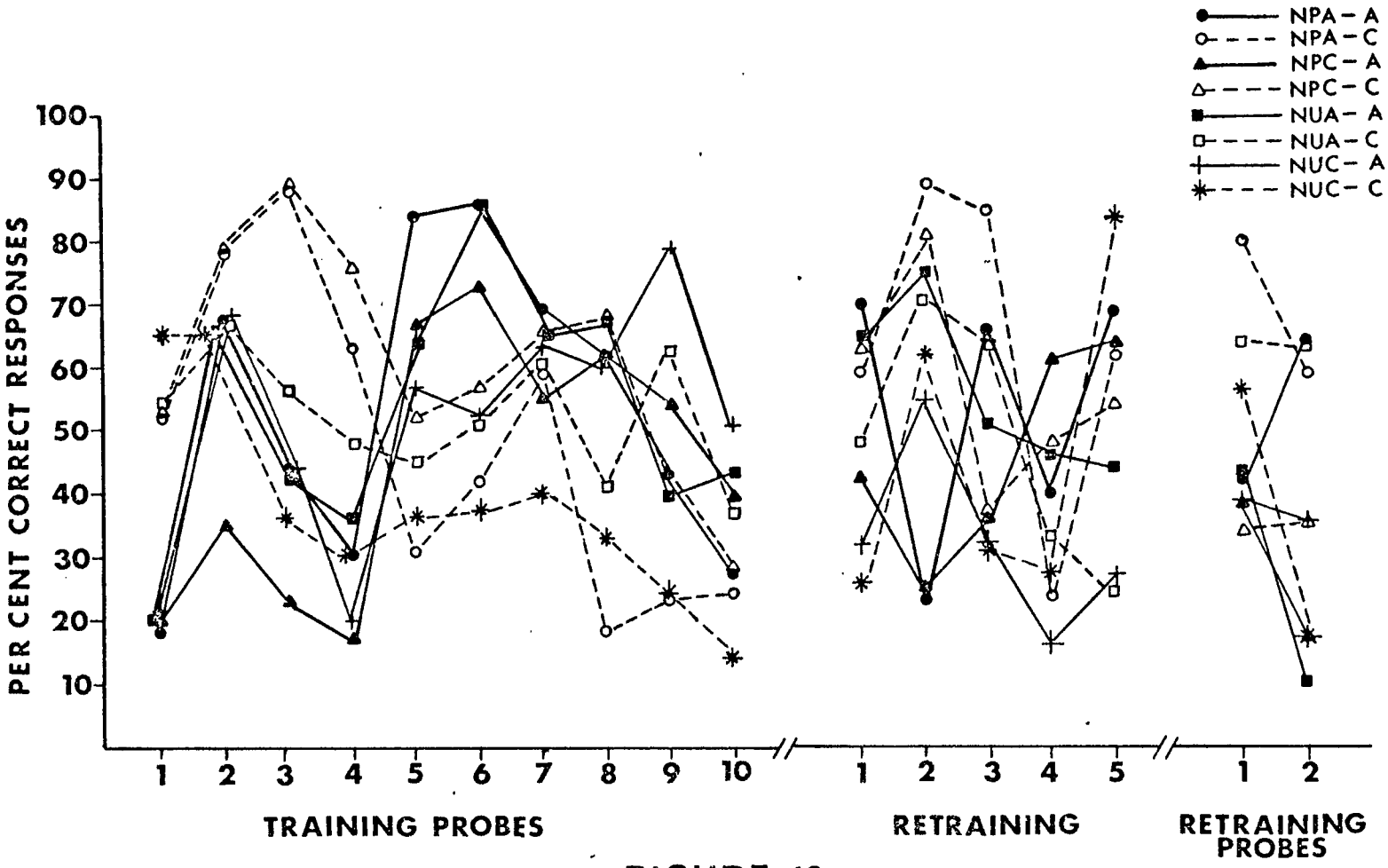


FIGURE 13

MEAN PER CENT CORRECT DURING TRAINING PROBES FOR DISCRIMINATION AND NONDISCRIMINATION GROUPS (EXPERIMENT III)

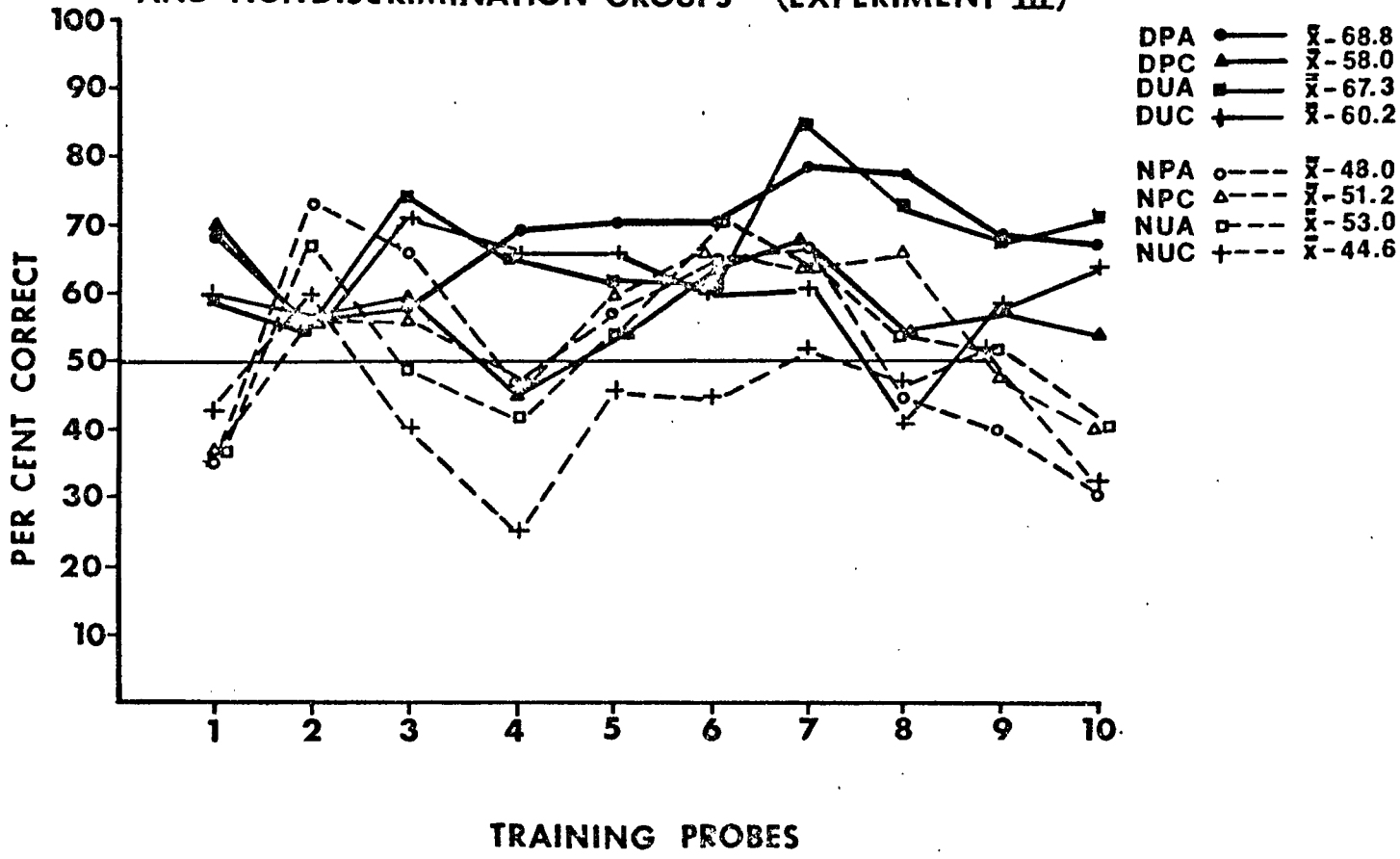


FIGURE 14

sessions for each group also produced no significant scores. Mean total responses for all Paired (solid lines) and all Unpaired (broken lines) groups combined for amphetamine and cocaine sessions are presented in Figure 15. Among the Discrimination groups the group which had received paired drug-shock experience (DPA,DPC) tended to emit fewer responses per session than did the groups which had not received paired drug-shock experience (DUA,DUC). This relationship does not appear for the Nondiscrimination-Paired and -Unpaired groups.

Figure 16 depicts the mean total responses for combined Discrimination-Paired (DP) and Nondiscrimination-Paired (NP) groups. The total response scores for Discrimination-Paired groups (solid lines) are generally lower than for the Nondiscrimination-Paired groups (broken lines).

Comparison of combined DP and NP groups resulted in a significant score ($t=-2.042^{*}$, $df=16$, $p=.050$), whereas the DU vs NU comparison produced a nonsignificant score ($t=0.269$, $df=15$, $p>.500$). In addition, there was a significant difference between the DP and the DU groups ($t=-3.137^{**}$, $df=17$, $p=.004$), but the difference between the NP and NU groups was not significant ($t=0.144$, $df=14$, $p>.500$). These four comparisons suggest that both the type of training (Discrimination or Nondiscrimination) and shock condition (Paired or Unpaired) significantly affect the total number of responses per session.

