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Resistance to Change of Ethanol Self-Administration: Effects of Naltrexone and Extinction

Corina Jimenez-Gomez

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RESISTANCE TO CHANGE OF ETHANOL SELF-ADMINISTRATION:
EFFECTS OF NALTREXONE AND EXTINCTION

by

Corina Jimenez-Gomez

A thesis submitted in partial fulfillment
of the requirements for the degree
of
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ABSTRACT

Resistance to Change of Ethanol Self-Administration:
Effects of Naltrexone and Extinction

by

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Utah State University, 2005

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Drug self-administration has proven to be an adequate model for assessing variables that contribute to the maintenance of drug taking. The present experiment was concerned with the persistence of drug self-administration, a defining characteristic of drug dependence and abuse. Findings from studies of the resistance to change of food-maintained responding may contribute to a better understanding of the persistence of drug abuse and dependence. Using an animal model of alcohol self-administration, this study evaluated the effects of rate of reinforcement on the persistence of ethanol self-administration in rats in the face of behavioral (i.e., extinction) and pharmacological (i.e., naltrexone) disruptors. Four experimentally naïve Long Evans rats were trained to respond for a 10% (vol/vol) ethanol solution on a multiple variable-interval (VI) 15-s VI 45-s schedule of reinforcement. Baseline response rates were higher in the component that provided higher rates of ethanol delivery. Consistent with behavioral momentum
theory, responding was more resistant to extinction in the component with higher rates of ethanol delivery. Conversely, disruption with naltrexone (1.0, 3.0, 10.0 mg/kg, s.c.), injected one hour before the session, resulted in no differential resistance to change of responding. The results are interpreted in terms of the effect of naltrexone on the incentive-motivational properties of the stimulus context.
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Corina Jimenez-Gomez
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INTRODUCTION

Drug self-administration has been considered an adequate procedure for the study of the reinforcing effects of drugs (Pickens, Meisch, & Thompson, 1978). As with any operant conditioning procedure, a specific response (e.g., pressing a lever) is followed by the delivery of a reinforcer (e.g., ethanol), which increases the probability of the behavior occurring in the future. Drugs operate like more conventional reinforcers (e.g., food), and the contingency between the response and reinforcer seems to be critical in determining response rates. Considering the social and health issues that accompany drug seeking and taking, it is important to understand factors that govern the persistence of such behavior. Although several attempts have been made to elucidate factors contributing to drug-taking behavior, variables contributing to the persistence of drug self-administration have not been widely investigated. Findings regarding the persistence of operant behavior from the perspective of behavioral momentum theory may aid in understanding the persistence of drug-maintained behavior.

Within the framework of behavioral momentum theory, a distinction is made between response rates and resistance to change as two separable aspects of behavior (Nevin & Grace, 2000). Rate of responding is determined by the response-reinforcer relation that is established by the contingency between a response and a reinforcer as described by the relative law of effect (Herrnstein, 1970). Conversely, the strength of behavior (i.e., resistance to change) depends on the Pavlovian stimulus-reinforcer relation, which refers to the control that the context of reinforcement exerts on behavior through a classically conditioned process (i.e., independent of the contingency between
the behavior and the reinforcer). The main finding in resistance to change studies is that behavior occurring in a context that provides more frequent or larger magnitude reinforcers is more resistant to disruption than behavior occurring in a context with smaller or less frequent reinforcers, regardless of whether some of the reinforcers are not contingent on the target response (e.g., Grimes & Shull, 2001; Harper, 1999a; Nevin, 1974; Nevin, Tota, Torquato, & Shull, 1990; see Nevin, 1992, for a review).

Shahan and Burke (2004) extended the study of resistance to change to drug self-administration procedures. Rats were trained to self-administer an ethanol solution on a multiple schedule of reinforcement in which one of the components provided additional response-independent food. The main finding was that although the rate of baseline responding was lower in the component with additional response-independent food, responding in the presence of the stimulus that had previously signaled this component was more resistant to extinction. Consistent with behavioral momentum theory, these results suggest that the stimulus-reinforcer relation has an important role in the maintenance of alcohol consumption.

Treatment of alcohol abuse and dependence in humans typically consists of behavioral and pharmacological therapies that, when combined, result in decreased alcohol use. One such pharmacological treatment, naltrexone, has proven to effectively reduce alcohol consumption in animal and human studies (see Ulm, Volpicelli, & Volpicelli, 1995, for a review). The role of environmental variables in modulating the disruptive effects of naltrexone on alcohol drinking has received little experimental attention.
The purpose of the present study was to examine the role of the reinforcement context on ethanol-maintained responding when behavioral and pharmacological disruptors are introduced. For this purpose, a traditional disruptor, as well as an accepted pharmacological treatment for alcoholism (i.e., naltrexone), was used to assess the resistance to change of ethanol-maintained responding under a multiple schedule of reinforcement. Consistent with behavioral momentum theory, the persistence of ethanol self-administration was governed by the stimulus-reinforcer relation when responding was disrupted with extinction. That is, responding was more resistant to change in the component that provided higher rates of ethanol deliveries during baseline. Conversely, alcohol self-administration was equally resistant to change in the contexts with high and low rates of alcohol delivery when disrupted with naltrexone. This finding suggests that naltrexone may eliminate the incentive-motivational properties of the stimulus context.
The effects of drugs can be either relatively independent of environmental variables or dependent on functional relations with the environment. These two effects of drugs are generally categorized within behavioral pharmacology as direct and functional effects, respectively. Direct effects refer to actions of the drug that are relatively independent of contextual variables and are limited to the metabolic life of the drug (i.e., the duration of the drug in the organism). An example of such effect is pupillary miosis (i.e., dilated pupils) after receiving 25 mg of intravenous heroin. This change is relatively independent of the behavioral or functional relations (i.e., effects that are not necessarily governed by environmental factors; Katz, 1989; Pickens et al., 1978). Functional effects are the observed changes in behavioral patterns as a result of the role of the drug in the environment, and not merely its pharmacological properties. Drugs can establish, maintain, and control behavior based on the behavioral relations formed between the drug and the behavior (Young & Herling, 1986).

