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Application of Differential Outcomes to a Cocaine-Saline Discrimination Procedure: Assessment of Stimulus Generalization to Dopamine D_3 Receptor Agonists

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APPLICATION OF DIFFERENTIAL OUTCOMES TO A COCAINE-SALINE DISCRIMINATION PROCEDURE: ASSESSMENT OF STIMULUS GENERALIZATION TO DOPAMINE D_3 RECEPTOR AGONISTS

by

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This study replicated the effects of differential outcomes on the acquisition of a cocaine-saline discrimination in rats and examined whether learning via differential outcomes (DO) influenced stimulus generalization to other drugs. Previous investigations have suggested that the dopamine (DA) D_3 receptor subtype may modulate the reinforcing effects of cocaine. Pharmacological compounds which have been identified as having a greater affinity for DA D_3 receptors are 7-OH-DPAT and PD 128907. The present study examined whether the DO conditions applied during training had an impact on the generalization of these test compounds. Two groups of male Sprague-Dawley rats were trained to discriminate 10 mg/kg cocaine from saline. After reaching discrimination criterion, subjects were exposed to stimulus generalization tests. Results show that the DO group met the discrimination criterion in significantly fewer sessions than the control group. Results of stimulus generalization tests show no significant differences between training groups. Data suggest that differential outcomes can be applied to a cocaine-saline discrimination without altering stimulus generalization.

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INTRODUCTION

The Drug Discrimination Assay

Drug discrimination assays are used to examine the stimulus properties of drugs. "In discrimination training, the effects of a drug serve as discriminative stimuli that indicate to a subject when or how it can obtain reinforcers" (Stolerman, 1993, p. 218). Typical drug discrimination assays involve the use of a two-lever operant conditioning procedure. A drug discrimination is established by differentially reinforcing one response (e.g., a press on one lever) after drug administration and another response (e.g., a press on the other lever) after administration of vehicle (no drug) or another drug (Branch, 1991). If differential performance is established, that is, if the subject presses one lever after drug administration and the other lever after vehicle administration, one can conclude that the interoceptive physiological and psychological stimulus effects of the drug are serving as discriminative stimuli. Therefore, it can be concluded that the behavior of the subject is under discriminative stimulus control of the drug. Once a discrimination is established, novel compounds can be administered via the assay in order to classify their effects compared to the effects of known compounds.

The Differential Outcomes Procedure

Drug discrimination research is labor intensive, requiring one to invest a

great deal in time, effort, and planning (Stolerman, 1993). Most studies require 10-12 months to complete. One possible way to reduce the time needed for acquisition of discrimination involves the use of differential outcomes. The differential outcomes effect "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). Previous research has shown that the acquisition of a cocaine-saline discrimination is accelerated when differential outcomes (water vs. diluted sweetened-condensed milk) are used during discrimination (cocaine vs. saline) training (Morgan & Baker, 1997). The same research has also shown that the use of differential outcomes does not significantly alter the cocaine dose-response curve, although there is some variability between groups. However, it has not been determined whether learning via differential outcomes, as opposed to non-differential outcomes, has an effect on organisms' ability to generalize to the stimulus effects of other drugs given during later testing phases (i.e., substitution tests). It is important to know whether there would be such an effect, especially if investigators use differential outcomes conditions in drug discrimination research.

Pharmacology

Because a major focus of drug discrimination research is to identify compounds that may aid in the pharmacological treatment of drug/substance abuse, it is important to control for factors that may affect the generalization (i.e., substitution)

of a particular compound. It is generally well established that drugs with similar pharmacological mechanisms exhibit generalization to one another in drug discrimination investigations. To determine whether the differential outcomes effect influences generalization of test compounds, a suitable test compound must be selected.

Many investigations have focused on identifying the neuronal systems involved in the mediation of reinforcement of drugs of abuse. Initial studies of brain self-stimulation have shown that the areas to which rats will work to self-administer electrical stimulation are specifically those areas that contain a greater concentration of dopaminergic (DA) neurons (Gallistel, Gomita, Yadin, & Campbell 1985; Olds & Fobes, 1981); those areas are the mesolimbic regions of the brain. The finding that mediation of reinforcement is related to the concentration levels of DA neurons present in certain areas of the brain suggests that DA is involved in the modulation of reinforcement. Further evidence for this hypothesis is seen in the relationship between psychomotor stimulants, such as cocaine, and the neurotransmitter dopamine, which has been extensively examined and documented. As a DA agonist, cocaine produces its reinforcing effects by blocking pre-synaptic reuptake of DA (Koob & Bloom, 1988; Johanson & Fischman, 1989). By preventing the reuptake of DA, the intensity and functional availability of pre- and post-synaptic DA is sustained for a greater period of time (Caine & Koob, 1995). Those brain areas that are hypothesized to mediate reinforcement of psychomotor stimulants contain a greater number of the D_2 subfamily of DA receptors (Bouthenet, Souil, Martres, Sokoloff,

Giros, & Schwartz, 1991; Landwehrmeyer, Mengod, & Palacois, 1993). Recent investigations have suggested that psychomotor stimulants specifically target the D_2 subfamily of DA receptors, which consist of the D_2, D_3, and D_4 subtypes. In fact, research investigating the relation between cocaine and DA has recently focused on the DA D_3 receptor subtype (Spealman, 1996; Gehlert, Gackenheimer, Seeman, & Schaus, 1992). A greater concentration of this subtype is found in the mesolimbic areas of the brain, areas that play a role in mediating the reinforcing properties of psychostimulants (Levesque, Diaz, Pilon, Martres, Giros, Souil, Schott, Morgat, Schwartz, & Sokoloff, 1992). These findings suggest that this subtype in particular may modulate the reinforcing effects of cocaine (Acri, Carter, Alling, Douglass, Dijkstra, Wikstrom, Katz, & Witkin, 1995; Landwehrmeyer et al., 1993). Therefore, it could be argued that the compounds to be tested in the present study have a greater affinity for the D_2 subfamily of DA receptors, especially the D_3 subtype.

Pharmacological compounds which have been identified as having a greater affinity for DA D_3 receptors are 7-OH-DPAT, in both is racemic and (+) isomer forms, and PD 128907. It has been reported that 7-OH-DPAT exhibits a 100-fold or greater affinity for D_3 over D_2 receptors (Burris, Pacheco, Filtz, Kung, Kung, & Molinoff, 1995; Levesque et al. 1992), and PD 128907 has been reported to have at least a 300-fold or greater D_3 vs. D_2 selectivity (Pugsley, Davis, Akunne, MacKenzie, Shih, Damsma, Wikstrom, Whetzel, Georgic, Cooke, DeMattos, Corbin, Glase, Wise, Dijkstra, & Heffner, 1995; Spealman, 1996). At this time, these compounds are two of the most selective DA D_3 agonists available for study.