Mean percent correct scores for reinforced practice during Retraining, for Discrimination and Nondiscrimination

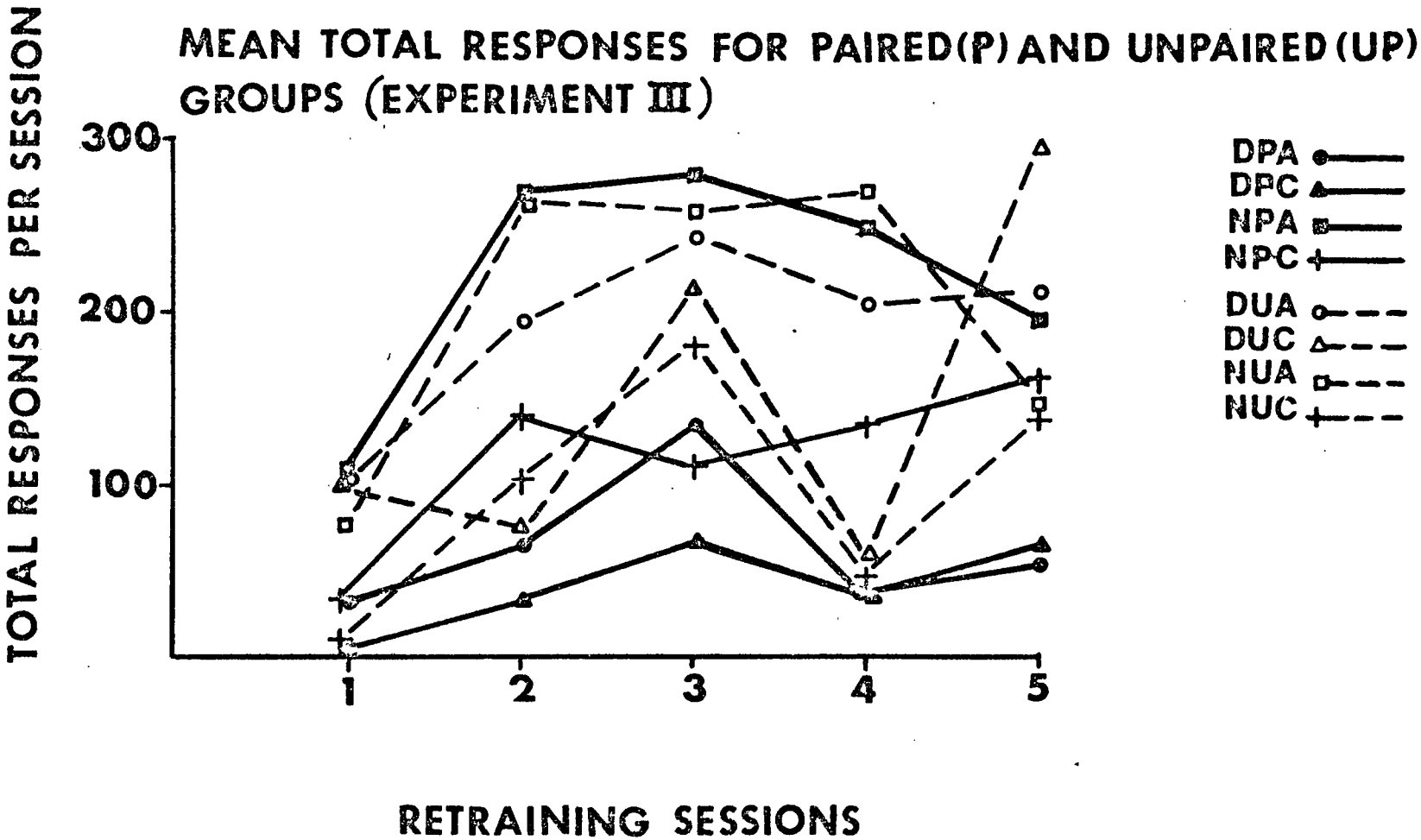

MEAN TOTAL RESPONSES FOR PAIRED(P) AND UNPAIRED(UP) GROUPS (EXPERIMENT III)
TOTAL RESPONSES PER SESSION
300
200
100
1
2
3
4
5
RETRAINING SESSIONS
DPA
DPC
NPA
NPC
DUA
DUC
NUA
NUC

FIGURE 15

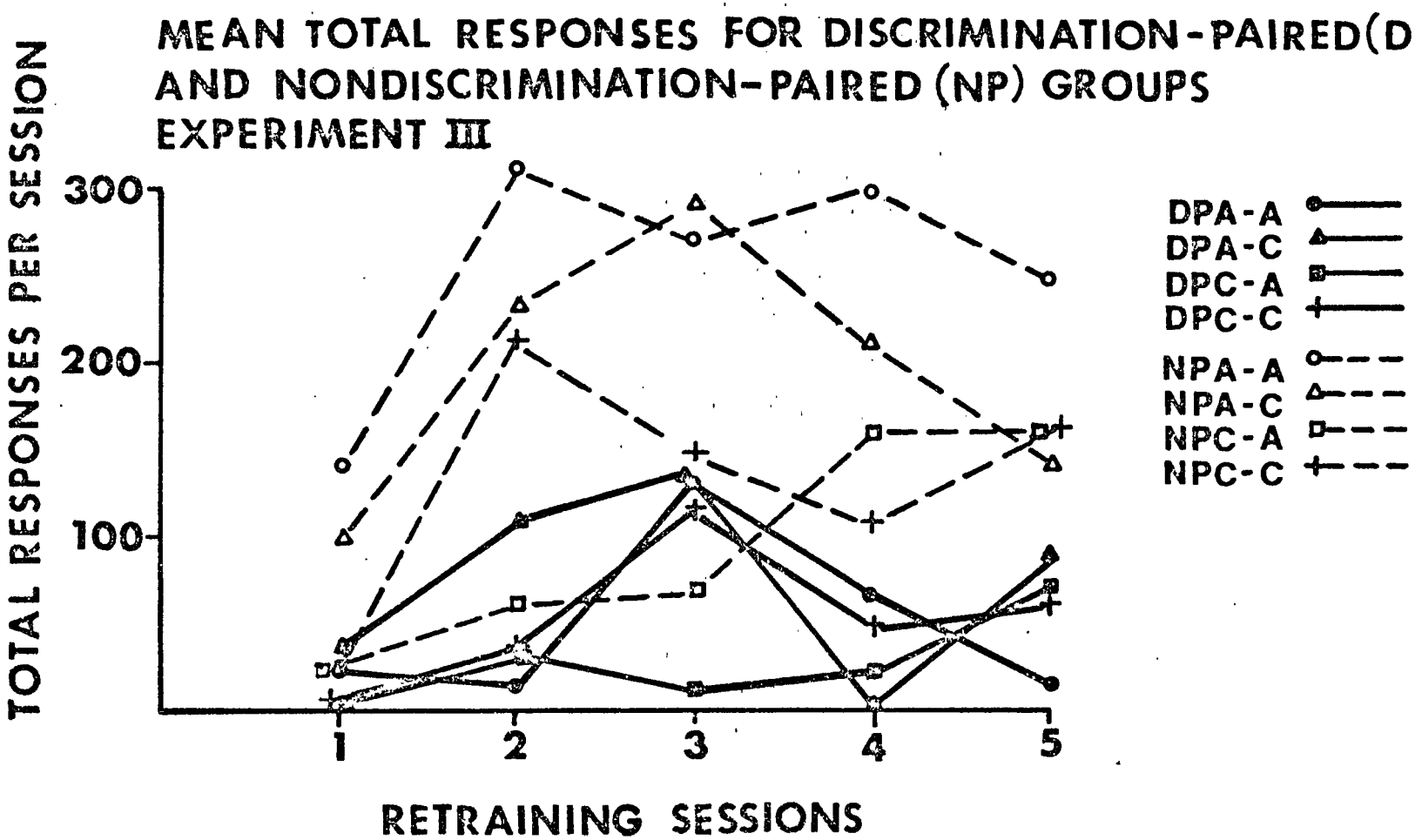

MEAN TOTAL RESPONSES FOR DISCRIMINATION-PAIRED(DP) AND NONDISCRIMINATION-PAIRED (NP) GROUPS
EXPERIMENT III
TOTAL RESPONSES PER SESSION
300
200
100
1
2
3
4
5
RETRAINING SESSIONS
DPA-A
DPA-C
DPC-A
DPC-C
NPA-A
NPA-C
NPC-A
NPC-C

FIGURE 16

groups are represented in Figures 12 and 13. No significant t-scores were obtained among the individual comparisons made (Appendix B). The nonsignificant scores suggest that neither the type of training (Discrimination or Nondiscrimination) nor shock condition (Paired or Unpaired) affected the percent correct scores of the subjects.

Retraining Probes

The number of extinction probes conducted during Retraining was small due to the early termination of the experiment. However, individual comparisons between d-amphetamine sessions and cocaine sessions were conducted for each of the experimental groups. No significant t-scores were obtained for mean total response measures or for arcsin percent correct scores. Mean total response during retraining probes are presented in Figures 10 and 11. Mean percent correct values are presented in Figures 12 and 13.

