Motivating Operations in Drug-Discrimination

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MOTIVATING OPERATIONS IN DRUG-DISCRIMINATION

by

Amin Duff Lotfizadeh

A dissertation submitted to the Graduate College
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy
Psychology
Western Michigan University
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Doctoral Committee:

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Cynthia Pietras, Ph.D.
Motivating operations (MO) play an important role in learning and performance. According to the behavior analytic conceptualization, MOs alter the probability of responses that lead to relevant reinforcers and alter the reinforcing “value” of those reinforcers (e.g., Michael, 1982, 1993). Recent research suggests that one way in which MOs influence stimulus control is by influencing the control of behavior by discriminative stimuli. Interestingly, in studies with nonhumans, such an effect is commonly observed when lights and tones are used as discriminative stimuli, but not when drugs are used. Procedural differences across studies involving the species studied, the measurement system used to quantify performance, and the manner in which MOs were manipulated, may account for the discordant results. The present research evaluated this possibility in a series of three experiments. Results of these experiments suggest that the discrepant results obtained in previous studies were not due to the measurement system, testing procedure, or the species used. The manner in which MOs are manipulated may, however, play a role, and it appears that such variables affect stimulus control only when motivation is increased relative to the baseline condition.
ACKNOWLEDGMENTS

I would like to thank my advisor Dr. Alan Poling for his guidance and support. I would also like to thank my dissertation committee members, Dr. Cynthia Pietras, Dr. Lisa Baker, and Dr. Steve Ragotzy. Thanks to my lab-mates for making the research environment the most pleasant place. Last but not least, I would like to thank my family, girlfriend, and the dogs for their love and support all along.

Amin Duff Lotfizadeh
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CHAPTER I

INTRODUCTION

Behavior analysts have long recognized the importance of motivation. Skinner certainly did so, as evidenced by his treatment of deprivation and satiation as sources of control with respect to verbal behavior (Skinner, 1957) and other responses (e.g., Skinner, 1938; 1953). Nonetheless, the systematic study of motivational variables within a behavioral framework was largely ignored until Michael’s (1982, 1993) conceptualization of establishing operations (EOs).

According to Michael, EOs are environmental events that have two distinct effects, which he termed value-altering and behavior-altering. The value-altering effect refers to changes in the effectiveness of a reinforcer or punisher relevant to the EO in place. The behavior-altering effect refers to changes in the probability of behaviors that historically have produced the reinforcers or punishers relevant to that EO.

Michael (1982, 1993) used "EOs" to refer to both environmental events that increase and decrease: (a) the effectiveness (value) of relevant consequences and (b) the rate of relevant behaviors. In 2003, Laraway, Snycerski, Michael, and Poling (2003) proposed the term "motivating operations" (MOs) to describe all environmental events that have rate and value-altering effects. They also proposed that the term "establishing operations" should be restricted to variables that cause an increase in the frequency of behaviors and the effectiveness of relevant
reinforcers, with the term "abolishing operations" (AOS) used to describe variables that decrease the frequency of relevant behaviors and the effectiveness of relevant reinforcers. This nomenclature is now generally accepted and will be used in the present manuscript.

Laraway et al. (2003) suggested that an aspect of the behavior-altering effect is that an MO will alter the evocative strength of relevant discriminative stimuli (S\textsuperscript{D}s). However, in addition to S\textsuperscript{D}s, stimuli that physically resemble an S\textsuperscript{D} also evoke responding, as is illustrated in stimulus generalization studies. As an example of a typical stimulus generalization procedure, a rat is initially trained to emit a food-reinforced operant response in the presence of a 10,000 Hz tone. Subsequently, responding is assessed across a range of stimuli that vary from the original training stimulus along the physical dimension that defines the S\textsuperscript{D} (Guttman & Kalish, 1956). For instance, the rat in our example might be exposed to 2,000, 4000, 6,000, and 8,000 Hz tones. In this case, each tone would probably engender some responding, but the level (e.g., rate) of responding would be inversely related to the difference between the test and training (S\textsuperscript{D}) stimulus. Such an effect is clearly illustrated in a generalization gradient, which depicts relative level of responding as a function of antecedent stimulus value. If MOs alter the evocative strength of established S\textsuperscript{D}s, it seems reasonable to assume that MOs would affect the evocative strength of other stimuli as well.

Skinner (1953) proposed such an effect in a discussion of the effects of deprivation and satiation on generalization, as follows:
By increasing the deprivation we increase the range of effective stimuli or, to put it another way, reduce the importance of differences in stimuli. When a young man deeply in love mistakes a stranger passing in the street for his beloved, the strong motivation has made a wider range of stimuli effective in controlling the response of seeing his beloved. (p. 218)

To evaluate Skinner’s contention, Lotfizadeh, Edwards, Redner, and Poling (2012) recently conducted a review of studies that obtained stimulus generalization gradients under different deprivation levels. The results of the studies that utilized exteroceptive stimuli are summarized below. In addition, a further analysis of relevant data not discussed by Lotfizadeh et al. is provided.

**Literature Review**

A total of seven studies examined the influence of food or water deprivation on stimulus control exerted by visual or auditory stimuli. The MOs were manipulated by either altering the animals’ weights relative to their free-feeding weights, or by altering the number of hours the animals were deprived of food or water. Three of the seven studies altered the animals’ weights as the MO for food reinforcers, whereas four studies utilized hours without food or water as the MO.

In three experiments, the authors examined the influence of varying levels of food deprivation, as defined by varying percentages of free-feeding weights, on stimulus generalization in pigeons (Jenkins, Pascal, & Walker, 1958; Kalish & Haber, 1965; Thomas & King, 1959). The pigeons’ body weights during test conditions ranged from 60% to 90% of free-feeding values, while being
maintained at 80% during training in most studies. In all three studies, key-peck responses were established according to a variable-interval (VI) 1-min schedule of reinforcement or according to an unspecified intermittent schedule. These studies utilized exteroceptive visual stimuli as the $S^D$ and as test stimuli and both relative measures of responding (e.g., response frequency relative to $S^D$ conditions) and absolute measures (e.g., mean responses) were obtained.

The results of the studies suggested that, as deprivation increased, the birds responded more in the presence of the $S^D$ and all other stimuli, but the increase in response strength varied as a function of how similar the test stimulus was to the $S^D$. Increasing deprivation also increased the range of stimuli that evoked responding. One exception to these findings was that when the animals were deprived to 60% of their free-feeding weights (Thomas & King), they responded less frequently in the presence of the $S^D$ than when they were less deprived (70% and 80% of their free-feeding weights). This exception may have been due to the extreme level of food deprivation in place.

Four studies examined the influence of hours deprived of food or water on stimulus generalization in rats (Brown, 1942; Coate, 1964; Healey, 1965; Newman & Grice, 1965). Three of these studies examined the approach response by training the subjects to traverse a runway in order to obtain food when an exteroceptive $S^D$ was present. In the fourth study, water-deprived rats were trained to lever-press for water according to a VI 1.5-min schedule of reinforcement (Coate). The exteroceptive stimuli that served as the $S^D$ and test stimuli were auditory (e.g., tone) and visual (e.g., varying illuminations of a disc, varying sizes
of a circular disc, and varying separations between two lights). The dependent variables of interest were response latency, response speed, response force (measured in grams), and mean responses.

Results of all of these studies suggested that, as deprivation increased, the animals responded more in the presence of all stimuli, but more so in the presence of those that more closely resembled the $S^D$. In addition, the range of stimuli that evoked responding increased directly with the number of hours the animals were deprived. An exception to these findings was that the 48-hr water-deprived rats did not respond more frequently in the presence of all test stimuli when compared to lower water-deprivation conditions (Coate, 1964). This exception may have been due to the physiological effects of extreme water deprivation.

**Gradients of Relative Generalization**

To facilitate comparisons across experiments, the data from studies that tested generalization across a minimum of five stimuli were transformed and analyzed to obtain gradients of relative generalization. Gradients of relative generalization were obtained for each deprivation condition by dividing the number of responses at each test stimulus value by the total number of responses that occurred across all test values under the corresponding deprivation level, and multiplying the result by 100. Figure 1 depicts the gradients of relative generalization for three of the studies (Thomas & King, 1959; Coate, 1964; Kalish & Haber, 1965). Visual inspection of the data reveals that the shapes of the gradients changed under different deprivation conditions. With the exceptions of the 90% free-feeding weight group in Thomas and King and the 48-hr deprivation
group in Coate, increasing deprivation caused the gradients to become increasingly sigmoidal (having an “s” shape). This pattern stands out in the Kalish and Haber study (bottom of Figure 1). This effect was the result of an increase in the relative frequency of responses in the presence of stimuli most similar to the training stimulus (denoted as “1” on the x-axes in Figure 1).