In operant conditioning, the functional relations established between a discriminative stimulus, a response, and a consequence (i.e., three-term contingency) determine the probability of occurrence of a response in the future. For instance, a person tells a joke (i.e., response) to co-workers during the coffee break (i.e., discriminative stimulus) and, as a result, people laugh and praise his sense of humor (i.e., reinforcer). This person will be more likely to tell jokes during future coffee breaks because the social reinforcers that occurred in this context in the past have strengthened joke telling. Similarly, drugs can function as discriminative stimuli or reinforcers depending on the...
contingencies established through training. As discriminative stimuli, drugs can signal the availability of a reinforcer for a particular response. For example, rats can learn to discriminate if reinforcement will be available on a left or right lever based on an injection received before the session. If they received a vehicle (i.e., saline) injection, reinforcers will be available on the right lever. If the injection contained a drug, however, reinforcers will be available on the left lever. Based on this training, rats readily discriminate on which lever they should respond, thus providing evidence for the discriminative effects of the drug. This procedure has been used with various species and drugs, and has consistently shown that drugs can act as discriminative stimuli (see Stolerman, 1993, for a review). In this sense, drugs exert stimulus control on behavior because the occurrence of the behavior depends primarily on the contextual variables that have accompanied it in the past.

When serving as consequences, drugs can act to reinforce or punish behavior. Many studies of the functional effects of drugs have focused on reinforcing effects because of the implications for understanding human drug abuse and dependence. Drug dependence can be defined as drug-taking behavior that occurs excessively or in a persistent manner (Griffiths, Bigelow, & Henningfield, 1980), or a maladaptive pattern of substance use that leads to clinically significant distress or impairment (American Psychiatric Association, 1994). The drugs that serve as potent reinforcers for nonhumans are the same that tend to be abused by humans (Griffiths et al.). As a result, many attempts have been made to study the reinforcing effects of drugs in behavioral laboratories using animal models.
Drug Self-Administration

By strengthening and maintaining behavior, drugs have been shown to have characteristics similar to those of other reinforcers (Pickens et al., 1978). Thus, the principles of behavior derived from the study of other types of reinforcers can be applied to drugs as reinforcers. That is, the reinforcing effects of drugs may depend on the same mechanisms that regulate the reinforcing effects of other types of stimuli (Katz, 1989). It follows that the rate of drug-maintained responding, as with food-maintained behavior, depends on the relation between the response and the reinforcer.

Drug self-administration has been used as a standard procedure for the study of the reinforcing properties of drugs in both human and animal research. These procedures consist of training an experimental subject to respond (e.g., press a lever) in the presence of a specific stimulus (e.g., houselight on) in order to have access to the reinforcer (e.g., intravenous cocaine via an indwelling catheter). As the trained behavior occurs more frequently, the subject’s behavior becomes controlled by the experimental contingencies. As a result, the occurrence of the response is said to depend on the reinforcing effects of the drug. The reinforcing effects of the drug can be assessed using various methods, including (a) comparing responding for a drug to responding for the vehicle control (i.e., saline), (b) putting drug-maintained responding on extinction, (c) replacing the drug with an ineffective drug or dose, or (d) disrupting the response-reinforcer contingency by delivering drug response-independently (Pickens et al., 1978). If responding decreases as a result of these experimental manipulations, then behavior is being maintained by the contingency between the drug delivery and the behavior that precedes it.
Pickens and Thompson (1968) tested whether rats' responding on a fixed-ratio (FR) schedule of reinforcement would be maintained by cocaine injections as a reinforcer. An FR schedule of reinforcement delivers a reinforcer after a fixed number of responses have occurred. The resulting pattern of responding is pause-and-run, that is, high and steady rate of responding followed by a pause after the delivery of the reinforcer (Ferster & Skinner, 1957). Pickens and Thompson delivered cocaine response independently to determine whether the reinforcing effects of cocaine were maintaining responding rather than the direct effects of the drug (i.e., psychomotor stimulant effects). As a result of the response-independent cocaine infusions, response rates decreased, showing that responding under the FR schedule was being maintained by the contingency between the response and the cocaine. Pickens and Thompson went a step further in testing the hypothesis of a generalized increase in responding due to the direct effect of cocaine by adding another manipulandum that did not provide reinforcers. The results showed that responding occurred mainly on the alternative that produced the cocaine injections and suggested that cocaine was functioning as a reinforcer.

The schedule of reinforcement used for drug self-administration has also been shown to be an important variable by determining both the rate and pattern of responding. For instance, responding maintained by ethanol reinforcers (8% vol/vol, oral) under FR and fixed-interval (FI) schedules has revealed patterns similar to responding on the same schedules of reinforcement using food as a reinforcer (see Meisch, 1977, for a review). Responding on the FR results in the pause-and-run pattern described previously. On a FI schedule a reinforcer is delivered for the first response that occurs after a fixed time has
elapsed. Under such a schedule of reinforcement, the pattern of responding shows increases as the end of the interval and reinforcer delivery approaches. This pattern has been termed the FI scallop (Ferster & Skinner, 1957).

In addition, stimulus control of drug taking has been obtained under various schedules of reinforcement using drugs such as cocaine (de Wit & Stewart, 1981; Pickens & Thompson, 1968) and heroin (de Wit & Stewart, 1983). That is, the occurrence of a behavior is controlled by the stimulus differentially correlated with drug availability. This has also been observed in rats trained to respond for ethanol deliveries on a FR schedule (Meisch & Thompson, 1973). Shahan (2002) trained rats to respond for ethanol on a multiple random-ratio (RR) extinction (EXT) schedule of reinforcement. Response rates were higher in the presence of the stimulus associated with the RR component than during extinction. This outcome shows differential control by the schedule-correlated stimuli.

Drug self-administration has been shown to be an adequate model for assessing the environmental and pharmacological variables that contribute to the maintenance of drug taking. Drugs such as morphine, cocaine, \(d\)-amphetamine, pentobarbital and ethanol have been shown to be effective reinforcers of operant behavior across various species (see Young & Herling, 1986, for a review). These findings have led to the development of animal models of drug abuse and dependence. Furthermore, drug self-administration is a procedure that allows the manipulation of variables such as magnitude of reinforcer or schedule of reinforcement that may contribute to the persistence of this behavior.
Generally, response rates under various schedules of reinforcement are used as the dependent measure of the reinforcing effects of drugs.

