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Differential Outcomes in a Cocaine versus Saline Discrimination

Thomas B. Morgan

DIFFERENTIAL OUTCOMES IN A COCAINE VERSUS SALINE DISCRIMINATION

by

Thomas B. Morgan

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Thomas B. Morgan, M. A.

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The effects of differential outcomes on the speed of acquisition of a cocaine vs. saline discrimination were examined. Two groups of male Sprague-Dawley rats were trained to discriminate 8.0 mg/kg cocaine from saline. The experimental group was exposed to differential outcomes, where correct responses following the different injections (discriminative stimuli) were correlated with a particular outcome (either sweetened condensed milk or tap water). The control group received either sweetened condensed milk or tap water at random following cocaine and saline injections. Acquisition of schedule control and three progressively difficult testing criteria were examined. The differential outcomes group came under schedule control and reached the three progressively difficult testing criteria in significantly fewer sessions than the control group.

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CHAPTER I

INTRODUCTION

Drug discrimination, the scientific study of the discriminative properties of drugs, has yielded a wealth of information concerning the sensory consequences of drugs and the biochemical mechanisms that mediate these consequences (Poling, 1986). Branch (1991) described the concept of drug discrimination: "reinforce one type of activity following drug administration and reinforce another activity following administration of either no drug or some other drug (or, in some cases, a different dose of the same drug). If differential performance is established, then one may conclude that stimuli arising from the drug are acting in a discriminative fashion" (p. 64). Drug discrimination has been demonstrated using amphetamine, cocaine, opiates, benzodiazepine, caffeine, nicotine, Δ9-tetra-hydrocannabinol, and ethanol as discriminative stimuli (Kamien, Bickel, Hughes, Higgins, & Smith, 1993).

Drug discrimination research has shown that pharmacologically similar drugs generally have similar subjective effects (Colpaert, 1986). After a drug discrimination is established, a different drug may be administered in place of the training drug. The accuracy of responding during the session that follows administration of the substitute drug may reveal the extent to which a drug's subjective effects are similar to the subjective effects of the training drug. Moreover, drugs that are classified as having similar subjective effects in humans have been shown to substitute for one

another in drug discrimination studies using nonhuman animals. It is for this reason that drug discrimination has played a role in the classification of drugs (Colpaert, 1987).

In a typical cocaine versus saline drug-discrimination procedure an animal is injected with either cocaine or its vehicle. After a pre-determined amount of time passes (in order for the drug to take action) the subject is placed in an experimental chamber that contains two response operandi. Responses on one operandum are reinforced on a given schedule during sessions that follow drug administration, and responses on the other are reinforced on a given schedule following vehicle injections. Because changes in discriminative stimuli occur between sessions, only one discriminative stimulus is in effect for each session. Overton (1979) reported that more than 30 sessions are required to train a two-lever drug discrimination using food on a FR schedule of reinforcement.

One way of possibly reducing the number of sessions needed to develop a drug discrimination would be to apply differential outcomes. Enhancement of conditional discriminations using differential outcomes has been considered one of the most consistent and powerful effects on the learning and retention of these discriminations (Urcuioli, 1990). The differential outcomes effect (DOE) is the term used to refer to the enhancement of performance resulting from differential outcomes (Peterson & Trapold, 1980). "The DOE refers specifically to the increase in speed of acquisition or terminal accuracy that occurs in discrimination training when each of two or more discriminative stimuli is correlated with a particular outcome (e.g., type of reinforcer)"

(Goeters, Blakely & Poling, 1992, p. 389). Although drug discrimination is a conditional discrimination, differential outcomes have not been applied to a drug discrimination assay. Application of differential outcomes to drug discrimination may reduce the time required to establish a discrimination.