<table>
<thead>
<tr>
<th>Thomas &amp; King (1959)</th>
<th>0=Training Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>60% of free-feeding weight</td>
<td></td>
</tr>
<tr>
<td>70% of free-feeding weight</td>
<td></td>
</tr>
<tr>
<td>80% of free-feeding weight</td>
<td></td>
</tr>
<tr>
<td>90% of free-feeding weight</td>
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<table>
<thead>
<tr>
<th>Coate (1964)</th>
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<tbody>
<tr>
<td>48-h deprivation</td>
</tr>
<tr>
<td>40-h deprivation</td>
</tr>
<tr>
<td>12-h deprivation</td>
</tr>
<tr>
<td>8-h deprivation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kalish &amp; Haber (1965)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% of free-feeding weight</td>
</tr>
<tr>
<td>80% of free-feeding weight</td>
</tr>
<tr>
<td>40% of free-feeding weight</td>
</tr>
</tbody>
</table>
Figure 1. Gradients of relative generalization. The percentage of responses that occurred at each test value under each deprivation condition (0= Training stimulus test value or $S^{D}$).

Discussion

All of the studies reviewed demonstrated a direct relationship between deprivation and level of responding in the presence of the $S^{D}$, an effect also observed in studies that did not ascertain generalization gradients (e.g., Powell, 1971; 1973). With the exceptions of the 60% of free-feeding weight group in Thomas and King (1959) and the 48-hr deprivation group in Coate (1964), relative response strength varied directly with deprivation level across all test values. As mentioned before, these two inconsistencies could have been due to the physiological effects of severe deprivation on responding. Additionally, there was a tendency for response strength to increase most at test values similar to the training stimulus. That is, the change in response strength was not the same across different test values, making the gradients of relative generalization increasingly sigmoidal under higher deprivation conditions.

The range of stimuli that evoked responding generally increased at high deprivation levels. At test values furthest from the training stimulus, relative response strength was higher under high deprivation conditions. The studies that were reviewed tested a limited range of test stimuli, however, which makes it difficult to determine whether responding would have eventually approached zero or would have reached an asymptote above zero at the tail ends of the gradients. Given the range of stimuli that were tested, response strength was higher at the tail ends of the gradients when the animals were more deprived, suggesting an
increase in the range of evocative stimuli. This effect is consistent with Skinner’s speculations.

For example, Skinner’s (1957) suggestion that “the lone man dying of thirst gasps Water!” (pp. 46) emphasizes that high deprivation can evoke a response in the absence of any relevant stimulus. Keller and Schoenfeld (1950) also make this point, contending that “extreme degrees of drive may precipitate ‘illusions’ wherein very weak or usually non-generalizing stimuli may be responded to” (pp. 290). Given the results of the studies reviewed, it seems as though the increase in the range of stimuli that evoke responding under high deprivation conditions is in part due to MOs influence on stimulus control, as well as direct effects on behavior. This is evidenced by MOs’ influence on responding at all test stimulus values and by changes in the shape of gradients of relative generalization.

In addition to food and water deprivation, the effects of MOs on stimulus control extend to shock avoidance paradigms. In such an arrangement, the organism is trained to avoid a shock when a particular stimulus is presented. Generalization tests are conducted across a range of stimuli under different shock intensities. Rosenbaum (1951, 1953) demonstrated that increasing shock intensity during generalization tests results in similar changes in stimulus control as those observed under increasing food or water deprivation. Note, however, that altering shock intensity, in contrast to altering level of food or water deprivation, could be construed as varying either reinforcement magnitude or motivation.
Although the relevant literature is not large, published studies provide relatively consistent evidence that altering level of water deprivation, food deprivation, and shock intensity affects stimulus control, as is evident in the shape of generalization gradients. This effect has been shown with both visual and auditory stimuli. Interestingly, however, somewhat inconsistent results have been observed under drug discrimination procedures. Relevant studies are discussed in Chapter 2.
CHAPTER II

REVIEW OF MOTIVATING OPERATIONS IN DRUG-DISCRIMINATION STUDIES

The influence of MOs on stimulus control has been demonstrated across studies that utilized visual and auditory stimuli as $S^D$s. Such stimuli are often considered as “exteroceptive.” Drug effects, in contrast, are commonly viewed as “interoceptive” stimuli, although the distinction is open to debate. In any case, a few studies provide information about the influence of motivation on performance under drug-discrimination. In a typical drug-discrimination paradigm, an organism is injected with a specific dose of a drug and trained to emit a response (e.g., right-lever press) in order to obtain food. On alternating training sessions, the animal is injected with a vehicle (e.g., saline solution) and a second response is differentially reinforced with food (e.g., left-lever press). Consequently, the interoceptive stimuli produced by the drug injection and by the vehicle injection (absence of drug) are established as $S^D$s for different responses. Following training, generalization gradients (dose-response gradients) are obtained across various doses of the training drug.

Three studies have investigated the influence of food deprivation under drug-discrimination procedures (Gaiardi, Bartoletti, Bacchi, Gubellini, & Babbini, 1987; Li, Garner, Wessinger, & McMillan, 1995; Massey & McMillan, 1987). The intent of these studies was to examine whether increasing food deprivation would affect the discriminative stimulus properties of drugs in the same way that
it affects the reinforcing properties of drugs (Carroll & Meisch, 1984). Carroll and Meisch demonstrated a direct relationship between food deprivation and drug self-administration across a variety of conditions and drugs. While the influence of food deprivation on drug self-administration is presumably due to changes in the reinforcing properties of drugs, these researchers speculated that food deprivation could also affect the discriminative stimulus properties of drugs.

In an early study, Massey and McMillan (1987) examined the influence of 70%, 80%, and 90% of free-feeding weights on phencyclidine (PCP) discrimination. Four pigeons were given intramuscular (i.m.) injections of PCP (1.5 mg/kg) or saline prior to sessions and trained to key peck using a color-tracking procedure. A training trial was initiated when the pigeon pecked a white center key, which resulted in extinction of the center key and illumination of one of the side keys red and the other green. Responding on the key color correlated with the injection according to a FR 5 schedule ended the trial. Food reinforcement occurred after completion of 10 trials. Dose-response gradients were obtained using a cumulative-dosing procedure (i.e., all doses tested in the same day cumulatively) across four doses of PCP (0.30, 0.56, 1.00, and 1.70 mg/kg) at 70%, 80%, and 90% of free-feeding weights.

The dependent variables of interest were the percentage of responses on the PCP-appropriate key, response rate, and latency of first response on the center white key. Deprivation level did not influence percentage of PCP-appropriate key responses, but there was a direct relationship between deprivation and response latency and an indirect relationship with response rate. It should be noted that in
addition to PCP, pentobarbital (3.0, 5.6, 10, and 17 mg/kg) and d-amphetamine (0.3, 1.0, 1.7, and 3.0 mg/kg) dose-response gradients were obtained across different deprivation levels in order to assess generalization across psychoactive drugs. The discriminative stimulus properties of PCP generalized only to pentobarbital, but deprivation did not influence generalization.

Gaiardi, Bartoletti, Bacchi, Gubellini, and Babbini (1987) examined the effects of pre-feeding and no pre-feeding conditions in six rats trained to discriminate morphine (10 mg/kg) from saline in a two-lever operant procedure. The rats received intraperitoneal (i.p.) injections of morphine or saline prior to training sessions and responding on the injection-appropriate lever was reinforced according to a tandem (VI 60-s FR 10) schedule of reinforcement. Dose-response gradients were obtained across four doses of morphine (2.5, 5.0, 7.5, and 10.0 mg/kg) under 15-min pre-feeding and no pre-feeding (same deprivation level as training) conditions. Testing was conducted using a dose-by-dose testing procedure (i.e., a different dose was tested on different days, with re-training sessions occurring in-between tests).

The dependent variables of interest were percentage of rats that selected the morphine-appropriate lever (i.e., percentage of rats that responded on the morphine-paired lever 10 times before emitting 10 responses on the saline-paired lever) and response rate. With the exception of the training dose (10.0 mg/kg morphine), a higher percentage of rats selected the morphine-paired lever at all test doses under higher deprivation conditions. The median effective dose (ED$_{50}$), the dose where 50% of the rats selected the morphine lever, was lower in the
deprived condition (6.09 mg/kg) than it was in the partially satiated condition (7.79 mg/kg), with the difference being statistically significant (Figure 2). On the other hand, deprivation did not affect response rate.

Figure 2. Percentage of rats that selected the morphine-appropriate lever (percentage that emitted a total of 10 responses on the morphine-appropriate lever before emitting a total of 10 responses on the vehicle-appropriate lever) under food deprived conditions and partially sated (15-min pre-feeding). This figure is based on the data reported by Gaiardi et al. (1987).

In an attempt to understand the discrepant results in the abovementioned drug-discrimination studies, in two studies Li, Garner, Wessinger, and McMillan (1995) systematically replicated Massey and McMillan (1987) using pentobarbital in Experiment 1 and Gaiardi et al. (1987) using morphine in Experiment 2. In Experiment 1, four pigeons were trained to discriminate i.m. injections of pentobarbital (5.0 mg/kg) from saline using a color-tracking procedure similar to Massey and McMillan. Generalization tests were conducted after the pigeons were given 0%, 25%, and 50% of the amount of food required for satiation 30 min prior to test sessions. A cumulative-dosing procedure was used and tests were
conducted across four pentobarbital doses (1.0, 3.0, 5.6, and 10.0 mg/kg). The dependent variables of interest were percentage of responses on the pentobarbital-appropriate key, latency of the first response, and response rate. Pre-feeding resulted in a general decrease in response rate and an increase in response latency. However, unlike Massey and McMillan, pre-feeding did not influence percentage of pentobarbital-appropriate key responses.