Persistence of drug-maintained responding, however, is not adequately assessed by response rates alone because this dependent variable directly depends on the schedule maintaining responding (e.g., response rates tend to be higher when using a ratio schedule than when using an interval schedule). Persistence is a central aspect that defines drug abuse and dependence, and yet little is known about the environmental variables that govern the persistence of drug self-administration. Findings derived from the study of the persistence of food-maintained operant behavior may contribute to an understanding of the persistence of drug abuse and dependence.

Behavioral Momentum Theory

A widely accepted account of the persistence of operant behavior is provided by behavioral momentum theory. Behavioral momentum theory suggests that the strength of a behavior can be evaluated by examining its resistance to change (see Nevin & Grace, 2000). Resistance to change is a measure of the change in response rates in the presence of an imposed disruptor relative to the preceding steady-state baseline response rates. Behavioral momentum theory has been shown to account for the persistence of food-maintained behavior, and may be valuable in understanding drug-maintained responding.

For the most part, research on resistance to change has used multiple schedules of reinforcement (see Nevin, 1992, for a review). In a multiple schedule, two or more
schedules of reinforcement alternate, with a different stimulus signaling the occurrence of each individual schedule of reinforcement (Ferster & Skinner, 1957). The most general and replicated finding in behavioral momentum is that responding is more resistant to change in the presence of a stimulus that signals the occurrence of a higher rate of reinforcement than in the presence of a stimulus that signals a lower rate of reinforcement (see Nevin, 1992, and Nevin & Grace, 2000, for reviews).

For instance, Nevin (1974) trained pigeons on a procedure that used a red keylight to signal a variable-interval (VI) schedule delivering reinforcers at a low rate, and a green keylight signaling a VI schedule delivering reinforcers at a high rate. The different components were separated by an intercomponent interval (ICI) during which no stimuli were on. Such a procedure is well suited for comparing the resistance to change of two independent operant behaviors because disruption can be introduced to both components in the same session, and any differential change can be assessed. Steady-state responding is disrupted by changing baseline conditions. For example, responding can be put on extinction or reinforcers can be delivered response-independently during the ICI. When food was delivered response-independently during the ICI, Nevin found that pigeons' responding in the component that delivered on average 60 reinforcers per hr decreased less relative to baseline than responding for the component that delivered on average 20 reinforcers per hr. Thus, responding in the component that provided a higher rate of reinforcement was more persistent. Response strength, as characterized by resistance to change, was related to baseline reinforcement rate in the component.
Nevin, Mandell, and Atak (1983) provided a new conceptualization of response strength with behavioral momentum theory. Based on an analogy with classical physics, Nevin et al. suggested that steady-state operant behavior could be considered to have momentum. The momentum of a moving body is the product of its mass and velocity. The velocity of a moving body can be readily observed. However, the same is not applicable to the mass. For instance, two objects moving at the same speed can possess different mass, but such information is unattainable unless an external force is applied and the differential change in velocity can be observed. The change in velocity depends on the mass of the moving body and the external force used. Applying this metaphor to operant behavior, velocity refers to steady-state response rates, mass refers to resistance to change (i.e., response strength), and the external force is the disruptor.

According to this metaphor, there are two separable and independent aspects of operant behavior: the rate of response and its resistance to change (i.e., persistence; Nevin, 1992). The response-reinforcer relation governs response rates (velocity). Such a relation is established through the contingency between a response and a reinforcer as described by the relative law of effect. According to the relative law of effect, the absolute rate of responding is directly proportional to the relative rate of reinforcement associated with responding (Herrnstein, 1970). Conversely, resistance to change (mass) refers to the persistence of the behavior under altered conditions (e.g., disruption) and depends on the Pavlovian relation between the stimulus context in which the response occurs and reinforcement (i.e., the stimulus-reinforcer relation; Nevin & Grace, 2000). This Pavlovian relation is established through the repeated occurrence of the reinforcer.
within a stimulus context. Resistance to change is examined by applying an external force (i.e., disruptor) that will alter response rates. This distinction between response rates and resistance to change is important because responding in two different components of a multiple schedule of reinforcement can be differently resistant to change even though baseline response rates are similar (Nevin, 1992). Conversely, baseline response rates can be different, but the resistance to change of both behaviors may be similar. In both cases, the strength of the behavior is not directly related to the observed pre-disruption response rates.

In order to study the roles of the response-reinforcer and stimulus-reinforcer relation on resistance to change, Nevin et al. (1990) examined the effects of additional sources of reinforcement on resistance to change. Pigeons were trained to respond on a multiple VI VI schedule of reinforcement, and reinforcers were added response-independently (Experiment 1) or contingent on an alternative response (Experiment 2) in one of the components. Because reinforcers may occur in the absence of a response, response-independent reinforcers degrade the contingency between the occurrence of a response and the delivery of a reinforcer. Conversely, when response-independent reinforcers are delivered the stimulus-reinforcer relation is strengthened because the stimulus context is richer in reinforcement (see Nevin & Grace, 2000).

Nevin et al. (1990) found that response rates were lower for the component with the added response-independent reinforcement. Responding for this component was consistently more resistant to change under extinction and satiation conditions. Similar results have been found with other species and using various disruptors and different
reinforcers (Cohen, 1986; Grimes & Shull, 2001; Harper, 1999a, 1999b; Mace et al., 1990; McLean & Blampied, 1995; Nevin et al., 1990; Shahan & Burke, 2004). Together, these findings support the distinction made by behavioral momentum between response rate and resistance to change as separable aspects of behavior. By adding response-independent reinforcers to one of the components of the multiple schedule, response rates decreased for that component but responding was more resistant to disruption. Thus, using response rates as a measure of response strength is inadequate.

Just as various types of disruptors have been used (e.g., free food, extinction, satiation), different types of reinforcers have also been included in resistance to change research. For instance, Grimes and Shull (2001) used food pellets as a reinforcer for rats responding on a multiple VI VI schedule with added response-independent condensed milk in one component. The main finding was that a response-independent reinforcer that is different from the one maintaining the response could enhance the persistence of behavior. This finding is consistent with the interpretation that all reinforcer deliveries occurring in the presence of a stimulus enhance the persistence of responding in the presence of that stimulus.