The DOE has been demonstrated using matching-to-sample (MTS), delayed MTS (DMTS) two-choice successive and two-choice conditional discriminations. The DOE has proven to be a robust phenomenon that shows greater effect when the discrimination is more difficult (e.g., longer delays in DMTS studies) (for a review see Goeters et al., 1992). In fact, the only study that did not demonstrate the DOE, using differential outcomes with nonhuman subjects (Santi & Savich, 1985), may have failed because of insufficient training with differential outcomes Also, studies using a between-subjects design showed a statistically significant difference between the differential outcomes group and at least one control group. The conditions when there was not a statistically significant difference occurred when control subjects exhibited high levels of accuracy, indicating the presence of a ceiling effect (Goeters et al., 1992).

A number of researchers have demonstrated that utilizing differential outcomes in experimental situations resulted in faster acquisition and better terminal accuracy of conditional discriminations (Goeters et al., 1992). For example, Carlson and Wielkiewicz (1976) trained a tone vs. clicker discrimination using rats as subjects. Left lever presses were reinforced in the presence of the clicker and right lever presses were reinforced in the presence of the tone. The differential outcomes group received

one pellet for correct responding on one lever and five pellets for correct responding on the other lever. The first control group received one or five pellets at an equal probability for correct responding on both levers. There were two other control groups, one received five pellets for correct responding on both levers while the other received one pellet for correct responding on both levers. The experimenters reported that subjects in the differential outcomes group demonstrated 90% accuracy after 15 training sessions whereas the control groups exhibited similar accuracy after 32 sessions.

Statement of Purpose

Given the practical benefits of speeding the process of drug discrimination, applying differential outcomes could potentially benefit this type of research. To test this possibility, the present study employed a cocaine versus saline discrimination using rats as subjects. Half of the subjects were exposed to differential outcomes while the remaining half received nondifferential outcomes. If response accuracy, on a fixed-ratio (FR) 20 schedule of reinforcement, was at or above 80% prior to the delivery of the first reinforcer over the course of 10 consecutive sessions, discrimination was said to have been acquired. However, before a drug discrimination could be trained the subjects had to meet the FR-20 response requirement (come under schedule control). Schedule control training was conducted after random cocaine or saline injections (Overton, 1979) in order to examine the effect that differential outcomes had on the number of sessions required to reach schedule control. The

total sessions required to reach schedule control and acquire the discrimination were compared between the differential outcomes group and the nondifferential outcomes group.

CHAPTER II

METHODS

Subjects

Sixteen male Sprague-Dawley rats, approximately 4 mo old at the beginning of the experiment, were used as subjects. The subjects were previously used in an acquisition study that consisted of two sessions. The first session followed a 23-h period of water deprivation. The rats then had a 90-min dipper training session where each rat was exposed to a variable-time 60-s schedule of water presentation and no levers were in the chamber. The test session occurred 23 h after the dipper training session. This training session lasted eight hours and occurred only one time. Both levers were in the chamber, one on a continuous-reinforcement schedule while there were no programmed consequences for responses on the remaining lever. Each subject received one of several doses of *d*-amphetamine (0.0, 1.0, 3.0, 5.6, 10.0 mg/kg) 15 min before the experimental session. All rats acquired the lever press by the end of the eight-hour training session. These rats were blocked according to dose of *d*-amphetamine injected before the training session and randomly assigned to two groups. Subjects were housed in groups of four for the acquisition study. Upon completion of the acquisition study, subjects were individually housed with unlimited access to food pellets in a room with controlled lighting (12 hr light 12 hr dark cycle).

Access to water was limited to 15 min each day following experimental sessions. The study was approved by the Institutional Animal Care and Use Committee of Western Michigan University (see Appendix A).

Apparatus

Eight aluminum operant conditioning chambers (Med Associates, East Fairfield, VT), measuring 28 cm long, 21 cm wide, and 21 cm high, were used. The top and sides of the operant chambers were constructed of clear Plexiglas and the work panel and back wall were made of aluminum. The front (21 x 21 cm) wall of each chamber was equipped with two response levers that were separated by 8.5 cm and centered horizontally 7 cm above the floor. Ambient illumination was supplied by a 7-w light (house light) centrally located 10 cm above the levers. Reinforcers consisted of tap water and a sweetened condensed milk solution (2 parts water to 1 part milk). A dipper through which 0.1 ml of either sweetened condensed milk or tap water could be delivered was centered 5 cm below the levers. An exhaust fan provided masking noise and ventilation. The minimum force requirement for operation of a lever was 14 g. Control of experimental events and data recording were accomplished through the use of a Zenith Z -320/SX microcomputer (IBM compatible) using software and an interface designed by Med Associates (East Fairfield, VT).