In the second experiment, Li et al. (1995) examined the influence of 15 min pre-session feeding vs. no pre-feeding in five rats trained to discriminate morphine (10 mg/kg) from saline. During training, the rats were given i.p. injections of morphine or saline prior to sessions and responding on the injection appropriate lever was reinforced according to a FR 15 schedule. During testing, generalization gradients were obtained using a dose-by-dose testing procedure across five doses of morphine (0.3, 1.0, 3.2, 10.0, and 13.0 mg/kg) under deprived conditions and partially sated conditions (15-min pre-session feeding). The dependent variable of interest was percentage of morphine-appropriate responses. Although a higher percentage of responses occurred on the morphine-appropriate lever across most test doses (except 13.0 mg/kg), the difference in the ED 50 values was not statistically significant (Figure 3).
Figure 3. Percentage of responses on the morphine lever under food deprived conditions and 15-min pre-session feeding conditions. This figure is based on the data reported by Li et al. (1995) in experiment 2.

**Discussion**

With respect to the primary dependent variables of interest (i.e., percentage of drug-appropriate responses or percentage of animals choosing the drug-appropriate lever), only one of four studies demonstrated that altering deprivation influenced stimulus control exerted by drugs (Gaiardi et al., 1987). While three out of four studies failed to demonstrate a statistically significant effect, Li et al. (1995; in experiment 2) found similar but non-significant results to Gaiardi et al. In addition, three of the studies measured response rate and two of those studies also measured response latency. Altering deprivation influenced response rate in two out of three studies, as well as response latency in both studies that measured it (see Table 1 for a summary of all results).
Table 1

Summary of drug-discrimination studies. Summary of results according to whether MOs influenced (“Yes”) the dependent variable or not (“No”).

<table>
<thead>
<tr>
<th>Study</th>
<th>% Drug-Lever Responses</th>
<th>% of Animals Selecting Drug-Lever Responses</th>
<th>Response Rate</th>
<th>Response Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaiardi et al. (1987)</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. (1995)-exp. 2</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massey &amp; McMillan (1987)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Li et al.–exp. 1</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Although these results seem inconsistent, the discrepancy may be due to certain procedural differences among the studies. First, with respect to the primary measure of interest, when a continuous measure was used (i.e., percentage of drug-lever responses), MOs did not influence stimulus control (Li et al. 1995; Massey & McMillan, 1987). In contrast, when a quantal measure was used (i.e., percentage of animals that selected the drug-lever), MOs did influence stimulus control (Gaiardi et al., 1987). Therefore, the discrepant results across studies may be due in part to the dependent variable used. A second notable difference between the studies was the testing procedure used. Two of the studies (Gaiardi et al.; Li et al., experiment 2) utilized a dose-by-dose testing procedure and obtained similar results. In one of these studies, the influence of MOs on stimulus control was statistically significant (Gaiardi et al.), while in the other study the results were in the same direction but not statistically significant (Li et al., experiment 2). In contrast, when a cumulative dosing procedure was utilized,
MOs did not influence stimulus control (Li et al., experiment 1; Massey & McMillan). The third notable procedural difference was the species used. In the studies that utilized pigeons as subjects, MOs influenced response rate (Massey & McMillan; Li et al., experiment 1), but not when rats served as subjects (Gaiardi et al.). In an attempt to examine the extent by which these procedural differences account for these discrepant results, the experiment described in Chapter 3 will examine the influence of MOs on stimulus control in rats trained to discriminate $d$-amphetamine from saline injections.
CHAPTER III

EXAMINATION OF THE INFLUENCE OF FOOD DEPRIVATION ON STIMULUS CONTROL EXERTED BY D-AMPHETAMINE

On the basis of the drug-discrimination studies reviewed in the previous chapter, the influence of MOs on discriminative stimulus control exerted by drugs seems limited. Altering deprivation reportedly influenced the discriminative stimulus properties of morphine, but failed to exert any influence on PCP and pentobarbital. In an attempt to further examine the effects of MOs on discrimination of other psychoactive drugs, this chapter will describe a study that examined the influence of food deprivation on stimulus control exerted by d-amphetamine.

As previously mentioned, the discrepant MO effects in prior drug-discrimination studies may have been due to the dependent variable used. In an attempt to examine this possibility, the present study obtained both a continuous and quantal measure of performance. Moreover, the only study that demonstrated that MOs affected stimulus control by drugs utilized a dose-by-dose testing procedure in rats. To examine if these variables were responsible for the observed effects of motivation on performance, the present study also utilized a dose-by-dose testing procedure with rats as subjects.

Methods

Subjects

Ten male Sprague-Dawley rats served as experimental subjects and six
additional rats served as a weight control to account for developmental weight gains (Lesser, Deutsch, & Markofsky, 1970). The rats had a prior history of lever pressing for water. Each rat was approximately 200 days old at the beginning of the study. The experimental rats were maintained at 80% of their free-feeding weights and had free access to water in their home cages, whereas the weight control rats had free access to both food and water at all times. The rats were individually housed in 20 cm x 40 cm cages in a colony room maintained at 20º C and 20% humidity on a 12-hr light/12-hr dark cycle. All experimental sessions were conducted during the light cycle.

The experimental rats’ weights were adjustment once every two weeks according to the percentage of baseline weight gained by the weight control group. Supplemental food was provided after the final session of the week, before the off day. Based on the percentage of baseline weight that was gained, each experimental rat’s expected weight was calculated and 80% of that was determined as the new target weight. Supplemental food was given following the last session of the week to allow for the rats’ weights to adjust during the off day. The weight adjustment procedure continued until the animals were 300 days old. The study was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2010) and approved by the Institutional Animal Care and Use Committee at Western Michigan University (Appendix).

**Apparatus**

Experimental sessions were conducted using five Med Associates (St.
Albans, VT) operant chambers measuring 31.5 cm long × 25.5 cm wide × 25 cm high. The chambers contained two retractable response levers on the front wall, with each lever 3 cm from the nearest sidewall and 6 cm above the floor. An opening 2 cm above the floor and between the two levers contained a food cup, where 45-mg (BioServ, Frenchtown, NJ) food pellets were delivered. A 7-W white bulb (houselight) centered at the top of the opposite wall provided illumination during sessions. Each chamber was placed inside a sound attenuating shell that contained an exhaust fan that provided ventilation and masking noise. A personal computer that used MED-PC® software (v. IV for Windows) was connected to the MED-Associates interface and controlled the operant chambers. Preliminary training sessions were conducted in five operant chambers similar to the ones described above, with the exception that it also contained a center lever beneath the food magazine. The rats were provided with Purina Rodent Chow (Brentwood, MO) in their home cages after experimental sessions or prior to sessions during the low deprivation conditions.

**Training**

**Preliminary training.** The rats were initially exposed to two 60-min sessions of fixed-time (FT) 60-s food delivery, during which a food pellet was delivered once every 60 s, irrespective of the rat’s behavior. Next, the rats were trained to press a center lever in order to obtain food pellets. An FR 1 schedule of reinforcement was in effect and the response requirement increased by 1 after every 12th reinforcer. Each session lasted until 60 reinforcers were obtained. As a result, the schedules progressed in the following order across consecutive sessions: FR 1, FR
5, FR 10, FR 15, and FR 20. Once FR schedule requirements reached FR 20, three additional sessions were conducted at this value.

**Discrimination-training.** Initially, an errorless-discrimination-training procedure was implemented (Overton, 1979). During this phase, the rats were given either i.p. injections of saline or d-amphetamine (1.0 mg/kg) and placed in their home cages for a pre-treatment time of 10 min before being placed in the operant chambers. During training sessions, only the lever corresponding with the injection was available for responding. An FR 10 schedule was in effect at the beginning of this phase for both drug and vehicle. The FR requirements increased by one after every tenth reinforcer until the requirement reached an FR 20, where an additional saline and drug session was conducted at FR 20. Sessions lasted until 50 reinforcers had been obtained or after 20 min had elapsed. The lever designated as the drug lever was counterbalanced across rats (left lever for half, right lever for the other).

Discrimination-training began once responding had reached FR 20 on both saline and drug-appropriate levers. Discrimination-training was similar to the errorless training phase, with the exception that both levers (right and left) were available for responding and only the injection appropriate lever yielded reinforcers according to an FR 20 schedule. The order of saline/drug sessions was random, with the exception that there were no more than two consecutive drug or saline days, in addition to an equal number of drug and saline days each week. Discrimination-training continued until the animals responded on the injection
appropriate lever at 80% or higher accuracy across 8 out of 10 consecutive sessions (a minimum of 4 saline and 4 drug sessions at 80% accuracy or higher).