Behavioral momentum theory has provided an account of the persistence of behavior when steady-state food-maintained responding is disrupted. The generality of these findings has been demonstrated by studies that have replicated these results across species responding under various procedures. Recently, behavioral momentum theory has also proven to be helpful in understanding drug effects. A few studies have shown that
the disruptive effects and reinforcing effects of drugs may depend on the conditions of reinforcement in a manner consistent with behavioral momentum theory.

Behavioral Momentum and Disruptive Effects of Drugs

Several studies of resistance to change have included the use of drugs. Of special interest have been the disruptive effects that drugs exert on responding and whether these effects are analogous to the disruptive effects of traditional disruptors (e.g., extinction). Egli, Schaal, Thompson, and Cleary (1992) assessed whether drugs could function as disruptors of steady-state responding in the same way as extinction or response-independent food during the ICI. Pigeons responded for food on a five-component multiple VI schedule of reinforcement. Each component provided reinforcers at different rates, and the pigeons received either methadone (0.5, 1.5, 2.5, 3.75, or 5.0 mg/kg, im) or buprenorphine (0.25, 0.5, 1.0, 3.0, or 5.0 mg/kg, im) 30 min before the session. Response rates decreased dose dependently in all components when either drug was administered. Furthermore, the decrease was greater in the components that provided lower reinforcement rates (VI 75-s and VI 150-s) than in the components with higher reinforcement rates (VI 5-s and VI 10-s). This finding is consistent with the predictions of behavioral momentum theory.

The findings of Egli et al. (1992) support the possibility that drugs act as disruptors of baseline responding similar to traditional behavioral disruptors (e.g., extinction, response-independent food during the ICI). In this study, however, the role of the stimulus-reinforcer and response-reinforcer relations in determining resistance to
change could not be separated. For this purpose, Harper (1999a) trained rats to respond for food on a multiple VI 30-s VI 30-s schedule of reinforcement with additional response-independent food in one of the components (variable time [VT] 30 s). By adding response-independent food, the stimulus-reinforcer and response-reinforcer relations could be separated. Separating these two aspects of behavior was possible because additional response-independent food degrades the response-reinforcer contingency (i.e., lower response rates) while strengthening the stimulus-reinforcer relation (i.e., higher reinforcement rates). The main question Harper addressed was whether haloperidol (0.1 and 0.5 mg/kg, oral) or clozapine (2.0, 5.0 and 10.0 mg/kg, oral) would disrupt responding similar to traditional behavioral disruptors. As predicted, both drugs disrupted responding in a manner analogous to traditional disruptors. Although baseline response rates were lower in the component with the added response-independent food, responding in this component was more resistant to the disruptive effects of the drugs. These findings suggest that resistance to the disruptive effects of drugs depends on the stimulus-reinforcer relation.

Harper (1999b) obtained similar results using quinpirole and fluoxetine as disruptors. When d-amphetamine was used as a disruptor, however, such an effect was not observed. Similarly, Cohen (1986) found that when d-amphetamine, sodium pentobarbital, haloperidol, and cholecystokinin were used to disrupt steady-state responding of rats, no consistent differences in resistance to change were observed. These results raise questions about the applicability of behavioral momentum to the disruptive effects of these drugs. As an alternative account of these results, Cohen suggested that the
direct effects of the drugs may have confounded the resistance to change results by degrading control by the multiple schedule stimuli. The direct disruptive effects of the drugs may diminish the discriminability between two reinforcement contexts (e.g., components of a multiple schedule), making it difficult to evaluate the effects of certain drugs as disruptors across the stimulus contexts.

Persistence of Drug Self-Administration

Little is known about the resistance to change of drug self-administration, but some research has examined the persistence of drug taking from other approaches. The most commonly used measure of the persistence of drug taking is derived from the use of progressive-ratio (PR) schedules. A typical PR procedure consists of increasing the ratio requirement using an exponential or logarithmic progression across the session until the breaking point is reached (e.g., when the subject has not emitted a response for 15 min). When using this procedure, the reinforcing efficacy of a drug can be indexed by the breaking point a drug reinforcer maintains. The breaking point is the largest ratio requirement a subject completes before responding ceases. An advantage of this measure is that the dependent measure is not response rates. Such a procedure has been used with a variety of species and drugs (see Stafford, LeSage, & Glowa, 1998, for a review). Although PR schedules have proven to be a valuable tool for the study of drug self-administration, the information derived from them is limited. The breaking point informs us of the maximum ratio value that the organism will complete in order to receive the drug under a specific controlled situation.
A similar approach to the study of the persistence of drug taking has been proposed by Meisch (2000). Meisch and colleagues (Lemaire & Meisch, 1991; Macenski & Meisch, 1998; Meisch & Stewart, 1995; Meisch & Thompson, 1973) have trained subjects on FR schedules of drug reinforcement and used various drug doses to obtain dose-effect curves. Dose-effect curves typically show an increase in responding with increases in the drug dose followed by decreases in responding as drug dose continues to increase (i.e., inverted-U shape). An additional manipulation involves increasing the FR value and obtaining dose-effect curves for each FR. This manipulation shows the combined effects of FR value and drug dose on responding. A measure of persistence is obtained by dividing the number of responses emitted at increasing FR values by the number of responses emitted at baseline. Meisch (2000) proposed relative persistence as a general method for measuring the reinforcing effects of drugs. A behavior is said to be more persistent if it continues to occur at higher FR values relative to a baseline FR value than responding for another drug or dose (i.e., if the relative persistence is greater).