Several studies have investigated the stimulus generalization of DA D_3 selective agonists in animals trained to discriminate specific psychomotor stimulants from saline. The discriminative stimulus effects of cocaine have been shown to generalize to the selective D_3 agonists (±) 7-OH-DPAT and PD 128907 in rats (Acri et al., 1995) and rhesus monkeys (Lamas, Negus, Nader, & Mello, 1996); that is, in those subjects, (±) 7-OH-DPAT and PD 128907 substituted for cocaine. Baker, Svenson, Garner, & Goodwin (1998) found that (+) 7-OH-DPAT exhibited partial substitution (between 20% and 80% drug-appropriate responding) in rats trained to discriminate cocaine (5 mg/kg) from saline. Spealman (1996) also found that both 7-OH-DPAT and PD 128907 partially substituted for cocaine in squirrel monkeys trained on a cocaine-saline discrimination. Other studies have noted similar results using self-administration assays. 7-OH-DPAT maintained self-administration responding when substituted for cocaine in rats (Caine & Koob, 1993, 1997) trained to self-administer cocaine. Both 7-OH-DPAT and PD 128907 have been shown to maintain self-administration when substituted for cocaine in rhesus monkeys (Nader & Mach, 1996) trained to self-administer cocaine. Similar results have been found in studies using other psychomotor stimulants. For example, Bevins, Klebaur, & Bardo (1997) and Baker et al. (1998) found that 7-OH-DPAT fully substituted for *d*-amphetamine in rats. Therefore, if these highly selective DA D_3 compounds are tested for generalization in subjects trained to discriminate between cocaine and saline using differential outcomes and in subjects trained without differential outcomes, it can be concluded that any differences observed in degree of

generalization are due to the use of differential outcomes.

Objectives

In summary, the two primary objectives of this study are (1) to replicate the differential outcomes effect on a saline-cocaine discrimination procedure in rats; and (2) to examine whether the differential outcomes conditions applied during training have an impact on the generalization of the dopamine D_3 receptor agonists (±) 7-OH-DPAT, (+) 7-OH-DPAT, and PD 128907 administered during substitution testing.

METHOD

Subjects

Twenty-four experimentally naive Sprague-Dawley rats (Harlan Breeding Laboratories, Indianapolis, IN), 60-90 days of age at the beginning of the study, served as subjects. Subjects were individually housed in wire mesh cages in a colony room maintained on a 12-h light/dark cycle and at a relatively constant temperature (20-22°C) and humidity (50-65%). Commercial rat feed was available ad libitum. For control subjects, water served as the reinforcer during experimental sessions. Subjects in the differential outcomes group alternately received a diluted (2 parts water: 1 part milk) sweetened condensed milk solution or water as reinforcers (Morgan and Baker, 1997). Additional access to water was given to all subjects during 20 min post-session periods and every 7^{th} day for approximately 24 h. The animals were maintained in accordance with the general principles of animal husbandry outlined by the National Institutes of Health and the experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Western Michigan University (see Appendix A).

Drugs

Cocaine-hydrochloride was obtained from the National Institute on Drug Abuse (Rockville, MD). (+) 7-OH-DPAT was obtained from Pharmacia & Upjohn,

Inc. (Kalamazoo, MI). PD 128907 and (±) 7-OH-DPAT were purchased from Research Biochemicals International (Natick, MA). All drugs were dissolved in 0.90% bacteriostatic sodium chloride. Cocaine and (±) 7-OH-DPAT were administered intraperitoneally (IP.); (+) 7-OH-DPAT and PD 128907 were administered both subcutaneously (SC) and IP. All doses of each drug were based on the salt.

Apparatus

All experimental sessions were conducted in eight standard light and sound-attenuating operant chambers (MED Associates, Inc., St. Albans, VT. ENV-001). Two response levers were mounted on the front panel of each operant chamber. Liquid reinforcers (0.1ml) were delivered via a dipper mechanism mounted between the two response levers. Each chamber contained a 28 V houselight to provide illumination and an exhaust fan to provide masking noise and ventilation. A Zenith 320-SX microcomputer programmed with MED-PC instrumentation and software (MED Associates Inc., St Albans, VT, version 2.0) was used to control experimental events and data collection.

Shaping

The shaping phase consisted of one 8 h experimental session. During this session subjects were placed in the operant chambers overnight. Only the center lever was present during this session, and responses on this lever were reinforced under a

fixed-ratio 1 (FR 1) schedule of reinforcement. Only water reinforcers were delivered during the shaping phase. No injections were given during this session. Those subjects that did not acquire the lever press response during this session received shaping during the experimental training sessions as needed.

Training Procedures

All subjects were trained to discriminate cocaine (10 mg/kg) from saline using a two-lever operant task under a fixed-ratio (FR) schedule of liquid reinforcement. Cocaine and saline injections were administered in a pseudo-random order across sessions to ensure that no subject was given more than two consecutive cocaine conditions or two consecutive saline conditions. All injections were administered 15 min prior to the beginning of each training session. Subjects were randomly assigned to either the differential outcomes condition or the control condition. Six of the 12 subjects in the differential outcomes condition received water as the reinforcer for correct responses during saline sessions and sweetened condensed milk as the reinforcer for correct responses during cocaine sessions; these conditions were reversed for the remaining six subjects. All subjects in the control condition received water as the reinforcer for correct responses during both saline and cocaine sessions. For half of the subjects in each group, left lever presses were reinforced after cocaine injections and right lever presses were reinforced after saline injections; these conditions were reversed for the remaining subjects in each group. Response levers were wiped with isopropyl alcohol prior to each session in order to reduce the

influence of olfactory stimuli on lever pressing (Extance & Goudie, 1981). Experimental sessions lasted 20 min and were conducted 5-6 days a week. To control for olfactory stimuli that may result from using sweetened condensed milk and water as reinforcers, small cups containing sweetened condensed milk were placed behind the front panel of each chamber. All subjects were trained under a FR 1 schedule of reinforcement. This response requirement was gradually increased until subjects were responding under a FR 20 schedule of reinforcement. The criterion for discrimination was specified as at least 80% responding on the correct lever prior to the delivery of the first reinforcer for nine out of 10 consecutive sessions.