**Pharmacological Preparation.** A sterile 0.9% saline solution served as vehicle. The \(d\)-amphetamine hemisulfate (Sigma Aldrich, St. Louis, MO) was dissolved in the saline solution and injected intraperitoneally (i.p.) at a volume of 1.0 ml/kg volume. Doses were calculated based on the salt weight.

**Testing**

Five doses of \(d\)-amphetamine (0, 0.03, 0.1, 0.3, & 1.0 mg/kg) were tested using a dose-by-dose testing procedure, whereby at least a saline and a drug discrimination-training session (with 80% accuracy or higher) was conducted between test sessions. Testing was conducted under extinction conditions and the sessions lasted until 5 min had elapsed or until a total of 20 responses had been emitted on a particular lever. Dose-response gradients were obtained across three levels of food deprivation: (a) after rats were given their daily rations an hour prior to test sessions (*non-deprived* condition), (b) after rats were given 1 g an hour prior to test conditions (*moderately-deprived* condition), and (c) without the rats being fed prior to test sessions (*deprived* condition). It should be noted that the moderately deprived condition was initially intended to serve as the deprived condition and the 1 g pre-feeding was in effect in order to prevent test sessions from becoming discriminable due to pre-feeding. However, upon obtaining the *non-deprived* and *moderately* deprived gradients, it was decided that *deprived* dose-response gradients be obtained as well. As a result, the *deprived* gradients were obtained last for all rats, while the order in which the other two gradients
were obtained was counterbalanced across the rats. The order of test doses was counterbalanced across rats so that each dose was tested in every possible order and remained the same during all deprivation test conditions for each rat.

**Statistical Analysis**

The response measures of interest were: (a) percentage of \textit{d}-amphetamine lever responses (continuous measure), (b) percentage of animals that selected the \textit{d}-amphetamine lever (percentage of animals that emitted a total of 20 responses on the \textit{d}-amphetamine lever first; quantal measure), (c) response rate, and (d) latency of the first response. Means were calculated for each response measure and were used for visual analysis. With the exception of the quantal measure, a repeated-measures ANOVA was conducted for all other response measures. Drug dose served as one factor (five levels) and deprivation condition served as the second factor (three levels). Mauchly’s test of sphericity was conducted and Greenhouse-Geisser corrections were applied when assumptions of sphericity were violated and the adjusted dfs are reported. Post-hoc testing was conducted on significant response measures using Bonferroni’s corrected t-tests for all pairwise comparisons. ED$_{50}$ values were obtained for the quantal measure using non-linear regression. Alpha levels were set at 0.05 for all statistical analysis.

**Results**

Figure 4 depicts the mean (± S.E.M.) percentage of drug-lever responses at each test dose as a function of deprivation level. Dose-response gradients were obtained under every deprivation condition, and with each step increase in test dosage, there was an increase in the percentage of drug-lever responses. Visual
inspection of the gradients does not reveal any differences in the gradients as a function of deprivation level. A two-way ANOVA revealed a significant main effect for dose [$F(4,36)=24.89, p<0.001$], but did not reveal a significant main effect for deprivation conditions [$F(1.213, 10.981)=0.968, p=0.365$] or a significant interaction. The difference between the ED$_{50}$ values across the deprived (0.36 mg/kg), moderately deprived (0.28 mg/kg), and non-deprived (0.22 mg/kg) gradients was not statistically significant with 95% CIs [0.173, 0.765], [0.195, 0.414], and [0.124, 0.387] respectively.

![Graph](image)

**Figure 4.** Percentage of drug-lever responses across test doses of d-amphetamine as a function of deprivation level. The training doses were 0 mg/kg and 1.0 mg/kg and the deprived condition was the deprivation level in effect during training.

Figure 5 depicts the percentage of animals that selected the drug-lever at each test dose as a function of deprivation. Visual inspection of these gradients did not reveal any differences between deprivation levels. The difference in the ED$_{50}$ values was similar across deprivation conditions. The ED$_{50}$ value that was
obtained for the deprived condition (0.49 mg/kg) was slightly higher than the moderately deprived (0.19 mg/kg) and non-deprived (0.23 mg/kg) conditions.

Figure 5. Percentage of rats that selected the drug-lever (emitted a total of 20 responses on the drug-lever before emitting a total of responses on the saline-lever) across test doses as a function of deprivation.

Figure 6 illustrates mean response rates across test doses and deprivation conditions. Mean response rates decreased with each step increase in \(d\)-amphetamine test value. In addition, response rate decreased as the animals became progressively less food deprived. A two-way ANOVA revealed a significant main effect for both deprivation level \([F(2, 18)=12.728, p<0.001]\) and dose \([F(4, 36)=19.661, p<0.001]\), but not for an interaction \([F(8, 72)=1.669, p=0.121]\). Post-hoc comparisons were conducted using Bonferroni-corrected t-tests. These post-hoc comparisons revealed that mean response rates were lower under non-deprived conditioned than they were under moderately deprived \((p<0.001)\) or deprived conditions \((p<0.001)\). Post-hoc analysis of drug dose revealed lower response rates at the training dose (1.0 mg/kg) than at 0 mg/kg.
(\(p<0.001\)), 0.03 mg/kg \((p<0.001)\), 0.1 mg/kg \((p<0.001)\), and 0.3 mg/kg \((p<0.001)\). Mean response rates were also lower at 0.03 mg/kg than they were at 0.03 mg/kg \((p=0.004)\).

![Figure 6](image.png)

**Figure 6.** Mean group response rates across different test doses under varying deprivation levels.

Figure 7 shows mean response latencies at each test dose as a function of deprivation level. Visual inspection reveals that the latency of the first response was slightly higher under *non-deprived* conditions than it was under the other deprivation conditions. In addition, response latencies increased with increases in the test dose. A two-way ANOVA revealed a significant main effect for deprivation \([F(1.143, 10.283)=4.813, p=0.0049]\) but not for dose \([F(1.622, 14.6)=3.007, p=0.089]\) or for an interaction \([F(1.789, 16.186)=0.917, p=0.410]\). Post-hoc comparisons were conducted using Bonferroni’s corrected t-test across deprivation conditions, but they failed to yield a significant main effect.
Discussion

The present study demonstrated that altering food deprivation did not influence the discriminative stimulus properties of \( d \)-amphetamine. These results are consistent with those reported by Li et al. (1995) and Massey and McMillan (1987), but in contrast with Gaiardi et al. (1987) who demonstrated that pre-feeding did in fact affect stimulus control exerted by morphine. In addition, in the present experiment deprivation affected response rate and latency of responding, which was once again consistent with Li et al. (experiment 1) and Massey and McMillan, but in contrast with Gaiardi et al. Some of these discrepancies may be attributed to various procedural differences that were not explored in the present study. Some of these differences include the schedule of reinforcement in effect, the sample size in each study, whether or not reinforcers were delivered during testing, and other procedural differences. Instead, the present study sought to
examine the extent by which the dependent variable used and the testing procedure accounted for the results.

The extent to which MO effects were demonstrated as a result of the dependent variables was examined by obtaining both a quantal and a continuous measure. While the only study that obtained statistically significant results utilized a quantal measure (Gaiardi et al., 1987), all other studies obtained a continuous measure and failed to demonstrate a statistically significant effect. In the present study, both measures yielded very similar gradients, suggesting that the discrepancies across studies were not due to the response measure used.

A second procedural difference that was examined was the testing procedure used in each study. Both Li et al. (experiment 2) and Gaiardi et al. (1987) used a dose-by-dose testing procedure and demonstrated that increasing deprivation caused a slight shift in the gradients to lower values (slightly decreasing the ED50 values). The present study carried out a dose-by-dose testing procedure as well, but obtained an effect that was not statistically significant in the opposite direction (slight increase in the ED50 values when deprived). Therefore, the testing procedure did not account for the discrepancies across studies either.

Given that the influence of MOs on stimulus control has been reliably demonstrated across studies using exteroceptive stimuli (see Chapter 1), it is unclear what aspects of the drug-discrimination procedure may account for the discrepant results. These differences can not be attributed to age, gender, or the specific breed of the subjects because these variables were the same as Gaiardi et
al. (1987) who found an effect. It is possible that MOs may influence stimulus control across a limited range of psychoactive drug classes. In an organism’s natural environment, it is unlikely that interoceptive stimuli may function as $S^D$s signaling the availability of food reinforcement. Therefore, the discriminative stimulus properties of interoceptive stimuli may not be as easily influenced by operations like food deprivation.