Drug

Cocaine-hydrochloride was provided by the National Institution on Drug Abuse. The drug was dissolved in 0.85% physiological saline and given in a volume of 1.0 ml/kg. Doses were expressed as the weight of the salt. Drug and saline were administered through sterile intraperatoneal injections.

Training Procedure

Cocaine hydrochloride (10.0 mg/kg) or vehicle was administered 15 min before the start of each session beginning with initial training (Overton, 1979). Because the initial training dose severely disrupted responding, the cocaine dose was reduced to 8.0 mg/kg following the fifteenth session. Daily injections were determined by coin toss with the stipulation that the same injection occurred no more than two consecutive days.

Four of the eight subjects in the differential outcomes (DO) group received tap water for correct responses during sessions that followed cocaine injections and sweetened condensed milk for correct responses following vehicle injections. The remaining subjects received sweetened condensed milk for correct responses following cocaine injections and water for correct responses that followed saline injections. For four of the eight subjects in the DO group, left lever presses were reinforced after cocaine injections and right lever presses were reinforced after saline injections. For the remaining subjects in the DO group, right lever presses were reinforced after

cocaine injections and left lever presses were reinforced after saline injections. Subjects in the nondifferential outcomes (NDO) group received sweetened condensed milk or water at random for correct lever presses following both saline and cocaine injections. For four of the eight subjects in the NDO group, left lever presses were reinforced after cocaine injections and right lever presses were reinforced after saline injections. For the remaining subjects in the NDO group, right lever presses were reinforced after cocaine injections and left lever presses were reinforced after saline injections. For both groups, all correct responding was reinforced on a fixed ratio (FR) 20 schedule of reinforcement.

Experimental sessions lasted 15-min and were conducted six days each week. Subjects received 15-min access to water following experimental sessions and 23-h access to water following the last session of each week. Before all sessions, in order to control olfactory stimuli that may result from using sweetened condensed milk and water as reinforcers, a small amount of sweetened condensed milk was wiped on the outside wall of the work panel just below the dipper cup in each of the chambers.

Behavioral Procedure

Schedule control and three progressively difficult criteria to testing were analyzed. Schedule control refers to the number of training sessions required for the animals to reach the FR 20 response requirement.

Responses were reinforced on a progressive-ratio (PR) schedule where the response requirement was increased by one following every tenth reinforcer. All

subjects started at a ratio requirement of one. Sessions, following the first session in which the response requirement of five was reached, were started at a response requirement that was three less than the previous session that followed the same drug or saline injection. For example, if a particular subject reached the response requirement of seven by the end of a session that followed a cocaine injection, the next session that followed a cocaine injection was started at the response requirement of four. This continued until the first session in which the animals reached the response requirement of 15. From this point on the subjects were started at the response requirement of 15 until they reached the response requirement of 20 for five consecutive sessions. It is this point that the animals reached schedule control.

Before any testing (e.g., substituting other drugs) can occur, some advanced criterion of accuracy must be met. Accuracy before first reinforcer is used as a measure because after that time reinforcer delivery can serve as a discriminative stimulus. The current study examined three progressively difficult testing criterion. Those criteria were: Eight of ten consecutive sessions above 80% correct responding before the first reinforcer, nine of ten consecutive sessions above 80% correct responding before the first reinforcer, and ten of ten consecutive sessions above 80% correct responding before the first reinforcer.