Testing Procedures

Upon reaching criterion, differential outcome subjects completed a no-odor-cue test. Subjects who received milk after saline injections received a saline injection and were tested without milk present in the chambers; subjects who received milk after cocaine injections received a cocaine injection (10mg/kg) and were tested without milk present in the chambers. This was done to determine whether subjects were discriminating between the presence and absence of drug or between olfactory stimuli. Stimulus generalization to the training drug was tested using several doses of cocaine (0.0, 1.25, 2.5, 5.0, 10.0 mg/kg). Following cocaine generalization tests, stimulus generalization tests were administered using several different doses of (±)-7-OH-DPAT (0.0, 0.01, 0.03, 0.1, 0.3 mg/kg SC), PD 128907 (0.0, 0.01, 0.03, 0.1, 0.3 mg/kg IP), and (+)-7-OH-DPAT (0.0, 0.01, 0.03, 0.1, 0.3 mg/kg IP). In

addition, two doses of (+)-7-OH-DPAT (0.1, 0.3 mg/kg) and PD 128907 (0.1, 0.3 mg/kg) were administered SC. Test sessions were conducted in a similar manner to training sessions with the exception that no reinforcers were delivered and subjects were removed from the chambers upon completion of 20 consecutive responses on either lever or when 20 min elapsed, whichever came first. Prior to each testing session, subjects received a drug and a saline training condition, and were required to maintain the 80% criterion under both training conditions before each test was administered.

Data Analysis

Dose response data were presented as the percent of total responses made on the drug-appropriate lever during test sessions. Response rate was presented as the number of responses made (on either lever) per second during test sessions. In the event that an animal did not complete at least 15 total responses during a test session, the percentage of drug-lever responses for that test was not included in the statistical analyses. The number of sessions required for each group to attain discrimination criterion was analyzed using a two-sample *t* test; the data from the substitution tests were analyzed using a two-factor (group x dose) analysis of variance. Because the data from substitution tests were presented as the percentage of the total responses made on the drug-appropriate lever, generalization was said to have occurred if responding on the drug-appropriate lever was at least 80%. Drug-appropriate responding between 20% and 80% was considered evidence for partial substitution.

For drugs that produced stimulus generalization, the dose-response curves were also analyzed using a nonlinear regression and ED_{50}s and confidence intervals were calculated. Statistical analyses were conducted using GraphPad Prism (GraphPad, Inc., San Diego, CA) software.

RESULTS

All subjects met the discrimination criterion stated above. After meeting the initial criterion for discrimination, five animals in the control group began to exhibit poor stimulus control due to equipment failure. After the equipment problem was fixed, these animals were required to meet the discrimination criterion (10 consecutive sessions above 80% correct lever prior to the first reinforcer) again before they were administered test sessions. Therefore, the sessions to criterion for these five animals were not included in the statistical analysis. Figure 1 illustrates the mean sessions to criterion for each group. The differential outcomes group met the discrimination criterion in significantly fewer sessions than the control group (t=2.823, $p< 0.05$). The mean number of sessions to criterion for the differential outcomes group (n=10) was 47.50 (S.E.M.= ± 2.491, Range: 31-59); the mean number of sessions to criterion for the control group (n=7) was 66.14 (S.E.M.= ± 7.130, Range: 37-95).

Subjects in the differential outcomes group also completed a no-odor-cue test upon reaching criterion. Subjects who received milk as the reinforcer after cocaine injections received a cocaine injection (10 mg/kg) and were tested without milk present in the chambers; subjects who received milk as the reinforcer after saline injections received a saline injection and were tested without milk present in the chambers. This was done to determine whether subjects were discriminating between