Both relative persistence and PR schedules are the traditional methods for studying the reinforcing efficacy of drugs. By using ratio schedules of reinforcement, however, changes in response rate directly affect reinforcement rate. That is, the rate of reinforcement directly depends on the rate of responses emitted. As a result, the dependent measure (i.e., response rates) is intimately related to the independent variable (i.e., reinforcement rate; Nevin, 1995). The problem this poses is that one cannot assess response rates independently and the changes observed in response rates cannot be solely attributed to the experimental manipulations. Furthermore, relative persistence evaluates
the effect of disruptors (i.e., increases in FR schedule) across conditions instead of within session. As a result, other confounding variables such as sequence effects or the passage of time can affect behavior. Additionally, measuring persistence across conditions results in a measure that is less sensitive to experimental manipulations than measuring within the same experimental session (Nevin & Grace, 2000). Thus, the persistence of drug self-administration may be better examined using methods from the study of the resistance to change of food-maintained behavior. The theoretical approach and measures derived from behavioral momentum theory may provide a useful alternative framework for the study of the persistence drug self-administration.

Shahan and Burke (2004) extended what is known about the resistance to change of food-maintained responding to drug self-administration. For this purpose, rats were trained to self-administer an ethanol solution on a multiple random interval (RI) 15-s RI 15-s schedule of reinforcement with additional response-independent (random time [RT] 15-s) food deliveries in one of the components. Baseline response rates were lower in the component with the added response-independent food, consistent with a degradation of the response-reinforcer relation. When responding was put on extinction, responding in the presence of the stimulus associated with the added source of food was more resistant to change. This finding suggests that the persistence of alcohol-maintained responding depends on the stimulus-reinforcer relation and that behavioral momentum may be useful for understanding the persistence of drug self-administration.

Shahan and Burke (2004) used alcohol because it is a prototypical drug of abuse in humans. Alcohol abuse and dependence represents an enormous social and health
concern. Currently, approximately 9% of American adults abuse alcohol or are alcohol-dependent (National Institute on Alcohol Abuse and Alcoholism [NIAAA], June, 2004). The study of alcohol self-administration in nonhumans can be a useful tool for understanding this behavior in humans. Furthermore, it provides the advantage of using the typical route of administration used by humans (i.e., oral) in animal studies, thereby eliminating confounding effects due to a nontypical administration route.

Alcohol Self-Administration

When using the oral route of self-administration of ethanol, an ethanol solution is delivered to an animal in amounts controlled by the experimenter (i.e., magnitude of the reinforcer). Although most animals do not drink large amounts of ethanol without training, several procedures including water restriction (Eimer & Senter, 1968; Rodgers, Ward, Thiessen, & Whitworth, 1967), reinforcing ethanol drinking with some other reinforcer (Black & Martin, 1972; Martin & Myers, 1972), and schedule-induced polydipsia (Falk, 1961) have been developed to produce such behavior. The most commonly used method to generate alcohol self-administration is the sucrose-fading procedure (Samson, 1986). In the initial training session, lever pressing is shaped using a sucrose solution as a reinforcer. The next step is to slowly introduce ethanol into the solution across numerous sessions while the sucrose is gradually reduced (i.e., faded). Samson has found that solutions of up to 40% (vol/vol) ethanol maintain responding.

Animal models of ethanol self-administration have been extensively studied and have led to important contributions in understanding human alcohol abuse and
dependence. The variables that contribute to the maintenance of this behavior have been explored by altering schedules of reinforcement, reinforcer magnitude, and levels of deprivation (see Meisch, 1977, for a review). By using ethanol self-administration procedures, behavioral and pharmacological treatments for decreasing ethanol-maintained responding can be evaluated. For example, animal studies have shown that the use of opioid antagonists such as naloxone and naltrexone are effective in decreasing alcohol consumption (see Ulm et al., 1995, for a review). These studies have contributed to an understanding of the utility of such drugs for the treatment of alcoholism.

Treatment of Alcohol Dependence

The use of opioid antagonists to treat alcoholism arose from clinical observations suggesting that alcohol intake decreases with increases in opiate use, and vice versa. These observations suggested the possibility that these substances may have related pharmacological effects. It has been shown that opioid receptors modulate the reinforcing properties of alcohol. Thus, it appears that alcohol consumption is maintained in part by increases in opioid receptor activity (Ulm et al., 1995).

The opioid antagonists naloxone and naltrexone compete with opioid agonists for the µ, δ and κ receptor sites in the central nervous system (Froehlich, 1995). The main distinction between these two substances is that naltrexone has an added carbonyl group, which is related to a longer duration of action (Porter, Somogyi, & White, 2002). The effects of these substances on alcohol self-administration have been evaluated in both humans and nonhuman animals (see Ulm et al., 1995, for a review). Most studies suggest
that treatment with opiate antagonists reduces the reinforcing properties of alcohol 
(Anton et al., 1999; Carroll, Cosgrove, Campbell, Morgan, & Mickelberg, 2000; 
Davidson & Amit, 1996; Gonzales & Weiss, 1998; Goodwin, Campisi, Babinska, & 

Volpicelli et al. (1992) conducted a three-month clinical trial of naltrexone that 
contributed to its approval by the Food and Drug Administration (FDA) for use in human 
alcohol dependence treatment in 1994. Seventy male subjects were selected based on the 
DSM-III-R criteria for alcohol dependence. Participation in the study was voluntary after 
having received one month of outpatient rehabilitation treatment. Subjects were randomly 
assigned to either the placebo or naltrexone group and were instructed to take a tablet 
every day for the three-month duration of the study. The placebo tablets were identical in 
appearance to the naltrexone tablets. Weekly evaluations consisted of craving scales, 
alcohol consumption, mood and psychopathological condition, and a Breathalyzer test. 
By the end of the three-month period, 95% of the subjects in the placebo group that 
sampled alcohol met the criteria for relapse (i.e., five or more drinks per day), whereas 
only 50% of the naltrexone-treated subjects that sampled alcohol met the relapse criteria. 
Volpicelli et al. concluded that naltrexone may not significantly prevent alcohol drinking, 
but it reduces the likelihood of a relapse or clinically significant drinking.

Similarly, Anton et al. (1999) studied the effectiveness of naltrexone treatment of 
alcohol dependence while controlling for medication compliance and therapy received. 
Alcohol-dependent subjects were treated during 3 months with either placebo or 50 mg of 
naltrexone and received manual-guided cognitive behavioral therapy. Therapy
participation and compliance to the medication, measured by levels of riboflavin included in the tablets taken daily, were similar in the placebo and naltrexone groups. Furthermore, subjects in the naltrexone group took longer to relapse, had more time between relapses, and drank less alcohol when they did relapse. Treatment with naltrexone seems to be effective in controlling urges to drink in motivated subjects that comply with the medication. These results suggest that naltrexone may have an effect on alcohol craving.