Another possible reason why MOs did not reliably influence stimulus control exerted by drugs is the direction of change in deprivation relative to training conditions. In all of the drug-discrimination studies, except for Massey and McMillan (1987), generalization tests were conducted under training deprivation levels and deprivation levels lower (i.e., less hungry) than training. This was not the case in studies that used exteroceptive stimuli where testing was conducted under higher than training deprivation conditions as well. Although Massey and McMillan obtained dose-response gradients under higher deprivation conditions than initial training, discrimination-training had also been conducted at the high deprivation conditions. In order to assess the influence of higher deprivation levels on stimulus without the confound of training occurring under the high deprivation conditions, research reported in the next chapter will examine the influence of higher than training deprivation conditions on stimulus control exerted by $d$-amphetamine.
CHAPTER IV

EXAMINATION OF THE INFLUENCE OF INCREASING FOOD DEPRIVATION ON STIMULUS CONTROL EXERTED BY D-AMPHETAMINE

In Chapter 1 it was pointed out that under high deprivation conditions the gradients of relative generalization become increasingly sigmoidal and under low deprivation conditions these gradients become increasingly curvilinear. These effects suggest that the specific manner by which MOs influence stimulus control depends on the directional changes in deprivation. In all but one drug-discrimination study discussed so far, generalization gradients were obtained under training deprivation and less deprived states (i.e., decreased deprivation relative to baseline). Since only one study (Gaiardi et al., 1987) demonstrated an effect using such a MO manipulation, it is possible that MO effects are less evident in drug-discrimination when decreasing deprivation relative to baseline.

Although only Gaiardi et al. (1987) demonstrated that pre-feeding influenced stimulus control exerted by morphine, another explanation for their results may have been because a less strict stability criterion was used during their training compared to other drug-discrimination studies. Based on their criterion, testing was initiated if less than 12 incorrect responses occurred on the first trial across 8 out of 9 consecutive sessions. However, since a tandem VI 1-min/FR 10 schedule was in effect, such a criterion meant that the animals could have responded at 50% accuracy and still met the criterion. Thus, discriminated responding may not have been well established before testing and pre-feeding
may have influenced stimulus control more in that study. Only one study (Massey & McMillan, 1987) tested for generalization under a higher deprivation condition than initial training, but there were no differences across conditions. A possible reason why they did not demonstrate an effect under high deprivation may have been because the animals were trained to discriminate at all deprivation levels before testing at each deprivation condition. As a result, discriminated responding had been established to the same extent at all IV levels prior to testing.

In order to assess the influence of high deprivation conditions on stimulus control in drug-discrimination, it is essential that the organism does not receive discrimination-training sessions under the high deprivation conditions prior to testing. This can be accomplished by testing under various hours deprived rather than under different body weights, which would not require a weight adjustment period and re-training. The purpose of the present study was to examine the influence of high deprivation conditions on stimulus exerted by d-amphetamine.

In order to control for and prevent training from occurring under high deprivation conditions, testing was conducted after depriving the animals according to various time intervals (longer than training) without food.

**Methods**

With the exception of a few procedural differences described later, the experimental preparation and the apparatus were the same as those described in the previous chapter.

**Subjects**

Eleven experimentally naïve male Sprague-Dawley rats served as
experimental subjects. Each rat was approximately 50 days old at the beginning of the study. The rats had free access to water in their home cages and were provided with supplemental rat chow according to their feeding schedule. The rats were individually housed in 20 cm × 40 cm cages in a colony room maintained at 20º C and 20% humidity on a 12-hr light/12-hr dark cycle. All experimental sessions were conducted at the same time, six days a week, during the light cycle. The study was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2010) and approved by the Institutional Animal Care and Use Committee of Western Michigan University (Appendix).

**Apparatus**

The apparatus described in Chapter 3 was used in this study.

**Training**

**Preliminary training.** During magazine training, the rats were placed in the experimental chambers for 50 min and food pellets were delivered according to a fixed-time (FT) 60-s schedule. Following two magazine training sessions, lever-press training was initiated on a center lever that was not utilized throughout the remainder of the experiment. An FR 1 schedule of food reinforcement was initially in effect and FR requirements increased by 1 after every 10th reinforcer. Sessions lasted up to 30 min or until 50 food pellets had been obtained, whichever occurred first. Center-lever training progressed until FR requirements reached FR 20 and one additional session was conducted under an FR 20 schedule.
**Discrimination-training.** During this phase the animals were given i.p. injections of saline or \textit{d}-amphetamine (1.0 mg/kg) with a pretreatment time of 10 min in their home cages. The errorless-discrimination-training procedure that was described in Chapter 3 (Overton, 1979) was in place until the schedule values on both the drug and saline levers progressed from FR 10 to FR 20. The schedule requirement for each lever was increased by one after every tenth reinforcer earned on the corresponding lever. Each drug and saline session resumed at the FR value where the subject had finished during the prior drug or saline session. Sessions lasted 25 min or until 50 food pellets had been obtained, whichever occurred first. Once the subjects obtained a minimum of 10 reinforcers under an FR 20 schedule on both levers, discrimination-training was initiated. The lever assignment was counterbalanced across the rats and remained constant throughout the experiment.

During discrimination-training, both levers were present but only the injection-appropriate lever yielded food pellets according to an FR 20 schedule. Three saline and three drug sessions were randomly administered each week, with the exception that there were no more than two consecutive drug or saline days. Discrimination-training continued until the animals responded on the injection-appropriate lever at 80% or higher accuracy across 8 out of 10 consecutive sessions.

**Pharmacological preparation.** The \textit{d}-Amphetamine hemisulfate (Sigma Aldrich, St. Louis, MO) was dissolved in a sterile 0.9% saline solution. Injections were
administered intraperitoneally (i.p.) at a volume of 1.0 ml/kg volume. Doses were calculated based on the salt weight.

**Testing**

Five doses of d-amphetamine (0, 0.03, 0.1, 0.3, & 1.0 mg/kg) were tested using a dose-by-dose testing procedure. During testing, both levers were present and the sessions lasted until 20 responses were emitted on one lever or until 15 min had elapsed under extinction conditions. Dose response gradients were obtained under training deprivation conditions (22-hr food deprived; low deprivation) and 46-hr deprivation (high deprivation) conditions. The order by which the 22- and 46-hr deprivation gradients were obtained was counterbalanced across subjects. The order of test values was counterbalanced across subjects, but remained the same for each rat across conditions. Following each test session, at least one saline and one drug discrimination-training session was conducted under the low deprivation at 80% accuracy or higher. It should be noted that training sessions were not conducted under high deprivation conditions.

**MO manipulation.** Beginning in errorless-discrimination-training and in all phases that followed, the subjects were food-deprived for approximately 22 hr and this served as the training/low deprivation test value. Supplemental food was provided for 2 hours following each training session and 2.5 hours following test sessions. The day prior to high deprivation test days, the rats did not receive any supplemental food. Thus, during high deprivation test days the rats were tested approximately 46 hr after their most recent meal. In order to assure that the animals did not lose weight over time, supplemental food was provided once
every two weeks during the off day and their weights were monitored every day.

**Statistical Analysis**

The dependent variables of interest were percentage of $d$-amphetamine-lever responses, percentage of animals selecting the drug-lever, mean response rate, and mean latency of the first response. The group means for each response measure were plotted for visual analysis. A two-factor repeated-measures ANOVA was conducted for all response measures. Drug dose served as one factor (containing five levels) and deprivation condition served as the other factor (containing two levels). Mauchly’s test of sphericity was conducted and when assumptions of sphericity were violated, Greenhouse-Geisser corrections were applied with the adjusted dfs reported. Post-hoc tests were conducted on all significant response measures using Bonferroni’s corrected $t$-tests for all pairwise comparisons. Alpha levels were set at 0.05 for all statistical analysis.

**Results**

**Percentage of Drug-Lever Responses**

Figure 8 illustrates the mean (± S.E.M.) percentage of responses that occurred on the drug-appropriate lever across different doses and deprivation conditions. Dose-response gradients were obtained under 22- and 46-hr deprivation conditions. Visual inspection of the gradients reveals that when the animals were more deprived, a lower percentage of responses occurred on the drug-lever at the two highest test doses (0.3 and 1.0 mg/kg). A two-way repeated measures ANOVA revealed a statistically significant main effect for dose $[F(2.26,22.6)=50.095, p<0.001]$ and for deprivation $[F(1, 10)=12.857, p=0.005]$. 
However, there was not a statistically significant interaction between dose and deprivation \( [F(1.581, 15.815)=3.254, p=0.075] \). A significantly higher proportion of drug-lever responses occurred at 1.0 mg/kg than at the following doses: 0.3 mg/kg \( (p=0.01) \), 0.1 mg/kg \( (p<0.001) \), 0.03 mg/kg \( (p<0.001) \), and 0 mg/kg \( (p<0.001) \). In addition, a higher proportion of drug-lever responses occurred at 0.3 mg/kg than at 0.03 mg/kg \( (p=0.04) \) and 0 mg/kg \( (p=0.003) \). The ED\(_{50}\) value for the 46-hr deprivation condition (0.66 mg/kg) was significantly higher than the 22-hr deprivation condition (0.27 mg/kg), with 95% CIs [0.487, 0.899] and [0.173, 0.365] respectively.

![Figure 8](image)

**Figure 8.** Percentage of responses on the lever correlated with \( d \)-amphetamine (1.0 mg/kg) during 22- and 46-hr deprivation conditions. The training doses were 0 mg/kg and 1.0 mg/kg and training was conducted under 22-hr deprivation.