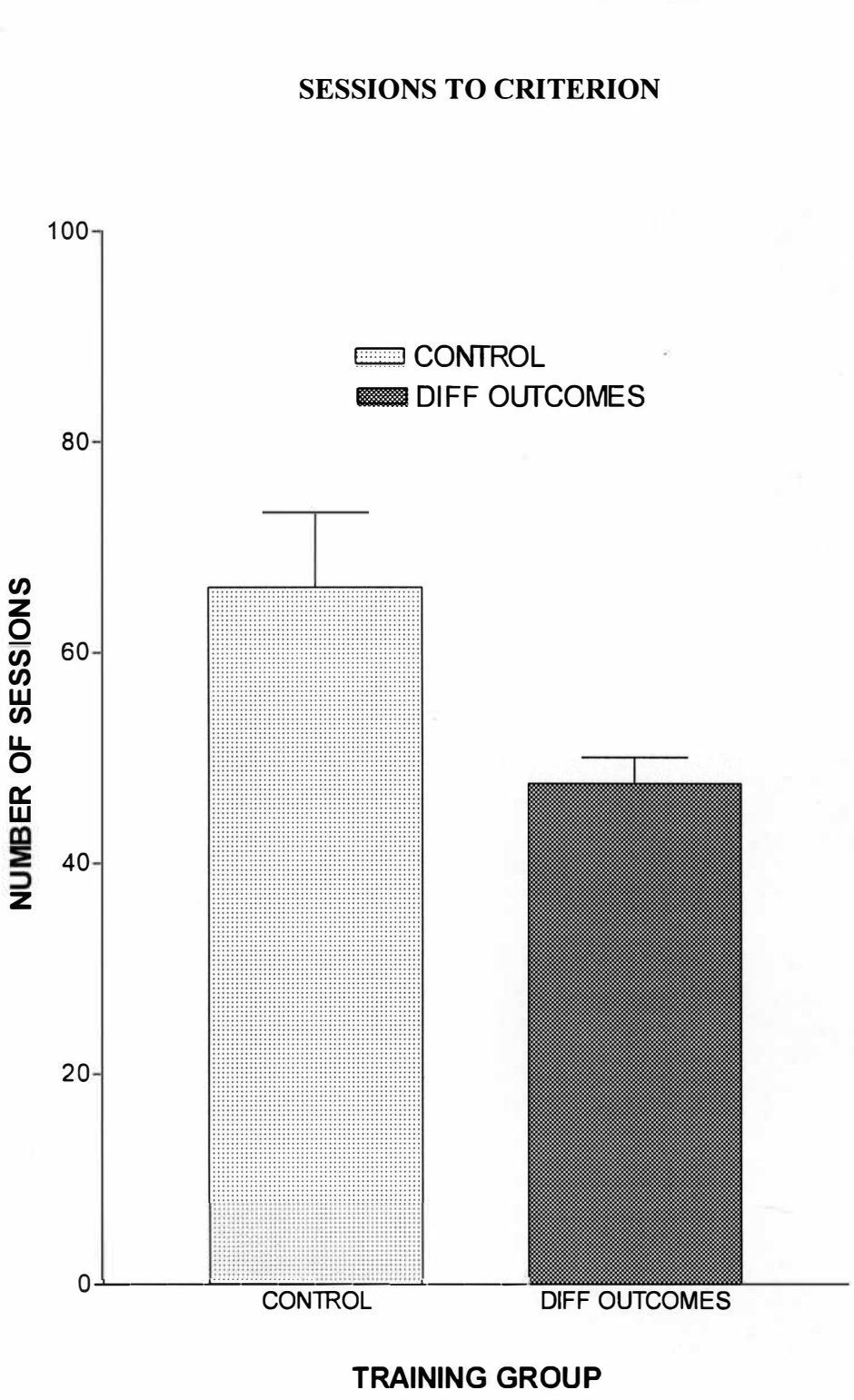

Figure 1. Sessions to Criterion.

the presence and absence of a drug or between olfactory cues. When tested in the absence of milk odor, 10 of the 12 subjects in the differential outcomes group made greater than 90% of their responses on the condition-appropriate lever. As it appeared that two subjects were discriminating between olfactory cues, their data were not included in any statistical analyses.

Since the remaining 22 subjects, including the five control subjects mentioned previously, were required to meet the discrimination criterion prior to test phases, all data from these 22 subjects are included in the tests of generalization and subsequent analyses. The cocaine dose response data are displayed in Figure 2. All subjects exhibited dose-dependent increases in drug appropriate responding. Statistical analysis revealed a significant main effect of dose on percent drug-appropriate responding ($F_{4,100}$=16.39, $p<0.001$). The ED_{50} for the control group was 1.34 mg/kg (95% Confidence Intervals: 0.36-4.93) and the ED_{50} for the differential outcomes group was 3.78 mg/kg (95% Confidence Intervals: 0.95-15.11). Although the ED_{50} for the control group was lower than the ED_{50} for the differential outcomes group, a two-factor (group x dose) ANOVA on the dose-response tests revealed no significant difference between training groups.

The results of stimulus generalization tests with (±)-7-OH-DPAT (SC) are displayed in Figure 3. (±)-7-OH-DPAT (SC) substituted for cocaine in a dose-dependent manner in both the control group (ED_{50}= 0.02, 95% Confidence Interval: 0.01-0.09) and the differential outcomes group (ED_{50}=0.04, 95% Confidence Interval: 0.01-0.20). Although this compound produced complete substitution for both groups

COCAINE DOSE-RESPONSE DATA

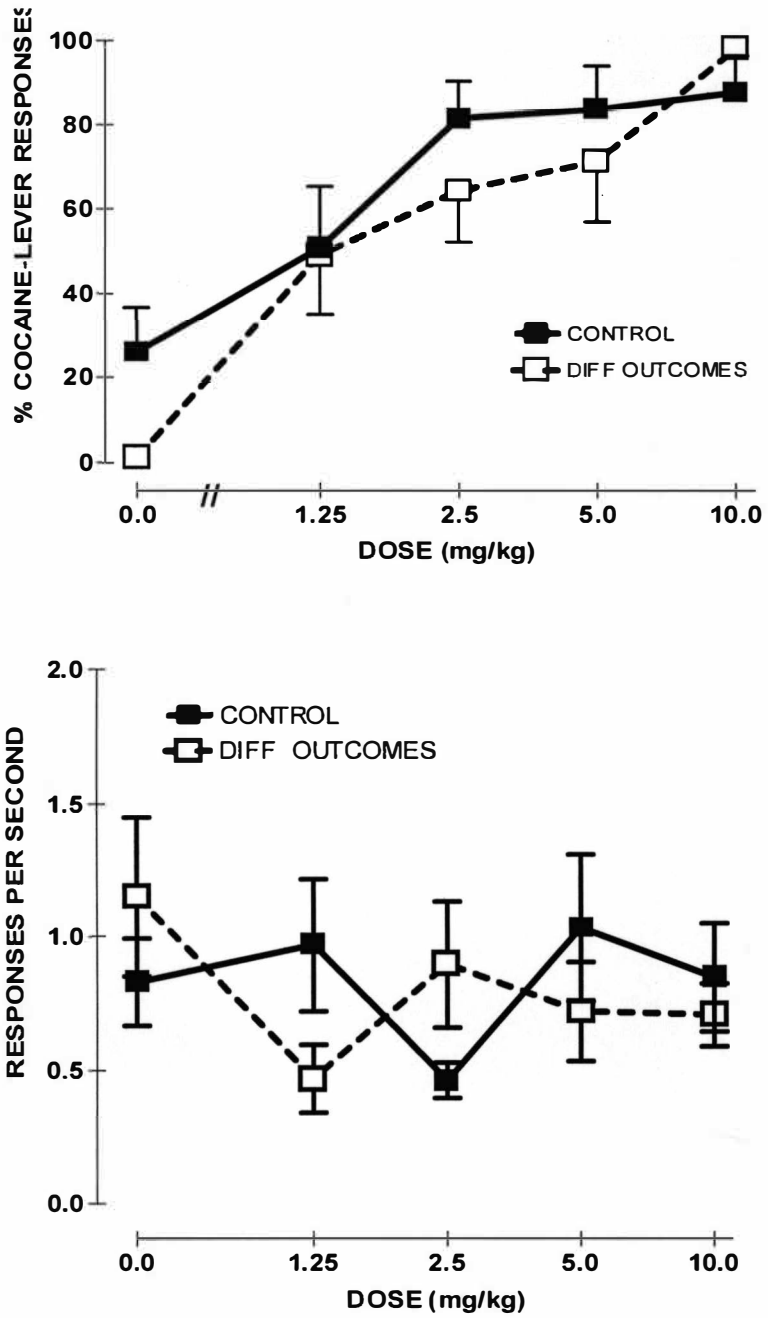

Figure 2. Cocaine Dose-Response Data.