EXPERIMENT IV

This experiment examined selective response suppression following discrimination between a drug and a nondrug state. Animals were trained on a d-amphetamine versus saline, two-bar discrimination task. It was hypothesized that suppression would be cue-specific if the cues could be discriminated.

Subjects

Twenty adult male Fisher rats of the type described in Experiment I were used. Weight maintenance and water access were the same as in the previous experiments.

Apparatus

The five operant chambers and programming equipment described in Experiment I were used.

Procedure

Design. The design was a 2x2 factorial design in which the variables examined were: (1) Drug-shock relationship during classical conditioning phase (Paired or Unpaired), and (2) Condition which was paired with shock (Drug or Nondrug state). Table 11 shows the four groups resulting from the factorial design. Nondiscrimination control groups were not employed in this study.

Training. The discrimination training procedure was the same as that described in Experiment III. Instead of two drugs, however, the discriminative cues used were either

TABLE 11

Design matrix for initial training groups and subsequent division into four shock treatment groups (Experiment IV).

TRAINING	DRUG-SHOCK PRESENTATIONS		Abbreviations
Discrimination (d-amphetamine vs. saline)	Paired	d-amphetamine n=5	PA
		cocaine	PC
	Unpaired	d-amphetamine	UA
		cocaine	UC

0.8 mg/kg d-amphetamine or an equivalent volume of saline solution. Cue-lever associations were consistent for all animals but randomized within the groups. Forty-three discrimination training sessions were conducted.

Drug-Shock Administration. Shock administration procedures were the same as in Experiment III. Five animals received amphetamine injections and five animals received saline injections 15 minutes prior to shock sessions. The remaining 10 animals received shock at approximately the same time but were given either drug or saline on a random time schedule.

Retraining. Following shock sessions fourteen days of reinforced practice were initiated. Each day subjects were injected with either d-amphetamine or saline, with the appropriate bar operative. On the second day and every fourth day after, a 10 minute extinction probe was conducted and followed by 15 minutes of reinforced practice. The experiment was terminated at this point because of the illness or death of a number of subjects. These procedures resulted in four extinction probes, two d-amphetamine probes and two saline probes. Cumulative recordings, total number of responses, and percent correct responses were recorded. No separate suppression tests were required since the discriminative cues (d-amphetamine presence or absence) were present immediately upon reinstatement of operant sessions.

RESULTS

Total response scores and arcsin percent correct values were obtained as in Experiment III. Scores were subdivided into four groupings (1) Training--reinforced practice sessions (2) Training Probes--10 minute extinction tests (3) Retraining--reinforced practice sessions following the drug-shock phase of the study during which no response measures were taken, and (4) Retraining Probes--10 minute extinction tests.

The data were analyzed by means of multiple t-tests selected on the basis of the experimental design. All t-tests for mean total response scores are presented in Appendix C. The individual comparisons which were made, the obtained differences, and the t-scores are presented. T-tests for arcsin percent correct values are presented in Appendix D.

Training

The mean total responses per session for the Paired and the Unpaired groups are presented in Figure 17. All animals received discrimination training between d-amphetamine and saline. The response total is generally lower for the d-amphetamine sessions than for the saline sessions (regardless of shock condition). Correlated t-tests between d-amphetamine sessions and saline sessions resulted in one significant score (PS-A vs PS-S, $t=-3.05^*$, $df=4$, $p=.038$).

T-tests examining effects of shock condition (Paired vs Unpaired) and drug (d-amphetamine vs cocaine) resulted in no

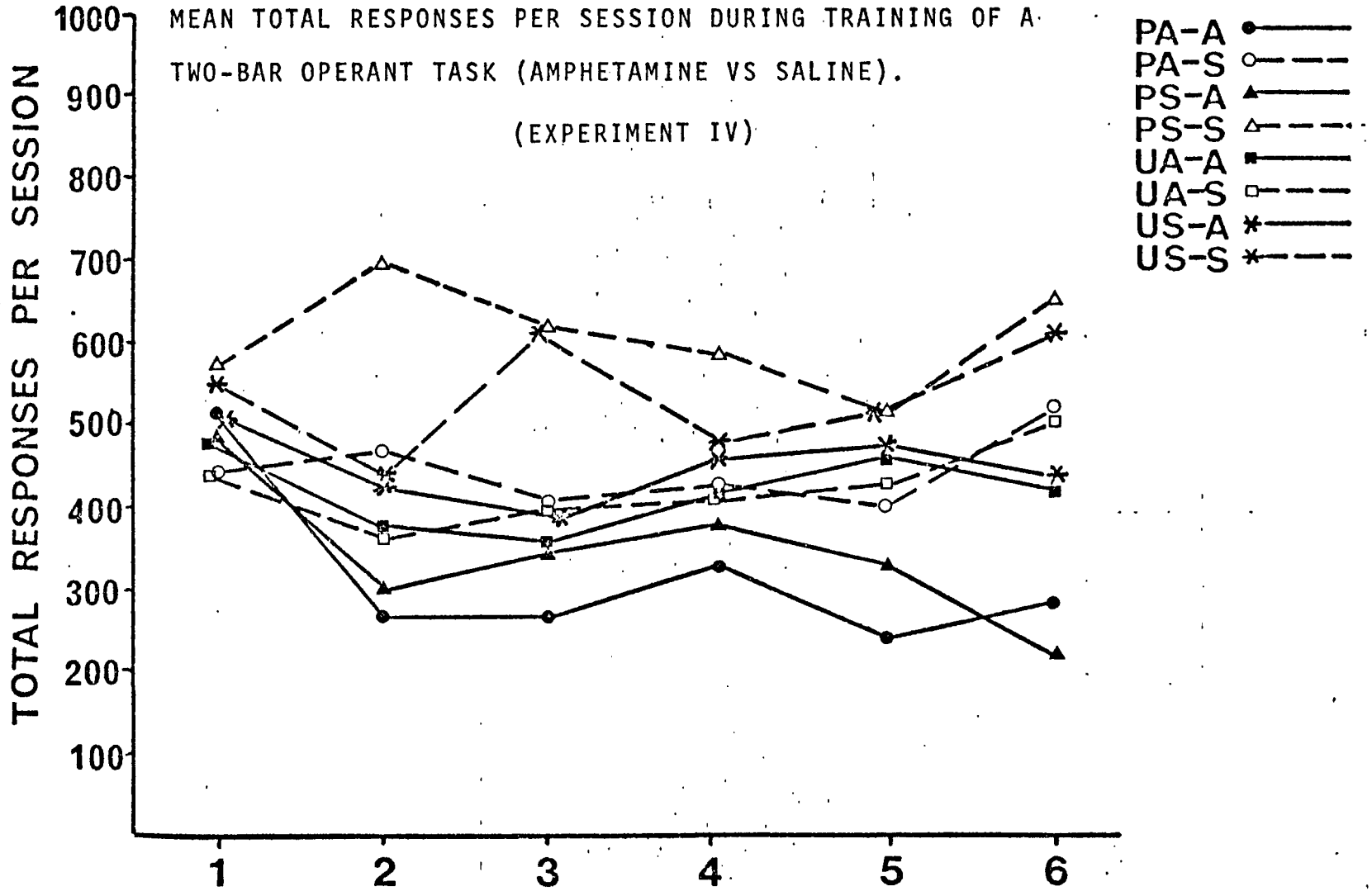

MEAN TOTAL RESPONSES PER SESSION DURING TRAINING OF A TWO-BAR OPERANT TASK (AMPHETAMINE VS SALINE).
(EXPERIMENT IV)
TOTAL RESPONSES PER SESSION
1000
900
800
700
600
500
400
300
200
100
1
2
3
4
5
6
TRAINING SESSIONS
PA-A
PA-S
PS-A
PS-S
UA-A
UA-S
US-A
US-S

FIGURE 17

significant scores.

T-tests for arcsin percent correct scores produced no significant scores.

Training Probes

Mean total response scores for all groups are represented in Figure 18. T-tests examining the effects of shock condition and of drug-shock experience produced no significant scores. However, correlated t-tests between d-amphetamine sessions and cocaine sessions resulted in significant scores for all groups (PA,PS,UA,US) (Appendix C, Table 3). All the correlated t-scores were negative in sign, a fact which indicated that the total response scores were higher during saline sessions than during d-amphetamine sessions.

Mean percent correct scores for all groups are represented in Figure 19. No t-scores indicating significant effects were obtained.

Retraining

Mean scores for total response measures and percent correct values during retraining are represented in Figures 18 and 19 respectively. The response total of all groups was higher during saline sessions than during d-amphetamine sessions. One significant t-score was obtained for arcsin percent correct values (UA vs US, $t=3.119^*$, $p=.017$).

Retraining Probes

The number of extinction probes conducted during retraining was small because of early termination of the experiment.