Sharpe and Samson (2001) conducted an experiment with the intention of determining the effects of naloxone on an animal model of craving. For this purpose, they designed a study that separated what they refer to as appetitive and consummatory processes, that is, the operant lever-pressing response and ethanol drinking, respectively. Two groups of six rats were trained to press a lever on a FR 16 for either a 3% sucrose solution or a 10% ethanol solution. After responding was stable, weekly intraperitoneal injections of naloxone (0.3, 1, 3, 5, or 10 mg/kg) were given immediately before the session. Naloxone significantly decreased the consumption of both solutions in a dose-dependent manner. The consumption of ethanol was significantly decreased at the 3 mg/kg dose and the consumption of sucrose at the 5 mg/kg dose. At the 3 mg/kg dose (the highest dose used for the ethanol group), three rats in the ethanol group and two in the sucrose group failed to complete the lever press (i.e., appetitive) requirement to gain access to the solution. This suggests that naloxone had an effect on the appetitive responding (i.e., craving) that was also dose-dependent.

As with other disruptors of steady-state responding, the effects of opiate antagonists may be modulated by environmental variables. For instance, the rate of
reinforcement in the context may determine whether treatment with naltrexone will be effective. Further, the effect of naltrexone may be enhanced or attenuated by these modulating environmental influences. Several studies indicate that environmental variables do need to be considered in the study of the persistence of drug self-administration.

Carroll et al. (2000) trained monkeys to respond under closed- and open-economy conditions in order to study the effects of naltrexone on ethanol-, phencyclidine- (PCP), and food-maintained behavior. In an open economy, supplemental amounts of the substance used as a reinforcer are provided in the home cage after the session is over. Conversely, in closed economies all reinforcers are earned during the session. The results of this experiment showed that naltrexone (0.1, 0.3 and 1 mg/kg, im) significantly reduced ethanol- and food- but not PCP-maintained responses in a dose-dependent manner. In fact, for many of the experimental subjects the highest doses of naltrexone almost eliminated all responding maintained by ethanol and food. The suppressant effect of naltrexone was stronger when the animals had access to the substance maintaining the behavior after the session ended (open-economy). In other words, the availability of the reinforcer (limited versus continuous) determined the effectiveness of naltrexone. This finding has important implications for the clinical treatment of drug abuse in humans because the conditions of reinforcement may affect the effectiveness of treatment with naltrexone.

Williams and Woods (1999) trained rhesus monkeys to respond for concurrently available ethanol and water. Different ethanol concentrations were tested in ascending
order from 1% to 32% vol/vol. The effects of naltrexone (0.1 mg/kg, im) were examined at each ethanol concentration. As the ethanol concentration increased (8, 16 and 32% vol/vol), the number of ethanol deliveries decreased and the number of water deliveries increased. In other words, the ethanol concentration determined which fluid was more preferred. The interesting and counterintuitive finding was that naltrexone reduced responding more for whichever fluid was more preferred (i.e., ethanol at low ethanol concentrations and water at high ethanol concentrations). Hence, the effect of naltrexone was not exclusive to the self-administration of alcohol. These findings suggest that, in a choice situation, naltrexone reduces consumption of the preferred reinforcer. Furthermore, the results of this study suggest that the distribution of reinforcement between two concurrent alternatives will not only determine the allocation of behavior but also resistance to the disruptive effects of naltrexone. Thus, the persistence of alcohol self-administration may be controlled by the context in which it occurs (i.e., stimulus-reinforcer relation). Additionally, the effects of naltrexone may differ depending on the reinforcement context in which the behavior occurs. The effects of naltrexone on alcohol self-administration have been extensively demonstrated across species and behaviors, but little is known about how the reinforcement context (i.e., stimulus-reinforcer relation) modulates the effects of naltrexone on alcohol-maintained responding.

Statement of the Problem

The use of naltrexone in the treatment of alcohol dependence has shown to be effective, especially when subjects take the medication regularly and receive some form
of therapy. The effectiveness of this drug has also been demonstrated in animal models of ethanol self-administration. The reduction in the amount of ethanol consumed depends on the dose used, that is, responding decreases more as the naltrexone dose is greater. Thus, the effect that naltrexone has on ethanol self-administration may be viewed as a pharmacological disruptor of alcohol seeking. The effect of naltrexone as a disruptor of ethanol self-administration, however, may be modulated by environmental factors (e.g., reinforcement context) as suggested by Carroll et al. (2000) and Williams and Woods (1999).

The present study extends the study of resistance to change to behavioral and pharmacological disruptors of drinking. More specifically, this study evaluated whether the context of reinforcement affected the persistence of alcohol-maintained behavior in the face of extinction and naltrexone treatments. For this purpose, rats self-administered an ethanol solution on a two-component multiple schedule that provided different reinforcement contexts (i.e., high and low rates of alcohol delivery, respectively). After responding stabilized, behavioral and pharmacological disruptors were introduced. This procedure allowed the assessment of the modulating effects of environmental variables in an animal model of alcohol abuse treatment.
METHOD

Design

The present study used a single-subject design in which all subjects experienced all the experimental conditions. In these designs, each subject serves as its own control (i.e., responding under the baseline condition is the control for the other experimental manipulations within the experiment). With this design, large quantities of data can be obtained using a small number of subjects. Each condition of the study was run for extended periods of time to minimize the effects of intersubject variability. Judgments about the stability and changes in data were made by visual inspection of individual subject data (Sidman, 1960). Such procedures are standard in operant conditioning and resistance to change research.