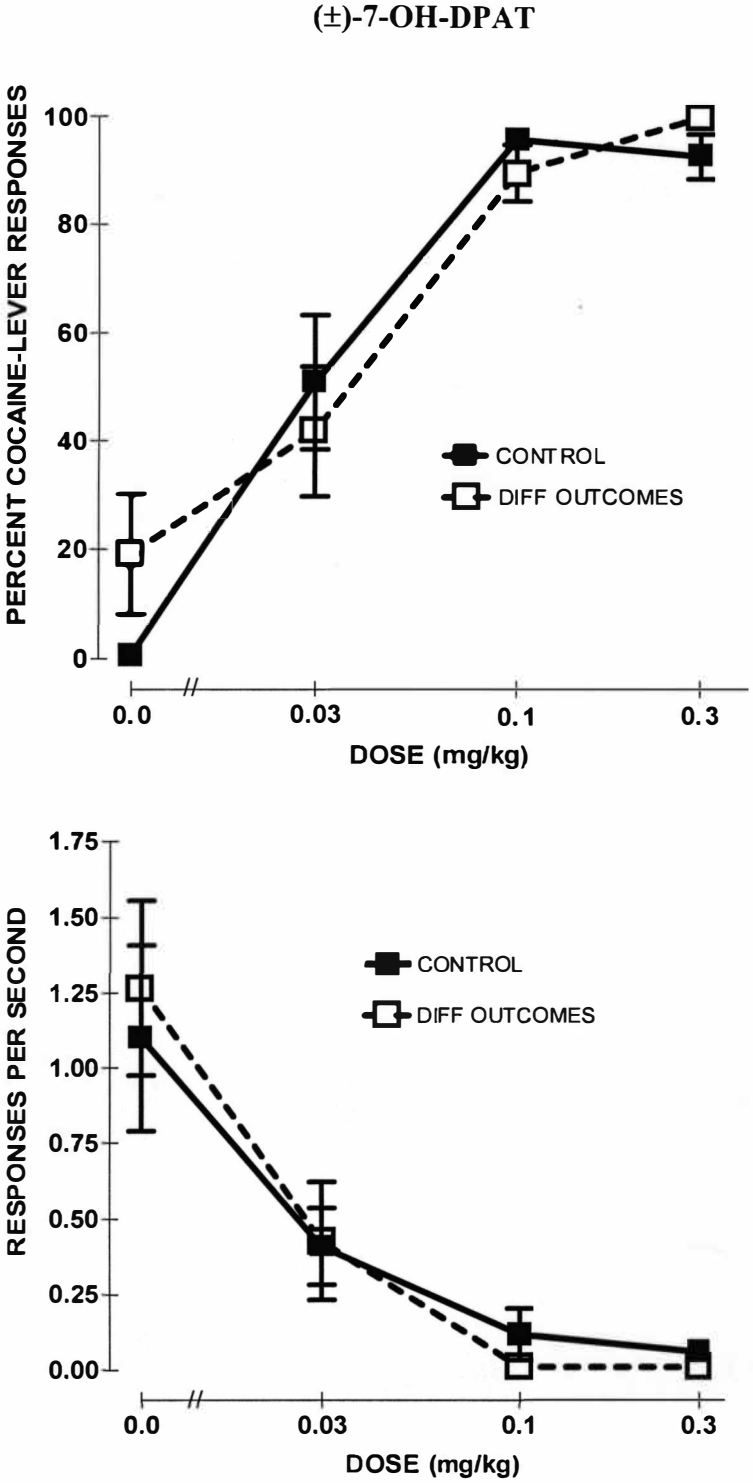

Figure 3. Results of Stimulus Generalization Tests With (±)-7-OH-DPAT.

at 0.1 and 0.3 mg/kg, it also dose-dependently reduced response rate. Fifteen of the 22 animals produced 9 or fewer responses when tested at 0.3 mg/kg. A two-factor ANOVA showed a statistically significant reduction in response rate ($F_{3, 80}$=18.49, $p<0.001$). Statistical analysis revealed no main effect of training group, indicating no significant difference in generalization of (±)-7-OH-DPAT between the control group and the differential outcomes group. Statistical analysis also showed a significant main effect of dose ($F_{3, 55}$=33.46, $p< 0.001$) on percent drug-appropriate responding.

Results of stimulus generalization tests with (+)-7-OH-DPAT (IP) are illustrated in Figure 4. (+)-7-OH-DPAT (IP) also produced dose-dependent increases in drug-appropriate responding, however, this compound produced only partial substitution in either group at 0.3 mg/kg. A two-factor ANOVA showed a significant main effect of dose on percent drug-appropriate responding ($F_{4, 73}$=4.67, $p<0.005$). IP administration of this compound also significantly reduced response rate ($F_{4, 100}$=11.84, $p<0.001$) in a dose-dependent fashion. Higher doses were not examined because 16 of the 22 animals produced 6 or fewer responses when tested at this dose. Subjects were also tested with two doses of this compound (0.1, 0.3 mg/kg) following SC injection (see Figure 5). At these doses, (+)-7-OH-DPAT (SC) produced complete generalization in both the control group and the differential outcomes group. However, statistical analysis of the data showed no significant difference in generalization of (+)-7-OH-DPAT (IP and SC) between the control group and the differential outcomes group.