TOTAL RESPONSES PER SESSION FOR SUBJECTS TRAINED ON A TWO BAR OPERANT DISCRIMINATION TASK (AMPHETAMINE vs. SALINE)
EXPERIMENT IV

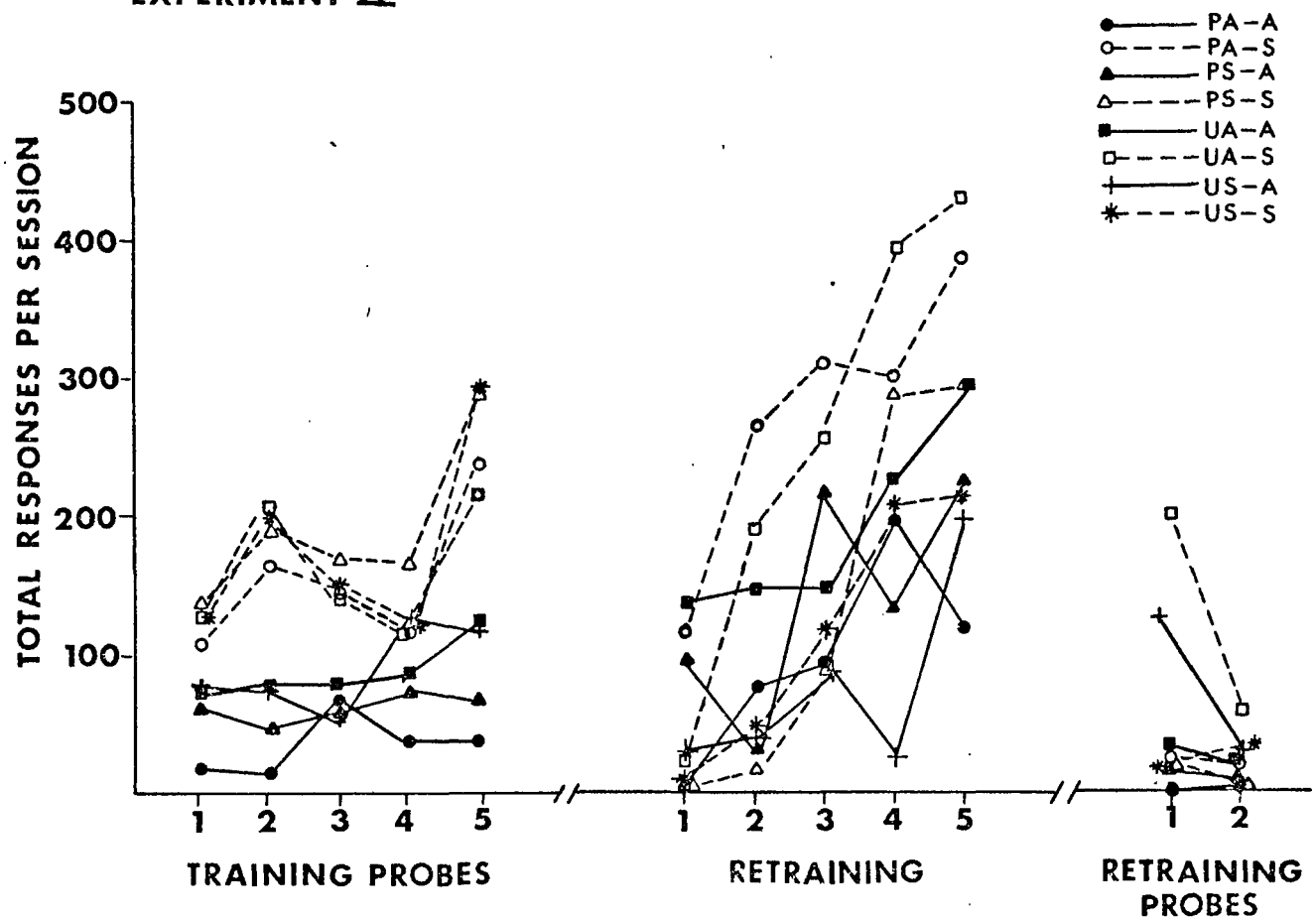


FIGURE 18

PER CENT CORRECT RESPONSES FOR SUBJECTS TRAINED ON AN OPERANT DISCRIMINATION TASK(AMPHETAMINE vs. SALINE) EXPERIMENT IV

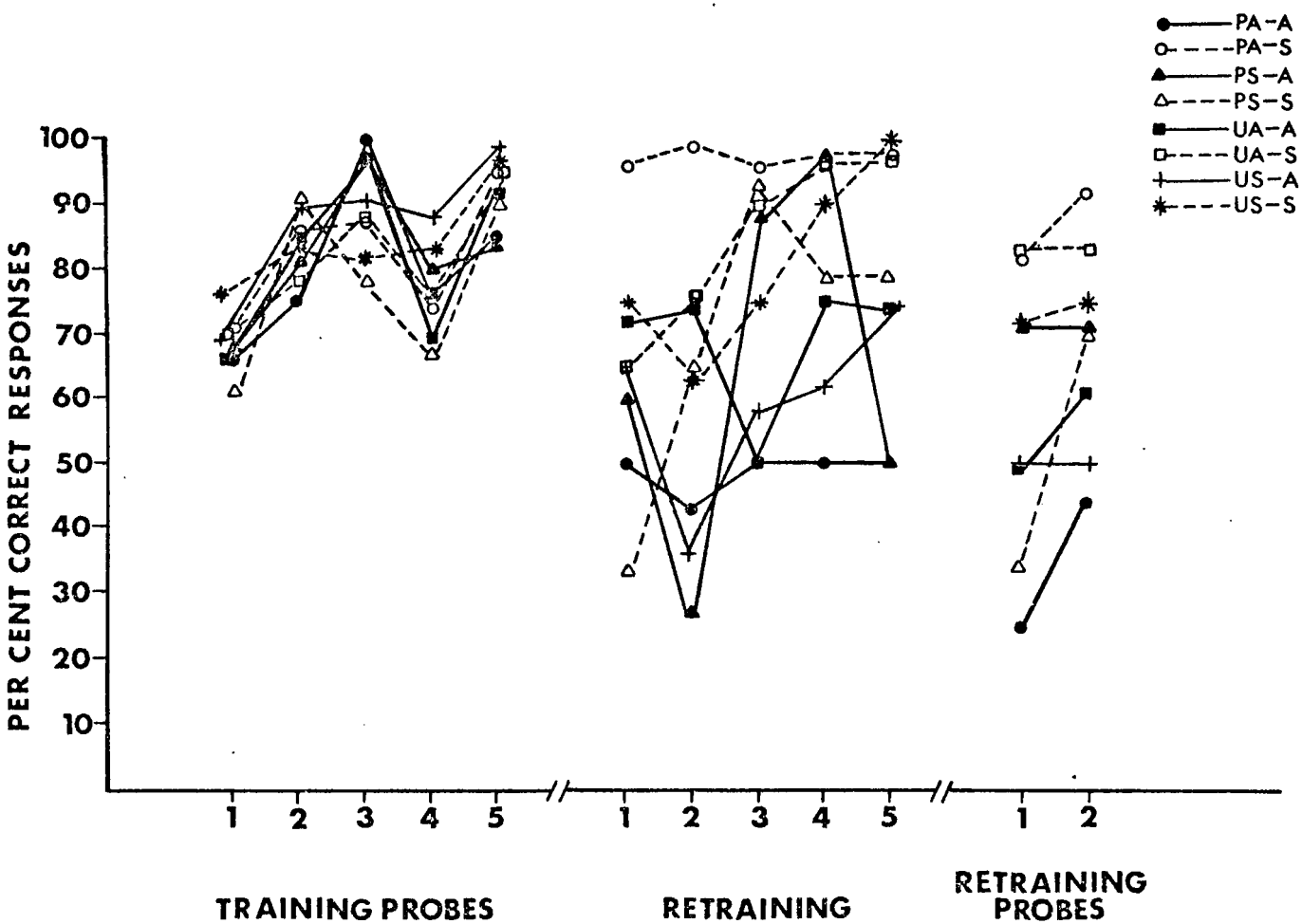


FIGURE 19

Comparisons were made, however, between d-amphetamine sessions and saline sessions within each group. No significant t-scores were obtained for mean total response measures or for arcsin percent correct scores.

DISCUSSION

The results of Experiment I indicate two major conclusions: (1) that a drug can serve as a conditioned stimulus (CS) for suppression of an operant response, and (2) that the suppression response conditioned to one drug state can generalize to a second drug state. Those subjects given paired d-amphetamine-shock experience subsequently suppressed their response rate on a VI operant response following d-amphetamine administration. Control subjects received equivalent but unpaired d-amphetamine-shock experiences slightly increased their response rates following drug administration. In addition, animals receiving paired d-amphetamine-shock experience suppressed their response rates following administration of cocaine hydrochloride. The suppressed response rates indicated that the animals generalized from d-amphetamine sulfate to cocaine hydrochloride, since they had not previously experienced cocaine injections. Response rates of animals with previous unpaired d-amphetamine-shock experience increased slightly following cocaine injections.

The amount of suppression exhibited by the animals in the paired groups (PA,PC) is striking in that it is much more

exaggerated than the suppression which occurred after a 20 day break between the Training and Retraining phases. The last day of Retraining and the first day of Suppression Testing were conducted in two consecutive sessions. These results suggest that the shock-paired d-amphetamine injections acquired aversive properties, although response suppression has also been reported for CSs signalling appetitive events (Azrin and Hake, 1969).