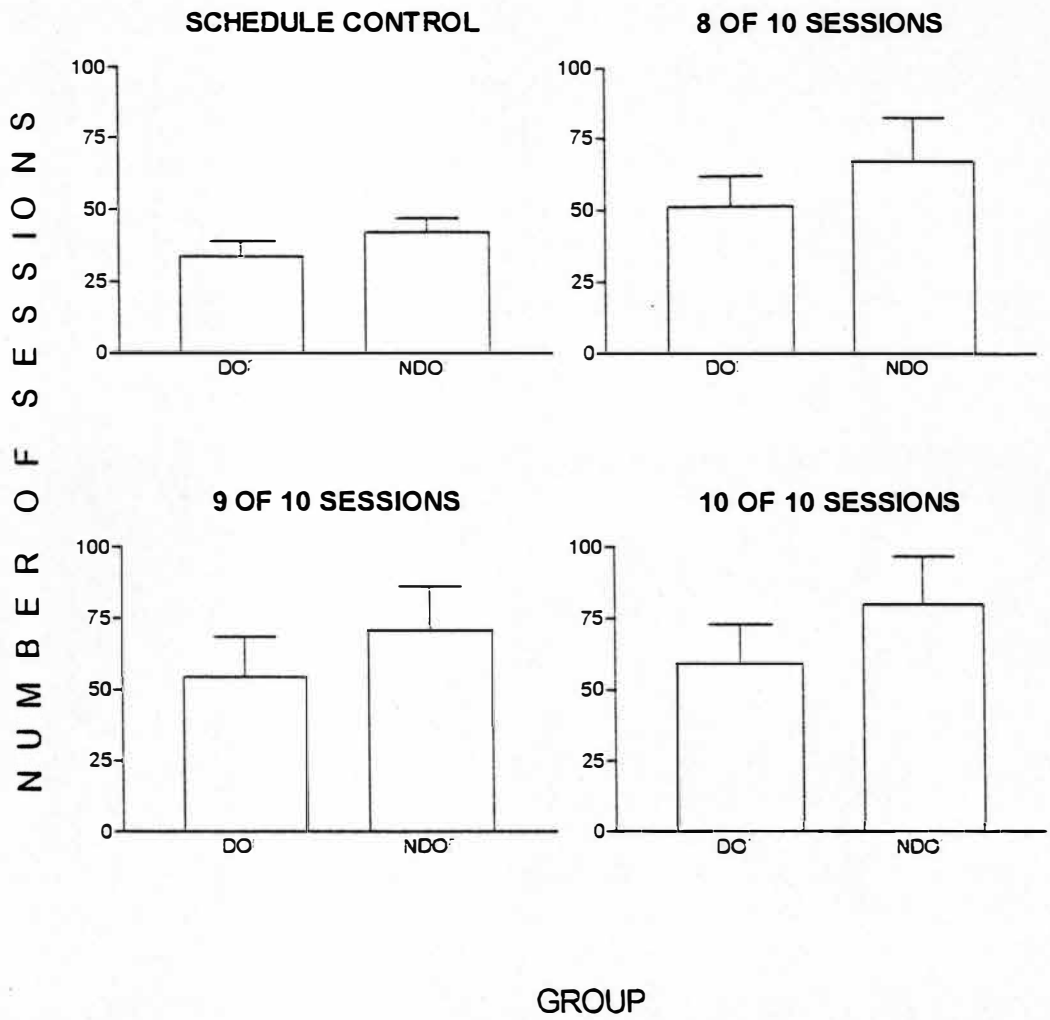
CHAPTER III

RESULTS

Statistical analyses were conducted via a two-sample t-test assuming equal variances. Figure 1 represents the mean sessions to criterion for each group coming under schedule control and the three testing criteria. One subject in the control group died before reaching 80% or better accuracy for 10 of 10 consecutive sessions before the first reinforcer. The number of sessions to criterion was estimated as the fewest number of sessions to reach that criterion for that subject.

The DO group reached schedule control criterion in significantly fewer sessions than the NDO group ($t = -4.30$, $p < 0.00042$). The DO group required a mean of 33.71 sessions to come under schedule control while the NDO group required a mean of 45.13 sessions. The NDO group required an average of 11.42 more sessions to come under schedule control than the DO group.