Results of stimulus generalization tests with PD 128907 (IP) are illustrated in

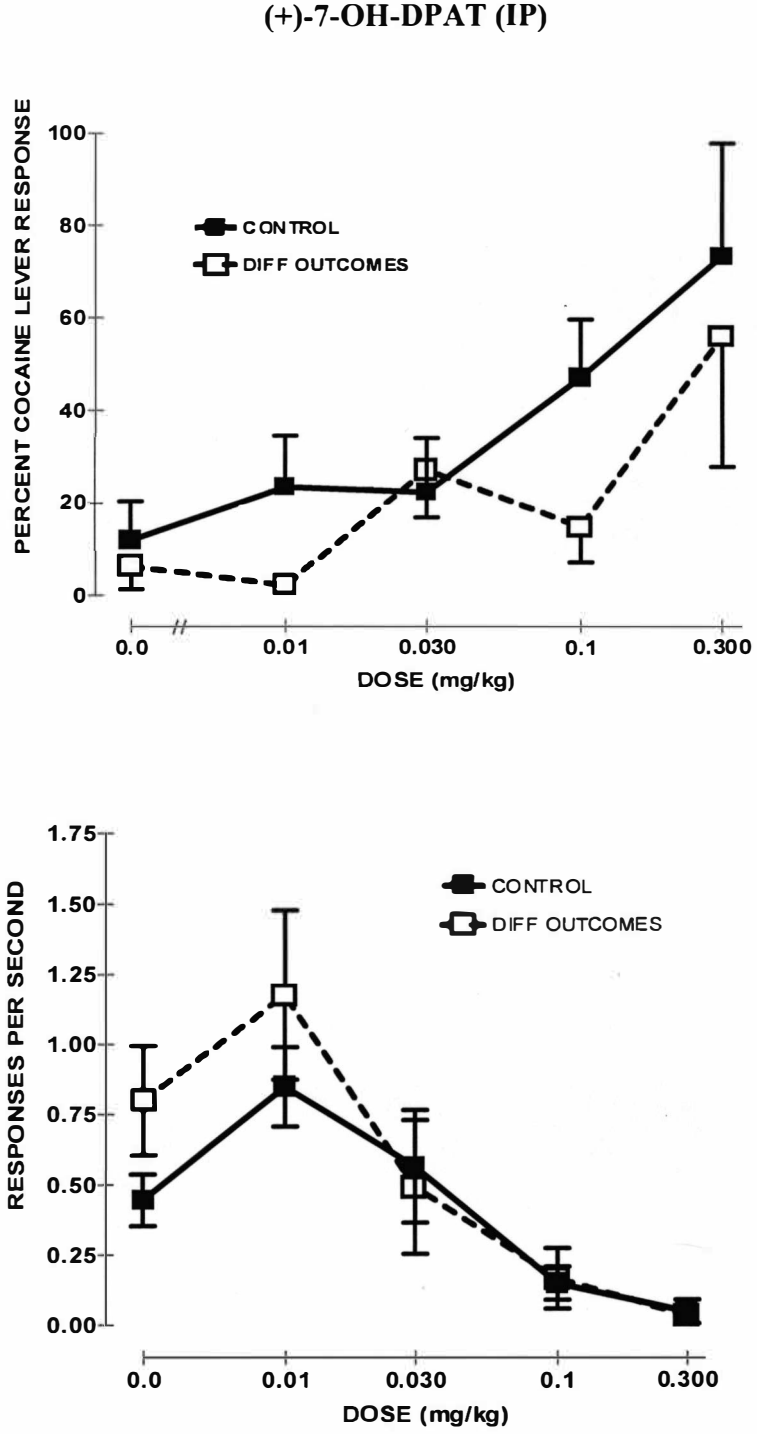

Figure 4. *Results of Stimulus Generalization Tests With (+)-7-OH-DPAT (IP).*

(+)-7-OH-DPAT (SC)

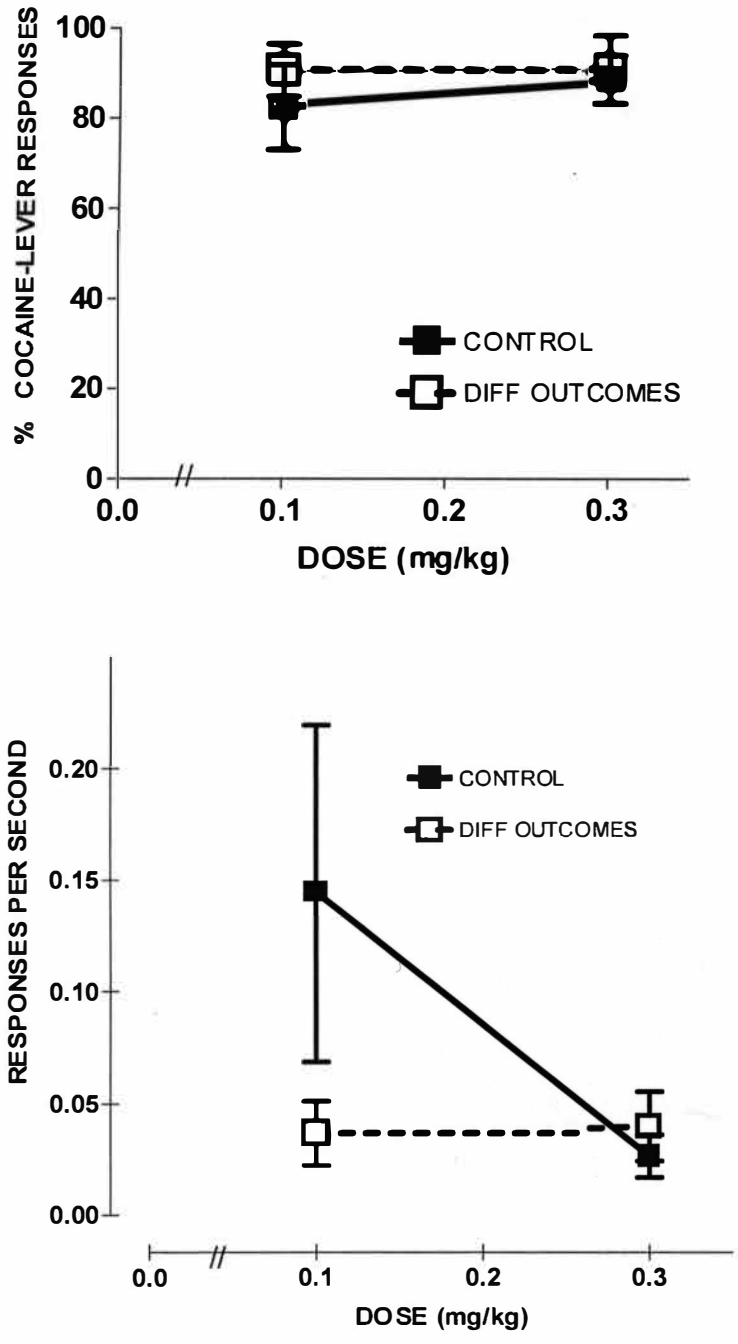

Figure 5. Results of Stimulus Generalization Tests With (+)-7-OH-DPAT (SC).

Figure 6. When administered IP, PD 128907 also produced only partial substitution for cocaine in either group. As 10 of the 22 animals did not complete the FR requirement when tested at 0.3 mg/kg, higher doses of this compound were not tested. Animals in both groups exhibited complete generalization when PD 128907 (0.1, 0.3 mg/kg) was administered via SC injection (see Figure 7). This compound also produced significant dose-dependent decreases in response rate, both IP ($F_{4,\ 100}$=5.09, $p<0.005$) and SC ($F_{1,\ 40}$=11.28, $p<0.005$). Again, a two-factor ANOVA showed no significant difference in generalization of PD 128907 (IP and SC) between the control group and the differential outcomes group. Statistical analysis revealed a significant main effect of dose on percent drug-appropriate responding when administered both IP ($F_{4,\ 95}$=14.44, $p<0.001$) and SC ($F_{1,\ 34}$=10.76, $p<0.005$).