Animals tested with cocaine displayed less response suppression and appeared to extinguish suppression in fewer trials than did those animals tested with d-amphetamine. Although the differences between the d-amphetamine-tested and cocaine-tested subjects were not significant, the lowered response suppression suggests a generalization decrement to the novel drug. An alternative explanation is suggested by performance of the Unpaired groups (UA,UC) during suppression testing. Response rates of both groups increased slightly from baseline. The increase in response rates was more pronounced for the cocaine-tested subjects than for the d-amphetamine-tested subjects. Since the cocaine-tested animals of the Paired group did not suppress their response rates as much as the d-amphetamine-tested animals, it is possible that an unconditioned effect of the cocaine, rather than a generalization decrement, caused the reduced suppression. Similar experiments using drugs with different unconditioned properties would be useful in separating conditioned effects from unconditioned effects.

Experiment II produced a slightly more durable suppression response than that obtained in Experiment I, by removing some of the possible exteroceptive cues from the testing situation. In addition, extended suppression testing provided further information concerning the time course of extinction of suppression. In Experiment I the suppression response was measured for six days. Operant sessions and drug-shock sessions were conducted in separate chambers. The shock apparatus did not have response levers, food dish, or sound-attenuating chambers. These differences between the two apparatuses could have provided differential exteroceptive cues concerning the delivery of shock. Testing in the operant chamber could have reduced the tendency of the animal to suppress due to removal of part of the CS complex of which the drug stimulus was a part. Experiment II was designed to test the hypothesis that limitation of such cues by conducting shock trials and test sessions in the same apparatus would increase the resistance to extinction of the suppression response. Suppression testing was extended to twelve sessions. Suppression was obtained as in Experiment I. Generalization from d-amphetamine to cocaine also occurred. Cocaine testing again resulted in less response suppression than d-amphetamine for the Paired groups and in greater response increase for the Unpaired groups. Comparison of Figure 4 and Figure 6 indicates that the amount of suppression obtained in Experiments I and II is approximately the same.

The suppression appears to be slightly more resistant to extinction in Experiment II. Response recovery lagged approximately two days behind the recovery rates observed in Experiment I. At the twelfth day of suppression testing, the highest response total observed among the session means was equivalent to 80% of the baseline rate. This resistance to extinction indicates that the suppression response is sufficiently durable to be used in parametric studies using repeated drug administration. Drug-shock sessions might be scheduled between testing days in a manner similar to that used in operant drug discrimination studies in which discrimination training sessions intervene between extinction tests (Kubena and Barry, 1969; Waters, Richards, and Harris, 1972; Winter, 1975). This possibility suggests that the conditioned suppression paradigm may be useful in studying drug stimulus control. Generalization gradients could be obtained with such repeated drug injections as they are obtained in discrimination experiments.

Another experimental possibility suggested by Experiment II is the use of the conditioned suppression paradigm for investigation of interoceptive-exteroceptive stimulus complexes. The relative contribution of the internal and external stimuli involved may be assessed. The weakness of the contribution of the external apparatus cues compared to the drug cue is suggested by the finding that no suppression occurred in the animals which had received only shock in the

operant chamber without drug pairing. The external physical stimuli of the apparatus did not elicit a suppression response in the absence of a drug CS. There are a number of possible causes for this finding. The stimulus situation of the operant chamber may have been too vague or diffuse to serve as a clear stimulus for shock delivery. The unconditioned effects of the drug stimulus may have dominated the conditioned stimulus properties of the apparatus. Previous reinforcement not associated with the drug in the operant chamber may have counteracted aversively conditioned drug effects.

Further information concerning the relative contribution of internal and external stimuli in learned behavior is provided by the observation that the presence of the negative apparatus cues in Experiment I did not produce an appreciably lower degree of conditioned suppression than that obtained in Experiment II. Removal of the external apparatus cues merely prolonged the duration of the suppression effect. These findings agree closely with the result of interoceptive studies involving stimulation of the viscera, which found that interoceptive stimuli generally dominate exteroceptive stimuli when the two types of stimulation interact (Razran, 1961).

Experiment III was designed to test the hypothesis that prior operant training of a d-amphetamine-cocaine discrimination might minimize generalization of a subsequent classically conditioned response from d-amphetamine to cocaine. In other words, the experiment explored whether discrimination learned

for one task would transfer to a second task.

Since two drugs were involved in the Training phase, each drug associated with a different lever, effects of the drug-shock pairing might have altered total response rate or discrimination accuracy as reflected by percent correct scores. These two response measures were analyzed for the Training phase and for Training Probes in order to provide a comparison for the measures taken after the drug-shock presentations. The total response scores for the Discrimination groups did not differ significantly from the total response scores for the Nondiscrimination groups. However, the Discrimination groups did perform significantly better in discriminating the two drugs, as reflected by percent correct scores, during both Training and Training Probes.

The finding that rats can discriminate two drugs at dosages which were previously reported to generalize agrees with the concept of "overinclusiveness" introduced by Overton (1972). Generalization of responses to different stimuli can be interpreted to reflect two possible situations: (1) that the subject cannot discriminate the stimuli, or (2) that the subject perceives the stimuli to be similar enough to be treated alike in a given situation. Overton proposed the term "overinclusiveness" to apply to those cases in which generalization occurs when discrimination is possible. The term is pertinent here because its connotations imply that while drug generalization studies are used to suggest

similarities between drug effects, discrimination studies may also delineate some differences. Such differences should not be overlooked.

Huang and Ho (1974) reported that 7.5mg/kg cocaine injections resulted in 90% "amphetamine" responses after training of a two-bar d-amphetamine vs saline discrimination using a d-amphetamine dose of 0.8mg/kg. Although the percent correct scores are somewhat low in Experiment III, the significant t-score obtained for Discrimination vs Nondiscrimination indicates that d-amphetamine can be discriminated from cocaine at doses which normally elicit generalization responses. This finding suggests the use of psychophysical techniques to analyze perception of drug states.

The analysis of total responses during Retraining suggests that training condition (Discrimination vs Nondiscrimination interacts with the drug-shock condition (Paired vs Unpaired) in its effect on total response scores during Retraining. Among the Discrimination groups, animals which received paired drug-shock experience emitted significantly fewer responses than those which received unpaired drug-shock experience. Among the Nondiscrimination groups, this relationship did not exist. The expected response suppression following drug-shock pairing occurred only for those subjects which were trained to discriminate the drugs. However, cue specific suppression did not occur. These data suggest that the discrimination acquired during the training phase of

Experiment III did not transfer to the classically conditioned response suppression phase. Suppression of response rate generalized from d-amphetamine to cocaine. External stimuli provided by the physical aspects of the apparatus were insufficient to produce suppression. Support for this conclusion is provided by the nonsignificant score resulting from the NP vs NU comparison ($t=0.144$, $df=14$, $p>.500$).

Since the number of extinction probes conducted during retraining was small, few conclusions can be made on the basis of the data. Furthermore, none of the t-tests conducted for the retraining probes of Experiment III produced significant scores.

Since cue-specific suppression was not obtained in Experiment III, despite the prior discrimination training, it was hypothesized that the generalization was due to the difficulty of the discrimination task. Although subjects were trained extensively, the obtained percent correct scores remained low throughout the study. Experiment IV was designed to provide an easier discrimination task, which might produce transfer from operant discrimination to response-suppression more readily than a difficult discrimination task. Subjects were trained on a two-bar d-amphetamine vs saline discrimination which (1) was quickly acquired, and (2) produced a higher percentage of lever appropriate responses. Richards and Meyer (1974, personal communication) also found the same characteristics of amphetamine vs saline discrimination on VI schedules.

Amphetamine vs saline discrimination has been produced with little difficulty by other investigators using DRL schedules (Huang and Ho, 1974) and using two schedules for a one-bar discrimination (Harris and Balster, 1968). Although discrimination was established during training, as indicated by high percent correct scores, the results obtained, concerning response suppression, were somewhat unexpected. No cue specific suppression was obtained. Total response scores were higher during saline sessions during the course of recovery in retraining regardless of shock condition (Paired vs Unpaired) or drug condition which was paired with shock (d-amphetamine vs saline). Comparisons made for these two factors resulted in no significant t-scores, in contrast to the significant differences between Paired and Unpaired groups obtained in Experiment III, after d-amphetamine vs cocaine discrimination training. These findings were not anticipated and are difficult to explain. However, two possible explanations may be proposed. Since response totals were higher during initial saline training sessions, the unconditioned differences between saline sessions and d-amphetamine sessions may have obscured the conditioned effects of the drug-shock exposures. Another more plausible hypothesis is that, without explicit discrimination training in the shock phase of the experiment, saline by itself cannot serve the eliciting function of a CS in a classical conditioning paradigm. The "normal" physiological conditions produced by saline injections

may not be associated easily with other stimuli due to their relatively constant presence. Associations with one set of stimuli would presumably be counteracted by associations with numerous other stimuli.