The DO group reached 8 of 10 consecutive sessions above 80% correct responding before the first reinforcer in significantly fewer sessions than the NDO group ($t = -2.31$, $p < 0.019$). The DO group required a mean of 51.29 consecutive sessions to reach 8 of 10 sessions above 80% correct responding before the first reinforcer while the NDO group required a mean of 67.25 sessions. The NDO group required an average of 15.96 more sessions to reach criterion than the DO group.



Note: The mean sessions to criterion for both the DO group and NDO group for schedule control and each of the three testing criterion. The error bars represent standard deviations.

Figure 1. Sessions to Criterion.

The DO group reached 9 of 10 consecutive sessions above 80% correct responding before the first reinforcer in significantly fewer sessions than the NDO group ($t = -2.10$, $p < 0.028$). The DO group required a mean of 54.57 consecutive sessions to reach 9 of 10 sessions above 80% correct responding before the first

reinforcer while the NDO group required a mean of 70.75 sessions. The NDO group required an average of 16.18 more sessions to reach criterion than the DO group.

The DO group reached 10 of 10 consecutive sessions above 80% correct responding before the first reinforcer in significantly fewer sessions than the NDO group ($t = -2.57$, $p < 0.012$). The DO group required a mean of 59.57 consecutive sessions to reach 10 of 10 sessions above 80% correct responding before the first reinforcer while the NDO required a mean of 80.13 sessions. The NDO group required an average of 20.56 more sessions to reach criterion than the DO group.

CHAPTER IV

DISCUSSION

The use of differential outcomes did speed the acquisition of a cocaine vs. saline discrimination. Although the extent to which the DOE can be generalized to other discriminations using other drugs has yet to be demonstrated, the possibility that differential outcomes could benefit researchers in developing discriminations of other drugs is promising.

The present study required more sessions to establish a drug discrimination than the number suggested by Overton (1979). Most drug discrimination literature does not include detailed reports of schedule control training and does not specify the criterion for determining whether or not the subjects have reached schedule control (e.g., Nader & Woolverton, 1995; Suzuki, Mori, Takamori, Onodera, & Misawa, 1996; Tomie, Peoples & Wagner, 1987). Also, testing criteria are sometimes determined by the average performance over the course of several sessions (e.g., an average of above 75% correct responding before first reinforcer over 5 consecutive sessions) which can also influence the number of sessions to criterion (Overton, 1979). Therefore, the differences in methods of training and testing criterion used between researchers make it difficult to compare the number of sessions required to meet the criteria examined by the present study to the average reported by Overton (1979).

Colpaert (1987) recommended training schedule control in the absence of administration of drug or vehicle in order to control for state-dependent learning. State-dependent learning is demonstrated when performance is better when the testing condition is the same as the training condition than when it is not. The drug can be considered to be serving a discriminative function being a key part of the context in which the original training occurred, so that when it is absent there is a decrement in performance of the trained response (Branch, 1991). Overton and Hayes (1984) demonstrated that random injections of either sodium phenobarbital or saline resulted in a more rapid drug discrimination than when drug and saline were systematically alternated or no drug was given before initial training sessions. Therefore, it would be of interest to study the effects of differential outcomes on a drug discrimination where schedule control is acquired in the absence of drug and saline injections.

Differential outcomes had an effect on schedule control. Although response rate determines the number of sessions required to reach schedule control, only correct responses can advance the PR response requirement. Therefore, accuracy may have influenced the rate of responding during acquisition of schedule control.

Research suggests that the DOE is greater when the task being measured is more difficult (Goeters et al., 1992). The most significant difference between the DO and NDO groups was seen during acquisition of schedule control, where responding had been most recently learned. Since behavior is most fragile when it is newly acquired (Mazur, 1990), it is not surprising that acquisition of schedule control is where the most significant difference was observed. Three progressively more

difficult testing criteria were also examined. As the criteria increased in difficulty, so did the average difference between groups. These data are in agreement with previous research that suggests that the DOE increases as the difficulty of the task performed increases (Goeters et al., 1992).