PD 128907 (IP)

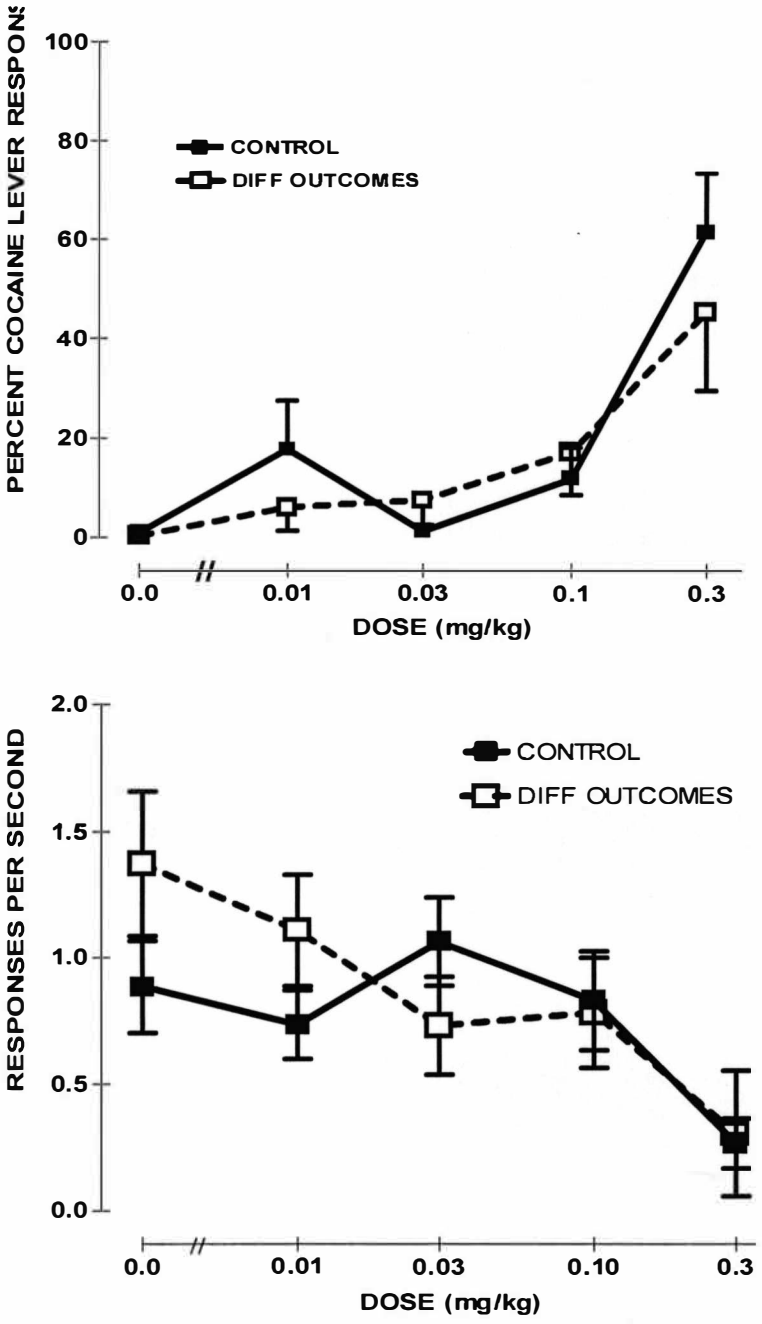

Figure 6. Results of Stimulus Generalization Tests With PD 128907 (IP).

PD 128907 (SC)

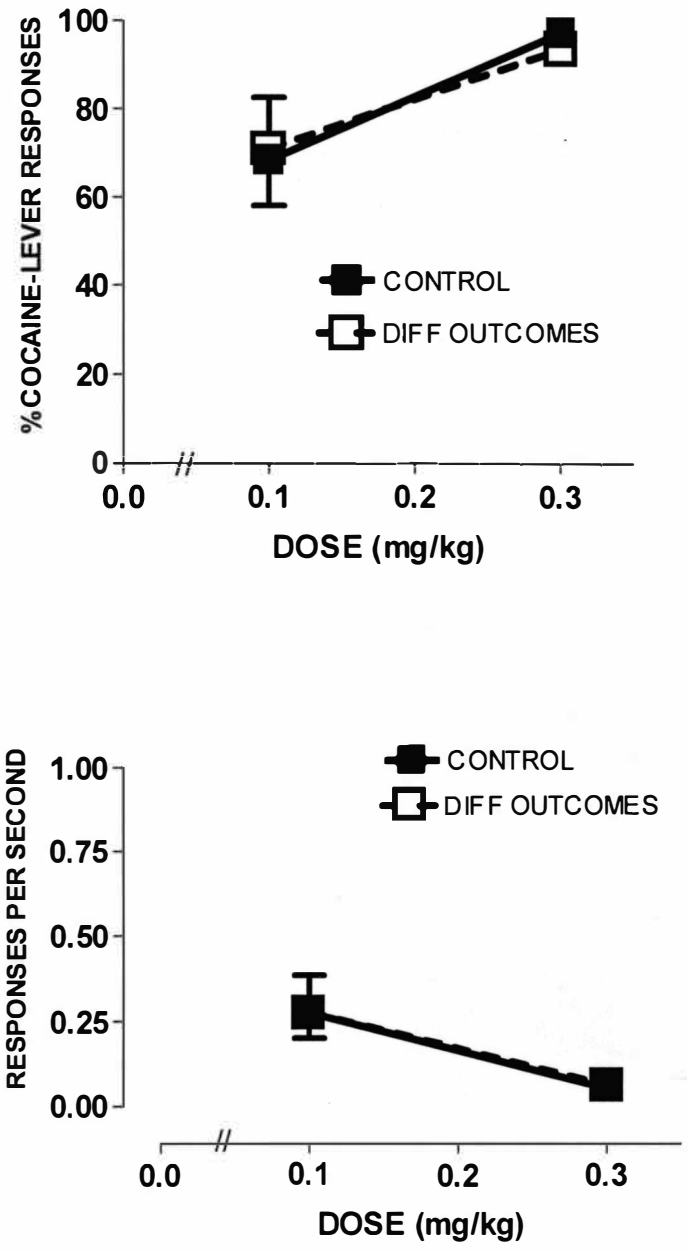

Figure 7. Results of Stimulus Generalization Tests With PD 128907 (SC).