The plausibility of such an hypothesis is supported by the findings of Turner, Broussard, and Braud (1974) who used d-amphetamine as a CS for conditioned shock-elicited aggression (Vernon and Ulrich, 1966). Pairs of subjects which received d-amphetamine injections paired with shock exhibited spontaneous aggressions during d-amphetamine probe sessions. On the other hand, control subjects which received saline injections paired with shock did not exhibit spontaneous aggressions during probe periods. These data suggest that saline injections do not serve as conditioned stimuli in the absence of explicit differentiation procedures. When combined, the findings of Experiments III and IV suggest that discrimination which is relevant to one stimulus situation does not automatically transfer to a second situation. Discrimination was obtained in both cases but differential suppression was not obtained for the cues involved. Since the cell numbers in Experiments III and IV were small, further experimentation would be useful in describing the acquired characteristics of drug states.

One major conclusion suggested by the combined findings of this series of investigations is that drug states can acquire properties differing from their unconditioned effects.

Drug self-administration studies have provided evidence of unconditioned reinforcing properties for both amphetamine and cocaine. Deneau, Yanagita, and Seevers (1964) produced an early example of cocaine self-administration in monkeys. Similar results were obtained by Pickens and Thompson (1966, 1968) with d-amphetamine and cocaine, using rats as subjects. Since neither drug is considered to cause significant physical dependence (Thompson and Schuster, 1968) the self-administration behaviors were interpreted to indicate reinforcing properties. In the present series of studies, the association of the drugs with response-noncontingent shock suggests acquisition of aversive properties.

The acquisition of aversive properties may have applications to the treatment of drug-abuse problems in the future. To date, behaviorally oriented attempts such as aversion therapy have had a low success rate in treatment of drug abuse. Both classical conditioning and operant models have failed to produce enduring results in drug aversion therapies (Rachman and Teasdale, 1969). It is probable that more thorough experimental examination of conditioning parameters will produce useful knowledge concerning manipulation of acquired drug properties (both positive and aversive). Such knowledge may ultimately produce more effective drug-abuse treatment programs.

While the applications of drug CSs to aversive therapy may prove useful, the extension of classical conditioning of

drug stimuli to interoceptive stimuli in general may have wider applications. The possible role of interoceptive stimuli in classically conditioned responses has been largely ignored. The general inaccessibility of internal conditions has been a contributing factor to this state of affairs. However, the generality of classical conditioning phenomena in terms of responses and species, suggests that such classical processes may strongly influence human behavior. A number of investigators have concluded that interoceptive stimuli and drug stimuli in particular are more effective in exerting stimulus control than exteroceptive stimuli when tested under comparable conditions (Razran, 1961; Balster, 1970; Kilbey, Harris, and Aigner, 1972). Overton (1971) provided evidence that marked differences between exteroceptive cues may reach the level of effectiveness of drug cues.

The reasons for the superior effectiveness of drug cues are unclear. Several possible factors have been proposed. Skinner (1953) proposed that differences in attention to particular stimuli may cause differential effectiveness. Terrace (1966) proposed a similar hypothesis. If attention is a crucial factor, then stimulus aspects which promote attention may influence effectiveness of stimulus control. Some such aspects of drug stimuli which could command the attention of the organism are (1) the internal and pervasive nature of stimulus changes which cannot be diminished by lack of external orienting responses (Skinner, 1963); (2) novelty

of the drug state (Bindra, 1959); and (3) a continuum of "preparedness" for different types of stimuli (Seligman, 1970). Although data definitively distinguishing between these alternative explanations are lacking, the relative effectiveness of drug stimuli and of interoceptive stimuli (Razran, 1961) imply that internal stimuli may be conditioned in routine behaviors.

In addition, the similarities between internal and external stimuli, suggest that increased attention to the stimulus role of internal events may prove useful. The tendency of internal events to dominate exteroceptively conditioned responses under laboratory conditions (Airapetyantz, 1952), implies that such interactions may occur outside of the laboratory situation (Razran, 1961; Adam, 1967). Therefore, explanations of behavior, treating only exteroceptive stimuli are likely to be inadequate (Razran, 1961).

Investigation of interoceptive stimulus control has wide research and therapeutic possibilities. It seems likely that although most interoceptive impulses influence behavior without awareness, the contribution of such stimuli to behavioral control is considerable. The assumption that an internal realm of behavior has a memory (an ability to be modified by experience) is not unwarranted considering visceral cueing and learning. It is probable that conditioned visceral reflexes are continuously established, modified, and extinguished.

Consequently, a complete elucidation of human "psychological" functioning cannot be attained without an understanding of interoceptive systems.

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APPENDIX A

T-TESTS FOR MEAN TOTAL RESPONSES FOR EXPERIMENT III

TABLE 1

T-TESTS FOR MEAN TOTAL RESPONSE SCORES GROUPED BY THREE VARIABLES (TASK, SHOCK CONDITION, AND DRUG) (EXPERIMENT III)

Tests were conducted separately for each cue condition (d-amphetamine or cocaine) and each training block (training and retraining).

TRAINING

Discrimination vs Nondiscrimination

Groups	Difference	df	T-test	Probability
Amphetamine Sessions				
DPA vs NPA	-187.3	7	-1.645	.152
DPC vs NPC	-171.6	7	-0.854	.422
DUA vs NUA	-265.4	7	-2.006	.085
DUC vs NUC	176.3	6	0.494	>.500
Cocaine Sessions				
DPA vs NPA	30.0	6	0.330	>.500
DPC vs NPC	-155.3	7	-0.783	.460
DUA vs NUA	-211.9	7	-2.648*	.034*
DUC vs NUC	176.3	6	0.494	>.500

Paired vs Unpaired

Amphetamine Sessions				
DPA vs DUA	-36.3	7	-0.300	>.500
DPC vs DUC	-201.9	8	-0.831	.431
NPA vs NUA	-114.5	6	-0.887	.410
NPC vs NUC	163.0	5	0.614	>.500
Cocaine Sessions				
DPA vs DUA	142.5	7	2.076	.077
DPC vs DUC	-266.6	8	-0.939	.376
NPA vs NUA	-99.5	6	-0.973	.369
NPC vs NUC	65.1	5	0.290	>.500

Amphetamine-Shock vs Cocaine-Shock

Amphetamine Sessions				
DPA vs DPC	49.8	7	0.328	>.500
DUA vs DUC	-115.8	8	-0.505	>.500
NPA vs NPC	65.4	6	0.347	>.500
NUA vs NUC	342.9	5	1.635	.164
Cocaine Sessions				
DPA vs DPC	203.7	7	1.440	.194
DUA vs DUC	-205.2	8	-0.783	.456
NPA vs NPC	18.5	6	0.101	>.500
NUA vs NUC	182.9	5	1.345	.237

*p<.05

TABLE 1 (Continued)

TRAINING PROBES

Discrimination vs Nondiscrimination

Groups	Difference	df	T-test	Probability
Amphetamine Sessions				
DPA vs NPA	35.8	6	0.85	.428
DPC vs NPC	-26.3	7	-0.381	>.500
DUA vs NUA	-74.1	7	-2.183	.066
DUC vs NUC	40.1	6	0.414	>.500
Cocaine Sessions				
DPA vs NPA	-51.3	6	-1.197	.277
DPC vs NPC	-62.5	7	-0.985	.358
DUA vs NUA	-66.3	7	-1.865	.105
DUC vs NUC	33.0	6	0.378	>.500

Paired vs Unpaired

Amphetamine Sessions				
DPA vs DUA	80.4	7	1.958	.092
DPC vs DUC	-35.4	8	-0.445	>.500
NPA vs NUA	-29.5	6	-0.897	.405
NPC vs NUC	31.0	5	0.394	>.500
Cocaine Sessions				
DPA vs DUA	17.3	7	0.493	>.500
DPC vs DUC	-31.4	8	-0.423	>.500
NPA vs NUA	2.3	6	0.055	>.500
NPC vs NUC	64.7	5	0.958	.382

Amphetamine-Shock vs Cocaine-Shock

Amphetamine Sessions				
DPA vs DPC	69.5	7	1.106	.306
DUA vs DUC	-46.3	8	-0.684	>.500
NPA vs NPC	7.3	6	0.138	>.500
NUA vs NUC	68.0	5	1.110	.173
Cocaine Sessions				
DPA vs DPC	39.1	7	0.660	>.500
DUA vs DUC	-9.7	8	-0.158	>.500
NPA vs NPC	27.8	6	0.555	>.500
NUA vs NUC	89.7	5	1.498	.195

(Table continued on next page)

TABLE 1 (Continued)

RETRAINING

Discrimination vs Nondiscrimination

Groups	Difference	df	T-test	Probability
Amphetamine Sessions				
DPA vs NPA	-202.9	6	-0.967	.371
DPC vs NPC	-65.1	7	-1.807	.114
DUA vs NUA	-16.1	7	-0.090	>.500
DUC vs NUC	74.6	6	0.588	>.500
Cocaine Sessions				
DPA vs NPA	-119.5	6	-0.9111	.398
DPC vs NPC	-80.3	7	-1.057	.326
DUA vs NUA	9.9	7	0.063	>.500
DUC vs NUC	35.3	6	0.436	>.500