Figure 9 depicts the percentage of animals that selected the drug-lever (i.e., emitted a total of 20 responses on the drug-lever before doing so on the saline-lever) across test doses and deprivation conditions. The gradients that were
obtained using this quantal measure were similar to those obtained using a continuous measure. Under the two highest test doses, a lower percentage of animals selected the drug-lever when deprived more. At low doses, all of the animals selected the saline-lever. The ED$_{50}$ value for the 46-hr deprivation condition (0.698 mg/kg) was significantly higher than the 22-hr deprivation condition (0.293 mg/kg), with 95% CIs [0.533, 0.915] and [0.169, 0.507] respectively.

![Graph](image)

**Figure 9.** Percentage of animals that selected the drug-lever (i.e., percentage of animals that responded on the drug lever a total of 20 times first).

Figure 10 illustrates mean (± S.E.M.) response rate on both levers across test doses and deprivation conditions. Response rates were higher under 46-hr deprivation than under 22-hr deprivation at the 0.3 and 1.0 mg/kg doses and similar at other doses. Across both deprivation conditions, response rates decreased at higher test doses. A two-factor repeated-measures ANOVA, with drug dose and deprivation condition as factors, revealed a statistically significant main effect for dose [$F(4,40)=12.021, p<0.001$]. There was not a statistically
significant main effect for deprivation condition \( [F(1,10)=1.484, p=.251] \) or an interaction \( [F(4,40)=1.890, p=0.131] \). Post-hoc tests revealed that response rate was lower at 1.0 mg/kg than it was at 0 mg/kg \( (p<0.001), 0.03 \text{ mg/kg (} p<0.001), 0.1 \text{ mg/kg (} p<0.001), \text{ and 0.3 mg/kg (} p<0.001). \) Response rate was also lower at 0.03 mg/kg than it was at 0.1 mg/kg \( (p<0.001). \)

\[ \text{Figure 10. Mean response rate (response frequency/min) across test doses, as a function 22- and 46-hr deprivation conditions.} \]

Figure 11 depicts mean latencies of the first lever response across test doses and deprivation conditions. Response latencies were slightly higher under 22-hr deprivation conditions, but this difference was not statistically significant \( [F(1,10)=0.309, p=0.591] \). The repeated-measures ANOVA did not reveal a statistically significant main effect for dose \( [F(1.059,10.590)=0.826, p=0.391] \) or an interaction \( [F(1.083,10.825)=1.151, p=0.313] \).
Figure 11. Mean latency of first response on either lever across $d$-amphetamine test doses and as a function of 22- and 46-hr deprivation conditions.

Discussion

The present experiment demonstrated that increasing deprivation relative to training conditions influenced the discriminative stimulus properties of $d$-amphetamine as measured by both graded and continuous response measures. Although response rate was slightly higher and response latency was slightly lower when deprived, these differences were not statistically significant. These results are in contrast with those obtained in the previous chapter.

At first glance it may appear that these discrepant results were due to larger differences in the deprivation conditions (i.e., larger difference in IV levels) in the present study than the study described in Chapter 3. However, this is most likely not the case because there was a smaller difference in responses rate in the present study than in the previous experiment (Experiment 1). Moreover, Gaiardi et al. (1987) demonstrated an effect using even less discrepant deprivation
conditions than those utilized in Chapter 3 (15-min pre-feeding vs. no pre-feeding as opposed to 1-hr pre-feeding vs. no pre-feeding).

In the current study and in the previous d-amphetamine experiment, the directional shift in the gradients was similar. Although only the present study found statistically significant effects, there was an increase in the ED_{50} values when the animals were deprived more in both d-amphetamine experiments. On the contrary, opposite patterns emerged when morphine was the training drug. Gaiardi et al. (1987) and Li et al. (1995) obtained lower ED_{50} values when the subjects were deprived. These findings may indicate that the specific direction in which food-related MOs shift dose-response gradients may depend on the drug stimulus used. It is not clear why this would be the case, although whether or not a drug has anorectic properties may be relevant, and future studies should examine whether such conflicting directional changes emerge using other stimulants.

Only one other study (Massey & McMillan, 1987) obtained gradients under relatively high deprivation conditions, but their results were in contrast with the present findings. These studies differed in how the MO was manipulated (hours without food vs. percentage of free-feeding weight). Due to the MO manipulation in the present study, a weight adjustment period was not required. As a result, discriminated responding was not established under high deprivation conditions prior to testing. This was not the case when the animals’ weights were adjusted in the Massey and McMillan experiment. It is, therefore, possible that
such a training arrangement was why Massey and McMillan did not demonstrate similar effect under relatively high deprivation conditions.

In summary, these findings demonstrate that manipulating MOs can affect stimulus control in drug-discrimination. In two studies so far, MOs influenced the discriminative stimulus properties of \(d\)-amphetamine and morphine, a stimulant and a depressant respectively. These effects were observed using different MO manipulations. However, the directional shift in the gradients differed depending on the drug that was administered. The next chapter will examine the influence of MOs on discriminative stimulus control exerted by exteroceptive stimuli under conditions similar to those typically used to establish drugs as discriminative stimuli.
CHAPTER V

THE INFLUENCE OF MOTIVATING OPERATIONS IN A NON-PHARMACOLOGICAL ANALOGUE TO DRUG-DISCRIMINATION

One limitation with examining the influence of food deprivation in drug-discrimination is that some drugs have anorectic effects (e.g., Sanger & McCarthy, 1980) that may confound the intended MO manipulation. For example, administration of amphetamine results in decreased food consumption and weight loss via other physiological mechanisms (see Caul, Jones, & Barrett, 1988), thereby functioning as an abolishing operation for food reinforcement. Moreover, administration of certain drugs may have unintended behavioral effects that may make interpretations imprecise. For example, administration of amphetamine increases response rate when baseline response rate is low, but decreases response rate when baseline response rate is high (e.g. Dews & Wenger, 1977). Such effects can make it difficult to interpret the influence of MOs in drug-discrimination procedures.

In the previous d-amphetamine studies, drug administration may have influenced the MO manipulation because drug dose exerted a statistically significant main effect on response rate. This suggests that the influence of deprivation may have been different at various d-amphetamine doses. Based on previous experiments it also seems possible that the specific manner by which MOs shift dose-response gradients may depend on the drug administered. Given these general patterns, the effects of MO manipulations on drug discrimination
can be better understood if comparisons can be made to the effects of MO manipulations on stimulus control by other stimuli examined under comparable conditions.

A series of studies has successfully established discrimination of exteroceptive stimuli using a procedure similar to drug-discrimination (Boakes, 1969, McMillan, Wessinger, Paule, & Wenger, 1989; Raslear, 1975; Raslear, Shurtleff, & Simmons, 1992). In these experiments rats and pigeons were trained to discriminate two exteroceptive stimuli in a two-choice operant procedure. One stimulus (e.g., bright light illumination) served as the S^D for one response (e.g., right-lever press) and the S^A for the second response (e.g., left-lever press). The second stimulus (e.g., dim light illumination) served the same dual functions with the direction of stimulus control reversed. Subsequent to discrimination-training, generalization gradients were obtained across test stimuli that varied along the dimension that defined the discriminative stimuli (e.g., brightness of illumination). This arrangement can reasonably be conceived as an analogue to the drug-discrimination assay.

With the exception of McMillan et al. (1989), there are two notable procedural differences between these studies and drug-discrimination experiments. First, Boakes (1969), Raslear (1975), and Raslear et al. (1992) utilized a multiple-schedule arrangement during training, resulting in both training stimuli being presented during each session. This differs from drug-discrimination in that, in drug-discrimination, only one stimulus condition is in effect during a session. The second notable difference is that the aforementioned studies utilized
an error-correction or punishment procedure during training. For example, in the experiment by Raslear, when incorrect responses occurred the trial was terminated and the schedule requirement was reset. Only McMillan et al. presented one training stimulus during each session and did not arrange for a punishment or correction procedure. McMillan et al. concluded on the basis of their results that, “there is little evidence that discriminative stimulus control maintained by drugs differs fundamentally from such control maintained by exteroceptive stimuli” (p. 646).

The purpose of the present experiment was to examine MO effects on stimulus control by auditory stimuli in a procedural analogue to the drug-discrimination assay. In an attempt to determine the extent by which \textit{d}-amphetamine administration may have influenced the intended MO manipulation in Chapter 3, the same pre-feeding and no pre-feeding conditions were examined in this study.

**Methods**

**Subjects**

Twelve male Sprague-Dawley rats served as experimental subjects. All of the rats had a prior history of lever pressing for water in an undergraduate psychology laboratory class and four had a prior history in a conditioned place preference experiment using water as the reinforcer instead of drugs. The rats’ ages ranged from 234 to 428 days old (average age 310 days old) at the beginning of the study. The subjects were maintained at 80% of their free-feeding weights
and had free access to water in their home cages. The rats were housed individually in 20 cm × 40 cm cages in a colony room maintained at 20º C and 20% humidity on a 12-hr light/12-hr dark cycle. All experimental sessions were conducted during the same time six to seven days a week during the light cycle.