DISCUSSION

The initial objective of this study was to replicate the differential outcomes effect on a saline-cocaine discrimination procedure in rats. The present study successfully replicated the findings of a previous study (Morgan & Baker, 1997) in which acquisition of a saline-cocaine discrimination was facilitated when differential outcomes were applied during discrimination training. The findings of the present study add more evidence to the hypothesis that differential outcomes can be used in drug discrimination training to speed the acquisition of stimulus control. As seen by the significant difference in sessions to criterion between the two training groups, the present study lends more credibility to the idea that the use of differential outcomes would enable investigators to reduce the time and effort necessary for such intensive research. Previous findings (Morgan & Baker, 1997) revealed that the use of differential outcomes during training did not significantly alter the cocaine dose-response curve. The results of the present study are consistent with this finding. The study by Morgan & Baker (1997) found no significant differences in generalization to other doses of the training drug, although there was some variability between the two groups. Similarly, results of the present study did not reveal any significant differences in the dose-response curves of the two groups, though it does appear that there is some level of variability between the control group and the differential outcomes group. Therefore, the present study offers more evidence that differential

outcomes can be applied to cocaine-saline discrimination research to facilitate acquisition of discrimination without significantly altering the cocaine dose-response curve. Possibilities for future research may involve the application of differential outcomes to other two-lever drug discriminations to investigate its potential to facilitate the discrimination of other drugs, and even application to three-lever discriminations. Although further research should be conducted to determine the potential of the differential outcomes effect in facilitating the acquisition of all drug discriminations, the results of the present study are promising.

Interestingly, stimulus generalization tests occurred more frequently for the differential outcomes group than for the control group. It is possible that the application of differential outcomes may have helped maintain stimulus control between test sessions, allowing animals in the differential outcomes group to be tested more frequently. Future research in this area should investigate differences in terminal accuracy and differences in maintenance of stimulus control between differential outcomes subjects and control subjects.

After completion of generalization testing, the differential outcomes group was run an additional 10 sessions without the use of the differential outcomes. All animals emitted 80% or greater responses on the condition-appropriate lever for at least nine of the 10 sessions, suggesting that stimulus control was maintained by the drug in the absence of olfactory cues.

The second objective of the present study was to examine whether the differential outcomes conditions applied during training have an impact on the

generalization of the dopamine D_3 receptor agonists (±) 7-OH-DPAT, (+) 7-OHDPAT, and PD 128907 administered during substitution testing. Results of the present study showed that there were no significant differences in generalization of any of these compounds between the control group and differential outcomes group. Results of generalization tests, with both the control and differential outcomes group, in the present study are consistent with the results of investigations where differential outcomes were not used. Results of the present study indicated that (±)-7-OH-DPAT completely substituted for cocaine in animals trained on a cocaine-saline discrimination. Acri et al. (1995) also found that (±)-7-OH-DPAT fully substituted for cocaine in rats trained to discriminate cocaine from saline. Similarly, Lamas et al. (1996) found that rhesus monkeys trained to discriminate cocaine from saline have been shown to exhibit complete generalization to the selective D_3 agonist (±)-7-OH-DPAT. Spealman (1996), however, found that 7-OH-DPAT only partially substituted for cocaine in squirrel monkeys trained on a cocaine-saline discrimination. In the investigations by Spealman, 7-OH-DPAT was administered intramuscularly (IM). In the present study, this compound was administered IP. The differences in generalization could be due the different routes of administration of 7-OH-DPAT or due to the different species studied. In other assays, such as the self-administration assay, 7-OH-DPAT has been found to substitute completely for cocaine in both rats (Caine & Koob, 1997;) and rhesus monkeys (Nader & Mach, 1996).

Data from the present study also show that when administered IP, (+)-7-OH-DPAT only partially substituted for cocaine in rats trained on a cocaine-saline

discrimination, regardless of training group. This finding is comparable to results of other similar studies. However, when administered SC, 7-OH-DPAT completely substituted for cocaine in both groups. This finding differs from that of other investigations. For example, Baker et al. (1998) found that rats trained to discriminate cocaine from saline exhibited only partial substitution to (+)-7-OH-DPAT. This could be due to the fact that Baker et al. (1998) used a lower training dose of cocaine (5.0 mg/kg), whereas a training dose of 10.0 mg/kg was used in the present study.

When administered IP, PD 128907 also produced only partial substitution for cocaine in both groups. This finding is consistent with other investigations. Spealman (1996) also found that PD 128907 only partially substituted for cocaine in squirrel monkeys trained on a cocaine-saline discrimination. However, when administered SC, PD 128907 produced complete substitution for cocaine in both training groups. This finding is consistent with other similar investigations. Acri et al. (1995) also found that PD 128907 fully substituted for cocaine in rats trained to discriminate cocaine from saline. Similarly, Lamas et al. (1996) found that rhesus monkeys trained to discriminate cocaine from saline have been shown to exhibit complete generalization to the selective D3 agonist PD 128907. In general, the overall results of the (±)-7-OH-DPAT, (+)-7-OH-DPAT, and PD 128907 substitution tests in the present study are consistent with the majority of the research on those compounds. The most important finding, however, is that there were no significant differences in the generalization of these test compounds between the two training

groups.

In summary, the two primary objectives of the present study were to replicate the differential outcomes effect on a cocaine-saline discrimination procedure in rats, and to examine whether the differential outcomes applied during training have an impact on the generalization of the selective dopamine D_3 receptor agonists (±)-7-OH-DPAT, (+)-7-OH-DPAT, and PD 128907. The present study successfully replicated the differential outcomes effect on a cocaine-saline discrimination in rats. Additionally, the present study found no differences in the generalization of selective DA D_3 agonists to cocaine in between a group that learned the discrimination via differential outcomes and a group that learned the discrimination without application of differential outcomes. The present study adds to the evidence that the use of differential outcomes in drug discrimination assays not only speeds discrimination acquisition, but also do not significantly alter dose-response curves or generalization to compounds with similar pharmacological mechanisms. Although more research is needed, it can be suggested that differential outcomes can only benefit individuals involved in drug discrimination research.

Appendix A

Protocol Clearance From the Institutional Animal Care and Use Committee (IACUC)

WESTERN MICHIGAN UNIVERSITY
INVESTIGATOR IACUC CERTIFICATE

Title of Project: D3 dopamine receptors in psychostimulant discrimination.

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 extramural 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 _____Approved ✓ Approved with the provisions listed below

Provisions or Explanations:
See attached e-mail amendment

Leonard Green
IACUC Chairperson

12-4-96
Date

Acceptance of Provisions

Lisa E. Baker
Signature: Principal Investigator/Instructor

12-4-96
Date

Leonard Green
IACUC Chairperson Final Approval

12-5-96
Date

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