Paired vs Unpaired

Amphetamine Sessions				
DPA vs DUA	-141.2	7	-1.418	.200
DPC vs DUC	-144.4	8	-1.744	.120
NPA vs NUA	45.5	6	0.169	>.500
NPC vs NUC	-4.7	5	-0.054	>.500
Cocaine Sessions				
DPA vs DUA	-134.6	7	-1.398	.205
DPC vs DUC	-70.0	8	-1.182	.272
NPA vs NUA	-5.3	6	-0.627	>.500
NPC vs NUC	45.6	5	0.437	>.500

Amphetamine-Shock vs Cocaine-Shock

Amphetamine Sessions				
DPA vs DPC	21.2	7	0.685	>.500
DUA vs DUC	18.0	8	0.153	>.500
NPA vs NPC	158.9	6	0.745	>.480
NUA vs NUC	108.8	5	0.503	>.500
Cocaine Sessions				
DPA vs DPC	20.9	7	0.385	>.500
DUA vs DUC	85.4	8	0.931	>.380
NPA vs NPC	60.1	6	0.416	>.500
NUA vs NUC	110.9	5	0.610	>.500

TABLE 2

T-TESTS FOR MEAN TOTAL RESPONSE SCORES GROUPED BY TASK (DISCRIMINATION vs NONDISCRIMINATION) (EXPERIMENT III)

	Difference	df	T-Scores	Probability
Training	-83.84	33	-1.235	.222
Training Probes	-26.28	33	-1.286	.203
Retraining	-47.18	33	-1.084	.299

TABLE 3

T-TESTS FOR MEAN TOTAL RESPONSE SCORES GROUPED BY TASK AND SHOCK CONDITION (EXPERIMENT III)

TRAINING

Discrimination vs Nondiscrimination

Group	Difference	df	T-Score	Probability
DP vs NP	-128.11	16	-1.646	.110
DU vs NU	-45.72	15	-0.404	>.500

Paired vs Unpaired

DP vs DU	-97.63	17	-0.981	.334
NP vs NU	-15.25	14	-0.173	>.500

TRAINING PROBES

Discrimination vs Nondiscrimination

DP vs NP	-29.10	16	-1.061	.297
DU vs NU	-22.46	15	-0.719	.478

Paired vs Unpaired

DP vs DU	4.75	17	0.158	>.500
NP vs NU	11.39	14	0.420	>.500

RETRAINING

Discrimination vs Nondiscrimination

DP vs NP	-118.09	16	-2.042*	.050
DU vs NU	18.05	15	0.269	>.500

Paired vs Unpaired

DP vs DU	-123.70	17	-3.137**	.004
NP vs NU	12.44	14	0.144	>.500

TABLE 4

CORRELATED T-TESTS FOR MEAN TOTAL RESPONSE SCORES GROUPED BY THREE VARIABLES (TASK, SHOCK CONDITION, AND DRUG) (EXPERIMENT III)

T-tests were computed for amphetamine sessions vs cocaine sessions.

Group	Difference	df	T-Score	Probability
		TRAINING		
DPA	-178.3	3	-7.74**	.004
DPC	-24.2	4	-1.49	.211
DUA	.5	4	0.01	.993
DUC	-88.9	4	-1.40	.234
NPA	39.0	3	1.93	.194
NPC	-7.9	3	-0.22	.841
NUA	54.0	3	0.84	.461
NUC	-105.8	2	-0.93	.449
		TRAINING PROBES		
DPA	14.5	3	0.47	.670
DPC	16.2	4	0.64	.559
DUA	-15.7	4	-1.41	.231
DUC	20.9	4	3.96*	.017
NPA	-10.5	3	-0.57	.609
NPC	-19.3	3	-1.11	.348
NUA	-7.8	3	-0.60	.593
NUC	13.8	2	0.95	.444
		RETRAINING		
DPA	-22.7	3	-2.28	.107
DPC	-23.0	4	-1.00	.374
DUA	-16.0	4	-0.85	.445
DUC	51.4	4	1.31	.262
NPA	60.7	3	0.73	.518
NPC	-38.2	3	-.56	.615
NUA	9.9	3	0.32	.767
NUC	12.1	2	0.65	.581
		RETRAINING PROBES		
DPA	-20.38	3	-1.22	n.s.
DPC	1.20	4	0.10	n.s.
DUA	-103.4	4	-1.789	n.s.
DUC	48.8	4	1.17	n.s.
NPA	39.75	3	.82	n.s.
NPC	-5.37	3	-0.27	n.s.
NUA	15.88	3	0.51	n.s.
NUC	-4.33	2	-0.30	n.s.

*$p<.05$
**$p<.01$

APPENDIX B

T-TESTS FOR ARCSIN PERCENT CORRECT SCORES FOR EXPERIMENT III

TABLE 1

T-TESTS FOR MEAN ARCSIN PERCENT CORRECT SCORES GROUPED BY THREE VARIABLES (TASK, SHOCK CONDITION, AND DRUG) (EXPERIMENT III)

TRAINING

Discrimination vs Nondiscrimination

Groups	Difference	df	T-test	Probability
Amphetamine Sessions				
DPA vs NPA	0.112	6	0.845	.431
DPC vs NPC	0.064	7	0.739	.484
DUA vs NUA	0.229	7	1.943	.094
DUC vs NUC	0.184	6	0.911	.398
Cocaine Sessions				
DPA vs NPA	0.140	6	1.248	.259
DPC vs NPC	0.055	7	0.678	>.500
DUA vs NUA	0.227	7	1.473	.185
DUC vs NUC	-0.016	6	-0.076	>.500

Paired vs Unpaired

Amphetamine Sessions				
DPA vs DUA	-0.066	7	-0.518	>.500
DPC vs DUC	0.057	8	0.349	>.500
NPA vs NUA	0.050	6	0.418	>.500
NPC vs NUC	0.176	5	2.582	.050
Cocaine Sessions				
DPA vs DUA	-0.052	7	-0.335	>.500
DPC vs DUC	0.066	8	0.398	>.500
NPA vs NUA	0.036	6	0.323	>.500
NPC vs NUC	-0.005	5	-0.065	>.500

Amphetamine-Shock vs Cocaine-Shock

Amphetamine Sessions				
DPA vs DPC	0.012	7	0.090	>.500
DUA vs DUC	0.136	8	0.861	>.500
NPA vs NPC	-0.035	6	-0.639	>.500
NUA vs NUC	0.091	5	0.633	>.500
Cocaine Sessions				
DPA vs DPC	0.024	7	0.221	>.500
DUA vs DUC	0.142	8	0.738	.482
NPA vs NPC	-0.060	6	-0.797	.456
NPC vs NUC	-0.101	5	-0.820	.450

TABLE 1 (Continued)

TRAINING PROBES

Discrimination vs Nondiscrimination

Groups	Difference	df	T-test	Probability
Amphetamine Sessions				
DPA vs NPA	0.160	6	1.615	.158
DPC vs NPC	0.136	7	0.871	.413
DUA vs NUA	0.157	7	1.625	.149
DUC vs NUC	0.213	6	1.301	.242
Cocaine Sessions				
DPA vs NPA	0.283	6	3.003	.024
DPC vs NPC	0.029	7	0.332	>.500
DUA vs NUA	0.288	7	4.292	.004
DUC vs NUC	0.207	6	1.030	.343
Paired vs Unpaired				
Amphetamine Sessions				
DPA vs NPA	0.004	7	0.038	>.500
DPC vs NPC	-0.191	8	-1.281	.237
DUA vs NUA	0.001	6	0.013	>.500
DUC vs NUC	-0.114	5	-0.686	>.500
Cocaine Sessions				
DPA vs NPA	-0.010	7	-0.115	>.500
DPC vs NPC	0.111	8	0.715	.496
DUA vs NUA	-0.005	6	-0.081	>.500
DUC vs NUC	0.288	5	2.755	.041
Amphetamine-Shock vs Cocaine-Shock				
Amphetamine Sessions				
DPA vs DPC	0.135	7	0.807	.447
DUA vs DUC	-0.059	8	-0.695	>.500
NPA vs NPC	0.112	6	1.567	.169
NUA vs NUC	-0.004	5	-0.020	>.500
Cocaine Sessions				
DPA vs DPC	0.103	7	1.027	.339
DUA vs DUC	0.224	8	1.491	.175
NPA vs NPC	-0.150	6	-1.940	.101
NUA vs NUC	0.143	5	1.561	.180

(Table continued on next page)

TABLE 1 (Continued)

RETRAINING

Discrimination vs Nondiscrimination

Groups	Difference	df	T-test	Probability
Amphetamine Sessions				
DPA vs NPA	0.121	6	0.415	>.500
DPC vs NPC	-0.091	7	-0.369	>.500
DUA vs NUA	0.295	7	1.195	.272
DUC vs NUC	0.336	6	0.982	.365
Cocaine Sessions				
DPA vs NPA	-0.085	6	-0.287	>.500
DPC vs NPC	-0.099	7	-0.308	>.500
DUA vs NUA	0.362	7	1.434	.195
DUC vs NUC	0.087	6	0.291	>.500