This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 2010) and approved by the Institutional Animal Care and Use Committee of Western Michigan University (Appendix).

Apparatus

The apparatus was the same as in the experiments described in previous chapters, with the exception that only two-lever experimental chambers were utilized. Auditory stimuli were generated by a Med Associates (St. Albans, VT) tone generator interface (model #SG-6010) and presented via a 5-cm diameter speaker mounted on the back wall of the operant chambers.

Training

Preliminary training. The rats were initially hand-shaped to lever press on the side levers according to an FR 1 schedule of food reinforcement. During this phase, either an 80 kHz tone at a loudness of 80 dB was present throughout the experimental session or no tone was present. Each stimulus condition was correlated with reinforcement on a particular lever and only the lever correlated with the stimulus condition was present for responding during this phase. This arrangement was intended to serve as an analogue to the errorless-discrimination-training phase (Overton, 1979) that was in effect in the previous studies. The FR
schedule requirement was increased by one after every tenth reinforcer delivery in each stimulus condition. The sessions lasted until either 50 reinforcers had been obtained or until 30 min had elapsed, whichever occurred first. This phase was in effect until the FR requirement for each lever reached 20, then two additional sessions were conducted at FR 20 under each stimulus condition (i.e., each lever).

**Discrimination-training phase 1.** In order to keep the procedures similar to those of drug-discrimination studies, during this phase only one stimulus condition (i.e., *tone* or *no-tone*) was in effect during each session. Prior to the onset of each session, the rats were placed in the operant chambers with the lever retracted, the house light off, and the fan on for 30 s prior to session onset. Once the session began, the stimulus condition was in effect for the entire session. Both levers were available for responding but only the lever correlated with the stimulus condition yielded reinforcers according to an FR 20 schedule of reinforcement. The *tone* and *no-tone* lever assignment was counterbalanced across the rats and the stimulus condition that was in effect during each session alternated semi-randomly, with no more than two consecutive *tone* or *no-tone* sessions.

Sessions lasted until 50 reinforcers had been obtained or until 30 min had elapsed, whichever occurred. Sessions were conducted seven days a week. Discrimination-training continued until the rats responded on the lever correlated with the stimulus condition at 80% or higher accuracy in 8 out of 10 consecutive sessions (a minimum of 4 *tone* and 4 *no-tone* sessions at 80% accuracy or higher). This phase was in effect for 60 sessions, but only one rat reached the testing
criterion. As a result, certain procedural modifications were made for all of the rats and are discussed next.

**Discrimination-training phase 2 (discrete-trials).** Although some of the subjects reached the overall session accuracy of 80% or higher, most did not reliably respond at 80% or higher on the appropriate lever during the first trial. As a result, a discrete-trials arrangement was arranged in order to minimize the probability of establishing a side-preference during a session. Here, the *tone* and *no-tone* conditions alternated at random for an equal number of times during each session. During each stimulus condition, both levers were available for responding. Responding (according to an FR 20 schedule) on the lever that was correlated with the stimulus in effect, which was counterbalanced, resulted in reinforcement. Once a reinforcer was delivered, both levers were retracted and the house light was turned off during an inter-trial interval (ITI) of 5 s.

During the inter-trial interval, the stimulus condition that was in effect prior to reinforcement continued to be in effect. Sessions were conducted seven days a week. This phase was in effect for 28 sessions but only two rats reached the criterion of 80% or higher accuracy on all trials, in 8 out of 10 consecutive sessions. As a result, an error correction procedure was implemented for all of the rats based on the procedures described by Raslear (1975).

**Discrimination-training phase 3 (correction procedure added).** A correction procedure was implemented whereby incorrect trials (less than 80% correct responses during a trial) resulted in re-presentation of the same stimulus condition after reinforcement. With the exception of repeating incorrect trials, all other
procedural arrangements were the same. Once the rat responded on the stimulus-appropriate lever at an accuracy of 80% higher on a trial, the stimulus condition for the next trial was determined at random with a probability of 0.5. The first trial of each session was pre-determined using a semi-random alternation method. Moreover, the same stability criterion as before was in place. Starting with this phase and all phases that followed, sessions were conducted six days a week.

Testing

**MO influences during generalization testing.** The initial intent of this study was to examine the influence of pre-feeding versus no pre-feeding conditions on generalization to different tone intensities ranging from 0-80 dB. Only two rats reached the criterion to begin testing; as a result generalization gradients were obtained for those rats only. Generalization tests were conducted after the rats were pre-fed their daily rations an hour prior to experimental sessions (*non-deprived* condition) and when they were not pre-fed (*deprived* condition). During generalization tests, the rats were placed in the operant chambers and after the 30-s pre-session interval elapsed, an 8 kHz tone came on and remained on until the end of the session at one of the following loudness intensities: 0, 1.25, 5, 10, 20, 80 dB. The order by which the stimulus values were tested was selected at random for each rat and remained the same across *deprived* and *non-deprived* test conditions. Test sessions were conducted under extinction with both levers available for responding. Sessions lasted until 5 min had elapsed or until a total of 20 responses had been emitted on one of the levers, whichever occurred first. Between test sessions, a minimum of two discrimination-training sessions (with
an accuracy of 80% or higher on all trials) were conducted as described in the
discrimination-training phase 3 section.

**MO influence during discrimination-training.** Because the training
arrangements did not result in any noticeable changes in discrimination in 10 out
of 12 rats, this phase sought to examine the influence of deprivation on
discrimination during training. If decreasing deprivation relative to training
conditions enhances discrimination after discriminated responding has been
established, then it may also enhance discrimination and accuracy before
discrimination has been established. To test this hypothesis, the rats were given
their daily rations an hour prior to experimental sessions on half of the training
sessions (non-deprived) and were not given any food prior to sessions (deprived)
prior to the other half. Training sessions were conducted according to the
procedures described in the discrimination-training phase 2 (discrete-trials)
section.

It should be noted that the correction procedure was not utilized in this
phase for the rats that did not test for generalization. A total of eight deprived and
eight non-derived sessions were conducted during this phase. The two deprivation
conditions alternated semi-randomly across sessions and were counterbalanced
across all subjects. In addition, on half of the sessions, the tone condition was in
effect first and for the other half, the no-tone condition was in effect during the
first trial. Sessions lasted until 30 reinforcers had been obtained or until 30 min
had elapsed, whichever occurred first.

**Data Analysis**
Generalization tests: The primary method of data analysis for the generalization gradients was visual inspection. The dependent variables of interest were percentage of responses on the lever correlated with a tone and tone-lever response rate.

Discrimination-training data. The primary dependent variables of interest were: (a) mean percentage of correct responses during the very first trial of a session, and (b) mean percentage of correct responses during the entire session. A repeated-measures ANOVA was conducted with deprivation and stimulus condition serving as the two factor, each with two levels. Alpha was set at 0.05 for the analysis of variance.

Results

Generalization Gradients

Generalization gradients were obtained under pre-feeding and deprived conditions for two rats. Figure 12 depicts the percentage of tone-lever responses for each of these subjects. For rat 10-4, the data points representing the training values (0 and 80 dB) under deprived conditions were obtained from the first trial of the corresponding training sessions. For this subject, under deprived conditions there was a slightly higher percentage of tone-lever responses at higher test values and a slightly lower percentage at the lowest value tested. A similar pattern emerged for rat 11-5 when it was more deprived. There was a lower percentage of tone-lever responses (i.e., higher percentage of silent-lever responses) at lower test values (0-10 dB) and a slightly higher percentage of tone-lever responses at the two highest test values (20 and 80 dB) when deprived. Interestingly, for both
rats there was a slight increase in tone-lever responses at lower values across all gradients.

![Figure 12](image)

**Figure 12.** Percentage of tone-lever responses that occurred under deprived and pre-feeding conditions at different loudness intensities of a 80 kHz tone.

Generalization gradients were also obtained for response rate on the tone-lever. Figure 13 illustrates response rates on the tone-appropriate lever under the two deprivation conditions for each subject. For rat 10-4, out of the three test values tested, response rate was only slightly higher at two values (10 and 20 dB)
when deprived. For rat 11-5, response rate was slightly higher at all but two test values (0 and 10 dB) under deprived conditions.

**Figure 13.** Response per minute on the tone-appropriate lever across test values under pre-feeding and deprived conditions.

**Group Data**

A total of 10 rats did not reach the criterion to begin generalization testing.

As a result, pre-feeding and non pre-feeding conditions alternated across 16
consecutive training sessions to assess the influence of MOs during training. One rat did not respond during pre-feeding conditions, as a result its data were omitted from the analysis. Figure 14 depicts the mean (± S.E.M.) percentage of stimulus-appropriate responses during the very first trials of the sessions across deprivation conditions and stimulus conditions. There were no notable differences across the deprivation conditions irrespective of deprivation or stimulus condition in effect. A two-way repeated measures ANOVA did not reveal a main effect for deprivation \([F(1, 116)=0.01, p=0.940]\) or for stimulus condition \([F(1, 116)=0.01, p=0.915]\). The ANOVA did not reveal a statistically significant interaction either \([F(1, 116)=1.980, p=0.162]\).