Subjects

Four experimentally naïve male Long Evans rats, approximately 180 days old at the beginning of the experiment, were maintained at 80% of their free-feeding weights. The rats were housed individually in a temperature-controlled colony with a 12:12 hr light/dark cycle (lights on at 7:00 a.m.). The experimental sessions were conducted daily during the light periods at approximately the same time every day. Water was freely available in the home cage except prior to the initial training session. Animal care and housing was conducted in accordance to the standards set by the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).
Apparatus

Four Med Associates® operant conditioning chambers were used. Each chamber was approximately 30 cm long, 24 cm wide, 21 cm high, and housed in a sound-attenuating cubicle. The front panel of each chamber was equipped with two response-levers centered 13 cm apart. Each chamber contained a 28-V houselight at the top center of the front panel, a sonalert, a solenoid-operated dipper located between the two levers which delivers the liquid solutions, and light emitting diodes (LEDs) in a horizontal array of red, yellow, and green lights located above each lever. Extraneous noise was masked by a chamber ventilation fan and white noise. Control of experimental events and data recording was conducted in an adjacent room with Med Associates® interfacing and programming. Solutions were prepared with distilled water, table sugar, and 95% stock ethanol. Sucrose solutions were prepared as percent weight per volume and ethanol solutions were prepared as percent volume per volume. All solutions were prepared approximately every two days and kept at room temperature.

Procedures

Training

A modified sucrose-fading procedure as described by Shahan (2002) was used. Prior to the first day of training, the rats were water deprived for approximately 18 hr. During the first session, the rats were trained to lever press using an ethanol solution as the reinforcer. Lever pressing was maintained using a FR schedule of reinforcement. The requirements started with FR1 and were rapidly increased to FR4 within the first two
sessions. These sessions ended when 200 reinforcers had been delivered. After five days of training under FR4, a RR schedule was introduced. The purpose of using RR for training was that it results in high rates of responding. The ratio requirements were increased from RR 2 to RR10 within the next sessions. These sessions ended after 30 min. This training phase lasted approximately two months, which was the time required for ethanol-maintained responding to be reliably acquired.

Across sessions, the ethanol concentration was increased from 2% to 10% while the sucrose was faded out by decreasing the weight per volume ratio of sucrose in the solution. The solution used for the rest of the experiment was 0% sucrose 10% (vol/vol) ethanol. Once responding under a RR10 had stabilized, the rats were introduced to a VI 10-s schedule. The VI was increased after several sessions to a VI 15-s schedule. After responding on this schedule of reinforcement had stabilized, the multiple schedule of reinforcement was introduced.

Multiple Schedule of Reinforcement

Sessions began with a 15-min blackout, after which the first component was randomly selected by a probability gate with $p = .5$. The components alternated throughout the remainder of the session. Components were 60 s long and were separated by a 30-s ICI in which all stimuli were turned off and responding had no programmed consequence (see Figure 1). The multiple schedule of reinforcement consisted of a VI 15-s component and VI 45-s component. First, responding for both components was
Figure 1. Schematic diagram of a multiple schedule of reinforcement. Stimuli S₁ and S₂ represent the two components of the multiple schedule, which are presented successively and separated by an ICI. Responses are intermittently reinforced according to two independent schedules (e.g., VI).

reinforced on a VI 15 s. The VI on one of the components was gradually increased across sessions until it reached VI 45-s.

Each component of the multiple schedule was signaled by different stimuli. One component was signaled by a steady tone and houselight, and the other component by a pulsing tone and blinking houselight. The stimuli associated with each component were counterbalanced across subjects. Only the right lever was used for this experiment, and the LED lights over the lever were lit during both components. The VI values were randomly chosen without replacement from a 10-interval list of a Fleshler and Hoffman (1962) progression. After a reinforcer became available because the VI timer had expired, the next lever press to occur resulted in a 3-s access to the dipper cup filled with the ethanol solution. After this predetermined time of access to the dipper cup had elapsed,
the dipper was withdrawn from the operant chamber into a tray containing the solution where the cup was filled again. Reinforcers scheduled but not obtained before the end of one component were held until the next occurrence of that component. Sessions ended when each component had occurred 10 times.

**Disruptors**

After responding reached stability under the multiple VI VI schedule, the disruptors were introduced. The first disruptor was extinction because its effects are well documented for food-maintained responding and its effects on ethanol-maintained responding corroborated the adequacy of the reinforcement parameters (i.e., VI values used and three-fold difference between these). After extinction, the subjects were returned on the baseline condition until stability had been reached again. The stability criterion used was a five-day period in which no increasing or decreasing trend in the rate of responding was observed.

Naltrexone (1.0, 3.0, and 10.0 mg/kg, sc) was used as the second disruptor. Vehicle (saline) injections were given in order to acclimate the rat to the injection procedure prior to disrupting with naltrexone. Naltrexone injections were given only after no saline effects were observed. Before starting the dosing sequence reported here, several naltrexone injections were given acutely or chronically (i.e., 5 consecutive days) at different times prior to the beginning of the session (15 min and 1 h) in order to determine the appropriate dosing regimen. These data are not reported. The data reported reflect three determinations of acute doses given 1 h before the session. Following
completion of disruption by naltrexone, stability in baseline responding was recovered and disruption by three days of extinction was replicated.

*Extinction.* Disruption with extinction was conducted across three sessions in which all discriminative stimuli were presented as in baseline condition but responding had no programmed consequences (i.e., reinforcers were not delivered).

*Naltrexone.* The naltrexone solutions were kept in a refrigerator. Approximately 15 min before the injection was administered, the solution was taken out of the refrigerator and the syringes were prepared with 1 ml/kg of body weight. Subcutaneous injections were given in the colony room approximately 1 hr before the subjects were weighed and the experimental session began. The order of the doses (saline, 1, 3, or 10 mg/kg, sc) was counterbalanced across subjects. Three determinations of each dose were given in different orders to control for possible sequence effects. The order in which the naltrexone doses were given to each subject is shown in Table 1. The naltrexone doses used were selected based on the results of previous studies (Critcher, Lin, & Patel, 1983; Davidson & Amit, 1996; Froehlich, Harts, Lumeng, & Li, 1990; Gonzales & Weiss, 1998; Sharpe & Samson, 2001; Volpicelli, Davis & Olgin, 1986) that obtained a decrease in alcohol consumption without impairing motor activity.