The present study demonstrated the DOE in discriminations using interoceptive discriminative stimuli. Catania (1971) suggested that drug stimuli and exteroceptive sensory stimuli have few important differences. Demonstrating the DOE using drugs (interoceptive stimuli) as discriminative stimuli showed the same lawful relations as when demonstrated using exteroceptive stimuli, further supporting Catania's contention. The present study also demonstrated the DOE using between-session changes in discriminative stimuli. Therefore, it would be of interest to apply differential outcomes to a discrimination involving between-session changes using exteroceptive discriminative stimuli.

In summary, the DOE was demonstrated in all components of the present study. The fact that drug discrimination involves two aspects of conditional discriminations that have not been studied using differential outcomes, between session changes in discriminative stimuli and the use of interoceptive discriminative stimuli, both extends the scope of the DOE and lends support to Catania's (1971) contention that there are few important differences between exteroceptive stimuli and the interoceptive stimuli produced by drugs. Furthermore, by reducing the number of training sessions, researchers can possibly benefit from implementing differential outcomes in drug discrimination studies.

Appendix A

Western Michigan University Institutional
Animal Care and Use Committee
(IACUC)

IACUC Number 95-01-03
Date of Receipt Jan 25, 95
Date of Approval 1-27-95

WESTERN MICHIGAN UNIVERSITY
INSTITUTIONAL ANIMAL CARE
AND USE COMMITTEE (IACUC)

Application to use Vertebrate Animals for Research or Teaching

The use of any vertebrate animals in research and/or teaching without prior approval of the Institutional Animal Care and Use Committee (IACUC) is a violation of Western Michigan University policies and procedures. This Committee is charged with the institutional responsibility for assuring the appropriate care and treatment of vertebrate animals.

Mail the signed original and five (5) copies of the typed application and any supplements to Research and Sponsored Programs, Room A-221 Ellsworth Hall, (616) 387-3670.

Any application that includes use of hazardous materials, chemicals, radioisotopes or biohazards must be accompanied with SUPPLEMENT A.

Any application that includes survival surgery must be accompanied with SUPPLEMENT B.

Thomas B. Morgan	Psychology	387-4480
Principal Investigator/Instructor	Department	~~Campus~~ Phone
Thomas B Morgan	Jan 20, 1995	
Signature	Signature	
Lisa E. Baker	Psychology	387-4484
~~Responsible~~ Faculty Member (if PI not faculty member)	Department	Campus Phone
Lisa E. Baker	Jan 20, 1995	
Signature	Date	

Title of Project/Course The Application of Differential Outcomes to A Two Lever Drug Discrimination

Check One: Teaching _____ Research ___X___ Other _____

I. ANIMAL USE CATEGORIES (check ONLY one category)

A. ___X___ Projects that involve little or no discomfort (including injections).
B. _____ Projects that may result in some discomfort or pain, but of short duration. Anesthetics, analgesics or tranquilizers will be used.
C. _____ Projects that may result in significant discomfort or pain. Anesthetics, analgesics, or tranquilizers will not be used.

II. ANIMAL USE FACILITIES

Please indicate the building and room(s) where the animal(s) will be housed and cared for as well as the location of the experiments and procedures if different from where housed.

Animals will be housed and cared for in Wood Hall, room 289. The experimental procedures will be conducted in Wood Hall, room 227.

III. ANIMAL USE SUMMARY

In language understandable to a layperson, summarize your primary aims and describe the proposed use of animals as concisely as possible. Bear in mind that the IACUC is primarily interested in the responsible, necessary, humane use of animals. Include a description of procedures designed to assure that discomfort and pain to animals will be minimized. It should include method of restraint; method of dosing with test compound; and methods of euthanasia or disposition of the animal after the experiment.

The purpose of the present experiment is to demonstrate the differential outcomes effect by comparing animals trained in drug discrimination using differential outcomes to the same number of animals trained in drug discrimination without differential outcomes.

Eight Sprague-Dawley rats will perform under a consecutive FR 20 schedule in a two-lever chamber using differential outcomes (reinforcement). The discriminative stimuli will be an amphetamine injection or a saline injection. Reinforcement will be water and saccharine-sweetened water. Four random selected rats will receive four seconds access to water for every 20th correct lever press during sessions following amphetamine administration, and four seconds access to saccharine-sweetened water following saline injection. The other four will receive sweetened water as the reinforcer following amphetamine administration, and plain water following saline.