Paired vs Unpaired

Amphetamine Sessions				
DPA vs NPA	-0.231	7	-0.794	.454
DPC vs NPC	-0.250	8	-0.993	.350
DUA vs NUA	-0.057	6	-0.743	>.500
DUC vs NUC	0.178	5	0.518	>.500
Cocaine Sessions				
DPA vs NPA	-0.259	7	-1.057	.326
DPC vs NPC	0.041	8	0.146	>.500
DUA vs NUA	0.188	6	0.619	>.500
DUC vs NUC	0.228	5	0.652	>.500

Amphetamine-Shock vs Cocaine-Shock

Amphetamine Sessions				
DPA vs DPC	0.307	7	1.082	.315
DUA vs DUC	0.287	8	1.114	.298
NPA vs NPC	0.094	6	0.385	>.500
NUA vs NUC	0.329	5	0.994	.366
Cocaine Sessions				
DPA vs DPC	0.073	7	0.215	>.500
DUA vs DUC	0.373	8	1.913	.093
NPA vs NPC	0.058	6	0.210	>.500
NUA vs NUC	0.098	5	0.251	>.500

TABLE 2

T-TESTS FOR MEAN ARCSIN PERCENT CORRECT SCORES GROUPED BY TASK (DISCRIMINATION vs NONDISCRIMINATION) (EXPERIMENT III)

	Difference	df	T-Score	Probability
Training	0.122	32	2.648*	.011
Training Probes	0.178	32	4.044***	.001
Retraining	0.104	32	1.06	.291

TABLE 3

T-TESTS FOR MEAN ARCSIN PERCENT CORRECT SCORES GROUPED BY TASK AND SHOCK CONDITION (EXPERIMENT III)

TRAINING

Discrimination vs Nondiscrimination

Group	Difference	df	T-Score	Probability
DP vs NP	.092	15	1.954	.060
DU vs NU	.156	15	1.937	.062

Paired vs Unpaired

DP vs DU	.000	17	0.005	>.500
NP vs NU	.065	13	1.336	.193

TRAINING PROBES

Discrimination vs Nondiscrimination

DP vs NP	.145	16	2.477*	.019
DU vs NU	.211	15	3.148**	.004

Paired vs Unpaired

DP vs DU	-.028	17	-0.435	>.500
NP vs NU	.038	13	0.658	>.500

RETRAINING

Discrimination vs Nondiscrimination

DP vs NP	-0.049	15	0.362	>.500
DU vs NU	0.255	15	1.839	.076

Paired vs Unpaired

DP vs DU	-0.185	17	-1.405	.169
NP vs NU	0.119	13	0.845	.406

*$p<.05$

**$p<.01$

***$p<.001$

APPENDIX C

T-TESTS FOR MEAN TOTAL RESPONSE SCORES FOR EXPERIMENT IV

TABLE 1

T-TESTS FOR MEAN TOTAL RESPONSE SCORES GROUPED BY SHOCK CONDITION (PAIRED vs UNPAIRED) (EXPERIMENT IV)

	Difference	df	T-Score	Probability
Training	10.37	15	0.170	>.500
Training Probes	-16.45	15	-0.609	>.500
Retraining	3.17	15	0.067	>.500

TABLE 2

T-TESTS FOR MEAN TOTAL RESPONSE SCORES GROUPED BY SHOCK CONDITION AND DRUG (EXPERIMENT IV)

TRAINING

Paired vs Unpaired

	Difference	df	T-Score	Probability
Amphetamine Sessions				
PA vs UA	-105.9	6	-2.075	.398
PS vs US	-32.6	7	-0.394	>.500
Saline Sessions				
PA vs UA	-144.6	7	-0.972	>.500
PS vs US	36.9	6	0.516	>.500

Amphetamine-Shock vs Saline-Shock

Amphetamine Sessions				
PA vs PS	-30.3	7	-0.403	>.500
UA vs. US	42.9	6	0.350	>.500
Saline Sessions				
PA vs PS	-144.6	7	-0.972	.364
UA vs US	-57.9	6	-0.596	>.500

TRAINING PROBES

Paired vs Unpaired

Amphetamine Sessions				
PA vs UA	-50.20	6	-1.538	.176
PS vs US	-27.53	7	-0.610	>.500
Saline Sessions				
PA vs UA	-6.95	6	-0.340	>.500
PS vs US	12.14	7	0.220	>.500

Amphetamine-Shock vs Saline-Shock

Amphetamine Sessions				
PA vs PS	-25.87	7	-.812	.444
UA vs US	-3.20	6	-.065	>.500
Saline Sessions				
PA vs PS	-34.94	7	-.812	.444
UA vs US	-15.85	6	-0.357	>.500

TABLE 2 (Continued)

RETRAINING

Paired vs Unpaired

	Difference	df	T-Score	Probability
Amphetamine Sessions				
PA vs UA	-92.95	6	-0.689	>.500
PS vs US	80.23	7	1.170	.281
Saline Sessions				
PA vs UA	17.00	6	0.182	>.500
PS vs US	19.15	7	0.339	>.500

Amphetamine-Shock vs Saline-Shock

Amphetamine Sessions				
PA vs PS	-41.73	7	-0.569	>.500
UA vs US	71.85	6	0.524	>.500
Saline Sessions				
PA vs PS	138.65	7	2.044	.081
UA vs US	140.80	6	1.691	.142

TABLE 3

CORRELATED T-TESTS FOR MEAN TOTAL RESPONSE SCORES GROUPED BY SHOCK CONDITION AND DRUG (EXPERIMENT IV)

Group	Difference	df	T-Score	Probability
		TRAINING		
PA	-149.9	3	-2.44	.093
PS	-264.1	4	-3.05*	.038
UA	-7.0	3	-0.07	.945
US	-107.9	3	-1.77	.174
		TRAINING PROBES		
PA	-118.9	3	-6.20**	.008
PS	-127.9	4	-9.06***	.001
UA	-75.6	3	-3.06*	.037
US	-88.3	3	-4.32*	.023
		RETRAINING		
PA	60.7	3	0.73	.518
PS	-38.2	3	-0.56	.615
UA	10.0	3	0.32	.767
US	12.1	2	0.65	.581
		RETRAINING PROBES		
PA	-82.8	3	-2.21	n.s.
PS	19.2	3	0.55	n.s.
UA	-51.5	3	-1.37	n.s.
US	-62.4	2	0.96	n.s.

*$p<.05$

**$p<.01$

***$p<.001$

APPENDIX D

T-TESTS FOR MEAN ARCSIN PERCENT CORRECT SCORES FOR EXPERIMENT IV

TABLE 1

T-TESTS FOR MEAN ARCSIN PERCENT SCORES GROUPED BY SHOCK CONDITION (PAIRED vs UNPAIRED) (EXPERIMENT IV)

	Difference	df	T-Score	Probability
Training	.005	15	0.094	>.500
Training Probes	-.025	15	-0.368	>.500
Retraining	-.036	15	-0.271	>.500

TABLE 2

T-TESTS FOR MEAN ARCSIN PERCENT CORRECT SCORES GROUPED BY SHOCK CONDITION AND DRUG (EXPERIMENT IV)

TRAINING

Paired vs Unpaired

	Difference	df	T-Score	Probability
Amphetamine Sessions				
PA vs UA	0.143	6	1.151	.294
PS vs US	-0.045	7	-0.326	>.500
Saline Sessions				
PA vs UA	0.062	6	0.728	.494
PS vs US	-0.124	7	-1.685	.136

Amphetamine-Shock vs Saline-Shock

Amphetamine Sessions				
PA vs PS	0.075	7	0.611	>.500
UA vs US	-0.112	6	-0.791	.459
Saline Sessions				
PA vs PS	-0.056	8	-0.494	>.500
UA vs US	-0.129	6	-1.767	.128

TRAINING PROBES

Paired vs Unpaired

Amphetamine Sessions				
PA vs UA	0.087	6	0.410	>.500
PS vs US	-0.024	7	-0.156	>.500
Saline Sessions				
PA vs UA	0.014	6	0.134	>.500
PS vs US	-0.168	7	-2.064	.078

Amphetamine-Shock vs Saline-Shock

Amphetamine Sessions				
PA vs PS	0.017	7	0.077	>.500
UA vs US	-0.094	6	-0.871	.418
Saline Sessions				
PA vs PS	0.089	7	1.212	.265
UA vs US	-0.093	6	-0.815	.447

TABLE 2 (Continued)

RETRAINING

Paired vs Unpaired

	Difference	df	T-Score	Probability
Amphetamine Sessions				
PA vs UA	-0.263	6	-0.884	.411
PS vs US	0.106	7	0.394	>.500
Saline Sessions				
PA vs UA	0.254	6	2.151	.075
PS vs US				

Amphetamine-Shock vs Saline-Shock

Amphetamine Sessions				
PA vs PS	-0.156	7	-0.653	>.500
UA vs US	0.396	7	3.119*	.017
Saline Sessions				
PA vs PS	0.214	6	0.646	>.500
UA vs US	-0.070	6	-0.248	>.500

*$p < .05$