![First Trial of Session](image)

*Figure 14.* Mean percentage of stimulus-appropriate responses under pre-feeding and deprived training conditions. The data represent the overall average scores for all subjects on the very first trial of a session and as a function of deprivation and stimulus conditions.
Figure 15 illustrates the mean (± S.E.M.) percentage of stimulus-appropriate responses across the entire session as a function of deprivation. Pre-feeding did not result in any noticeable differences in response accuracy during any of the stimulus conditions. A two-way repeated measures ANOVA did not reveal a statistically significant main effect for deprivation \([F(1, 260)=1.80, p=0.216]\) or stimulus condition \([F(1, 260)=0.460, p=0.516]\). A significant interaction did not emerge either \([F(1, 260)=0.760, p=0.385]\).

![Overall Session](image)

**Figure 15.** Percentage of stimulus-appropriate responses under pre-feeding and deprived training conditions during the entire session. The data represent average session scores for all subjects as a function of deprivation and stimulus condition.

**Discussion**
The present experiment examined the influence of deprivation on stimulus control exerted by auditory stimuli in a concurrent schedules arrangement analogue to the drug-discrimination assay. In an attempt to replicate the drug-discrimination procedure, at first only one stimulus condition was in effect during training. Following 60 sessions under this arrangement, the subjects still did not reliably discriminate at 80% accuracy or higher. As a result, a discrete-trials procedure was implemented to facilitate discrimination and prevent positional preferences. Difficulties in establishing discriminated responding continued, even after 60 additional sessions that utilized a correction procedure. Unlike previous experiments that established stimulus control under similar procedures (Boakes, 1969; Raslear, 1975), punishment was not utilized in the present study.

For the two rats that were tested for generalization, a slightly higher proportion of tone-appropriate lever responses occurred at test values that closely resembled the tone condition (i.e., higher test values) when the rats were more food deprived. Similarly, under higher deprivation there was a higher proportion of silent-lever responses at values that resembled the silent condition (i.e., low test values). Although these effects are small and require replications across more subjects, the directional shift in the gradients resembled those found with morphine as a discriminative stimulus (Gaiardi et al., 1987; Li et al., 1995), but not those found with \textit{d}-amphetamine (Chapter 3 and 4).

For the rats that did not meet the testing criterion, MOs did not influence accuracy across training sessions. Given that MO effects were demonstrated in
studies that had established discriminated responding prior to testing (e.g., Gaiardi et al., 1987; Thomas & King, 1959), it may be that such effects are to some extent dependent on the organism’s learning history. In fact, Powell (1971) demonstrated an inverse relationship between MO effects on stimulus control and accuracy of discrimination during training. In the present study the animals had an extensive training history and perhaps reached a plateau during training. Consequently, pre-feeding may not have influenced performance because of an extensive training history.

In summary, the initial intent of this study was to examine MO effects in stimulus-discrimination without the influence of drugs. Due to the limited number of animals that tested for generalization, no solid conclusions can be drawn based on its results. Nonetheless, the present experimental procedures may provide a means to further examine MO effects in drug-discrimination procedures using non-drug stimuli. These procedures also allow for direct comparisons between dependent variables used in drug-discrimination and those used in other studies. Lastly, based on the group results that were obtained, there is some indication, consistent with previous research (Powell, 1971), that learning history and baseline levels of performance may determine the extent by which MO effects are exhibited. Future research could examine the influence of this important variable.
CHAPTER VI

SUMMARY OF FINDINGS AND GENERAL DISCUSSION

The reported studies investigated the influence of MOs on stimulus control exerted by interoceptive and exteroceptive stimuli. In Chapter 1, studies that obtained generalization gradients under different levels of food or water deprivation were reviewed. Altering food or water altered stimulus control in most studies. In addition, the range of stimuli that evoked responding (i.e., the width of the generalization gradient) increased with increasing deprivation. Inspection of the gradients of relative generalization suggested that the inherent shape of the generalization gradients changed with deprivation. Therefore, the aforementioned effects were construed to be the result of MOs’ influence on stimulus control. These effects were reliably demonstrated using visual or auditory exteroceptive discriminative stimuli and across a variety of response measures including: response rate, relative frequency, latency of responding, response force, and speed of responding.

In Chapter 2, drug-discrimination studies that altered MOs were reviewed. Four studies obtained dose-response gradients across different deprivation conditions for morphine, pentobarbital, or PCP in rats and pigeons. The primary response measures of interest were percentage of drug-appropriate responses and percentage of animals that selected the drug response. A statistically significant difference emerged between the deprivation conditions in only one experiment
(Gaiardi et al., 1987), whereby lowering deprivation resulted in higher ED$_{50}$ values. These effects were obtained using a quantal response measure and other studies did not find statistically significant results when using a continuous measure. A number of procedural differences between the drug-discrimination studies may have accounted for the limited MO effects evidenced in these drug-discrimination studies.

There were three notable procedural differences among the drug-discrimination studies that were examined in Chapter 3. They consisted of: (1) the response measures that were obtained, (2) the testing procedure, and (3) the species used. In Chapter 3, rats were trained to discriminate $d$-amphetamine from saline injections. Dose-response gradients were obtained under pre-feeding and no pre-feeding conditions and a quantal and a continuous measure of discrimination were obtained. The results yielded similar gradients under deprived, moderately deprived, and non-deprived conditions regardless of whether a continuous or graded response measure was used. Thus, the discrepant results in the previous studies were not due to the response measures utilized. Moreover, because a dose-by-dose testing procedure was used (similar to Gaiardi et al., 1987) and no differences emerged, the testing procedure did not account for the MO effects reported by Gaiardi et al. either. However, pre-feeding did influence response rate and latency of responding, an effect only demonstrated in drug-discrimination experiments that utilized pigeons as subjects.

In Chapter 4 a systematic replication of the previous study was conducted to determine if increasing deprivation relative to baseline training conditions
would affect stimulus control by d-amphetamine. In the previous studies, the
animals were trained under the higher of the test deprivation conditions and tested
under those and lower deprivation conditions. The results of the studies reviewed
in Chapter 1 suggest that discrimination is worse under high-deprivation
conditions and better under low-deprivation conditions. As a result, pre-feeding
(i.e., lower deprivation conditions) in the study reported in Chapter 3 may have
facilitated discrimination, particularly at training stimulus values, making its
effects less detectable, because the rats were performing at a relatively high level
in the baseline (high-deprivation condition). Consistent with this hypothesis,
when in Chapter 4 d-amphetamine dose-response gradients were obtained under
22- and 46-hr deprivation conditions, increasing deprivation resulted in a lower
percentage of drug-lever responses at higher test values. Similar effects were
observed for graded response measures. At training values (i.e., 0 and 1.0 mg/kg),
responding was less accurate when the animals were more deprived, particularly
at 1.0 mg/kg. These results demonstrate that MOs can affect the discriminative
stimulus properties of drugs.

The final experiment in Chapter 5 utilized a procedure analogues to the
drug-discrimination assay to establish discrimination of auditory stimuli. The
purpose of this arrangement was to determine if, in the absence of drug stimuli,
MOs would more reliably influence stimulus control. Due to difficulties in
establishing discriminated responding, only two rats were tested for
generalization, making it difficult to draw any solid conclusions. Altering level of
deprivation did not, however, affect stimulus control under the final training conditions.

In sum, results of the present research suggest that whether or not MOs affect drug discrimination are influenced by how they are manipulated, that is, whether motivation is increased or decreased relative to the baseline training condition. This is a significant contribution to the literature, although further research is needed to explore the generality of this finding. The present research is limited in that only one type of drug, \(d\)-amphetamine, was examined, and it is of interest to determine whether similar effects would occur with other stimulant and non-stimulant compounds. A significant weakness of the reported research is that stimulus control was not consistently established in the final experiment, which limits the value of its results. If, however, procedures similar to those used in that experiment could produce consistent stimulus control, then such procedures would be useful in ascertaining whether the conditions commonly used to study drugs as discriminative stimuli significantly influence how MOs affect drug discrimination. Further research attempting to develop such procedures appears to be warranted.
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APPENDIX

WESTERN MICHIGAN UNIVERSITY

Institutional Animal Care and Use Committee

Date: April 20, 2011
To: Alan Poling, Principal Investigator
From: Robert Eversole, Chair
Re: IACUC Protocol No. 11-03-03

Thank you for submitting the requested revisions. Your protocol titled "Drug Discrimination and Motivating Operations" has received approval from the Institutional Animal Care and Use Committee. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: April 13, 2012
Date: October 10, 2012
To: Alan Poling, Principal Investigator
From: Robert Eversole, Chair
Re: IACUC Protocol Number 12-10-02

Your protocol entitled “Drug Discrimination and Motivating Operations” has received approval from the Institutional Animal Care and Use Committee. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: October 10, 2013