Eight other Sprague-Dawley rats will perform under a consecutive FR 20 schedule in a two-lever chamber using non-differential outcomes. Correct lever presses will be reinforced either with water or sweetened water. The type of reinforcer will be assigned at random from session to session.

Each session, all rats will be administered IP injections of either amphetamine (1.0 mg/kg) or saline (determined randomly) prior to each training session. There will be no more than three days under the same condition. Each injection will be given IP at a volume of 1 mg/ml with a sterile insulin syringe. The injection site will be cleansed with an alcohol swab and location will alternate laterally to minimize bruising and scaring. The drug will be prepared in a vehicle of sterile saline. Drug doses were chosen based on prior studies.

Following training, dose response curves for amphetamine (.25 mg/kg to 1.0 mg/kg) and cocaine (2.5 mg/kg to 10.0 mg/kg) will be tested. ~~Dose~~ Safe dosage rates established le Saga et al., Pharm Biochem & Behavi 48(3) 787 (1994)

Following completion of the experiment, rats will be euthanized by carbon dioxide

IV. JUSTIFICATION FOR ALL ANIMAL EXPERIMENTS

Please provide a narrative with reference sources which addresses each of the following:

A. What assurance can be provided to indicate that the procedure is not duplicative?
Although the differential outcomes effect has been demonstrated using various discriminative stimuli and postcedent stimuli, the use of drugs as antecedent stimuli has not been reported. Search of following literature: Psychlit, a Goetera, S. et al J. Exptl Anal. Behav. 1992, 58(42): 387

B. Have non-live animal techniques (e.g. in vitro biological systems, computer simulation, audiovisual demonstration) been considered? Explain why they have not been utilized.
In vitro systems, computer simulation, and audiovisual demonstration are not designed to examine the behavioral effects of drugs on operant behavior.

C. Why has this species been selected for this procedure?
Rats would be used primarily because they are readily available and because our equipment is specifically designed for use of this species.

D. How many animals will be used in this project? How often will its procedures be done and over what duration?
We will use 16 animals for this experiment. Experimental procedures will be conducted a minimum of five days per week for approximately six to eight months.

E. In light of concern to minimize the number of animals used in experimentation, how will you determine the number of animals to be used?
Data from the proposed experiment will be analyzed statistically. The minimum number of subjects required for an acceptable level of statistical power will be used.

F. What is the anticipated pain or distress response of the animal; and what is the duration of discomfort? (Injections not included.)
Not applicable

G. How will the pain in the animal be monitored?
Not applicable

H. What sedative, analgesic, or anesthetics will be used, if any? Include dose, route and frequency of administration.
Not applicable

I. What is the justification if pain relieving drugs are not used?
Not applicable

WESTERN MICHIGAN UNIVERSITY
INVESTIGATOR IACUC CERTIFICATE

Title of Project: The Application of Differential Outcomes to a Two Lever Drug Discrimination Procedure

The information included in this IACUC application is accurate to the best of my knowledge. All personnel listed recognize their responsibility in complying with university policies governing the care and use of animals.

I declare that all experiments involving live animals will be performed under my supervision or that of another qualified scientist. Technicians or students involved have been trained in proper procedures in animal handling, administration of anesthetics, analgesics, and euthanasia to be used in this project.

If this project is funded by an external source, I certify that this application accurately reflects all procedures involving laboratory animal subjects described in the proposal to the funding agency noted above.

Any proposed revisions to or variations from the animal care and use data will be promptly forwarded to the IACUC for approval.

_____Disapproved ___X___Approved _____Approved with the provisions listed below

Provisions or Explanations:

_____

_____

_____

_____

_____

_____

Donald Green
IACUC Chairperson

8-27-95
Date

Acceptance of Provisions

_____
Signature: Principal Investigator/Instructor

_____
Date

_____
IACUC Chairperson Final Approval

_____
Date

#95-01-03

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