**Dependent Measures**

The dependent measures were response rates and the proportion of baseline under disruption conditions. The proportion of baseline of responding under disruption conditions was obtained by dividing response rate under disruption by an average of
response rates for the last five days under the preceding baseline condition. When naltrexone was used as a disruptor, proportion of saline was calculated by dividing response rates under disruption by response rates during saline sessions. These values were then transformed into logarithms to show the increases or decreases under disruption relative to responding under baseline conditions. Converting them into logarithms permitted a comparison of functional relations without distortion due to scaling (e.g., floor effect), and it rendered proportional changes as equal differences (see Nevin & Grace, 2000). The slopes of the resulting functions relating proportion of baseline to the disruptor were compared as a measure of resistance to change. The slope is inversely related to resistance to change (i.e., the steeper the slope the less resistant to change a behavior is).

### Table 1

*Order of Naltrexone Injections for Three Determinations*

<table>
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<tr>
<th>Determination</th>
<th>Dose mg/kg</th>
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<th>N6</th>
<th>N7</th>
<th>N8</th>
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RESULTS

Baseline response rates

Figure 2 shows response rates for the two components in successive baseline conditions. Each data point represents the average baseline response rates across five days prior to extinction and each naltrexone injection. For all subjects, baseline response rates were consistently higher in the component that provided higher rates of alcohol delivery (i.e., rich component) than in the component that provided a lower rate of alcohol delivery (i.e., lean component). Across rats, there was a small decreasing trend in response rates across successive baselines. The decrease in response rates across successive baselines was greatest for N7 and N8.

Extinction

Figure 3 shows an analysis of resistance to change during disruption by extinction (Nevin et al., 1990). Each data point represents the logarithm of proportion of baseline response rates in successive days of extinction. Response rates in extinction sessions are expressed as a proportion of average baseline responding in the final 5 days of the preceding baseline condition. Relative differences in resistance to change are assessed by differences in the slope of the resulting functions. The steepness of the slope is inversely related to resistance to change. Thus, if the slope is steeper for one component than for the other, responding for that component was less resistant to change. For the first disruption by extinction (left column), response rates decreased for both components as
Figure 2. Response rates across successive baselines. Data are averages of the five days preceding each disruptor. Closed circles represent responses per min for the rich component and open circles represent responses per min for the lean component. Response rates for the first baseline represent responding prior to extinction. The following baselines correspond to sessions that preceded naltrexone injections. Error bars represent ± 1 SD. Note the different scales on the y-axes.
Figure 3. Resistance to disruption by extinction. Closed circles represent responding in the rich component and open circles represent responding in the lean component. Left column shows the data for the first extinction and the right column for the second extinction. Note the different y-axis for the first extinction of rat N7.
extinction days progressed. For all rats, the decrease in responding was greater for the component that provided lower rates of alcohol delivery during baseline (i.e., lean component) than for the component that provided higher rates of alcohol delivery (i.e., rich component). For the second disruption by extinction (right column), the differences in resistance to change between the two components were less than those obtained during the first extinction. The differences in resistance to change of responding for the two components were greater for rats N5 and N8. Overall, responding in the component that provided higher rates of alcohol delivery was more resistant to extinction. A repeated-measures analysis of variance with component, day of extinction, and replication as within-subject factors showed that the difference between the Rich and Lean components was statistically significant, $F(1, 3) = 28.28, p = .013$, responding decreased significantly across extinction sessions, $F(2, 6) = 8.99, p = .016$, and the decrease in responding was significantly different between the two extinction replications, $F(1, 3) = 18.64, p = .023$. Despite the difference between the replications, the difference in resistance to change between the two components was significant for both, the first, $F(1, 3) = 29.56, p = .012$, and second exposures to extinction, $F(1, 3) = 13.13, p = .036$. Although the effect of disruption by extinction was smaller for the second extinction, both disruptions significantly decreased responding in accordance to the predictions of behavioral momentum theory.
Naltrexone

Figure 4 shows dose-effect curves for response rates as a function of increasing naltrexone doses. The figure illustrates average response rates for each component of the multiple schedule during baseline control (C), following saline injections (S), and following naltrexone injections. Control response rates (C) were calculated by averaging response rates for the last baseline session preceding each injection. Control response rates and response rates following saline injections did not differ systematically. Naltrexone decreased responding dose-dependently for both components of the multiple schedule. The decrease in response rates was greatest for rats N6 and N7. For all rats, response rates were consistently higher in the Rich component.

Figure 5 shows a resistance to change analysis of responding disrupted by naltrexone. Each column of the figure shows the resistance to change data for each determination of naltrexone. Response rates following each naltrexone dose are presented as the logarithm of proportion of saline response rates. Details of the analysis are similar to those in Figure 3, except that responding during saline sessions was used for the comparison to responding during disruption. As evidenced by the slopes of the functions for the rich and lean components, responding in the two components was not systematically differentially resistant to the disruptive effects of naltrexone. A repeated-measures analysis of variance with Component, Dose, and Replication as within-subject factors showed that responding decreased significantly as a function of naltrexone dose \( F(2, 6) = 16.41, p = .004 \), but the differences between the Rich and Lean components
Figure 4. Naltrexone dose-effect curves. Closed circles represent average response rates for the rich component and open circles represent average response rates for the lean component. Control (C) is average response rates during baseline sessions and saline (S) is average response rates in saline sessions. Error bars represent ± 1 SD. Note the different scales on the y-axes.
Figure 5. Resistance to disruption by naltrexone. Closed circles represent responding in the rich component and open circles represent responding in the lean component. Proportion of saline responses per min are presented for each determination. Error bars represent ± 1 SD. Note the different y-axis for the second determination of rat N5.
were not statistically significant \([F(1, 3) = 2.99, p = .182]\). In addition, the decrease in responding was not significantly different across replications of disruption by naltrexone \([F(2, 6) = .014, p = .986]\).
DISCUSSION

Nevin (1974) showed that responding in the presence of a stimulus associated with a higher rate of reinforcement was more resistant to disruption than responding in the presence of a stimulus associated with a lower rate of reinforcement. In the present experiment, alcohol-maintained responding in a component that provided a higher rate of alcohol deliveries was more resistant to the disruptive effects of extinction than responding in a component maintained by a lower rate of alcohol deliveries. Conversely, no such difference in the resistance to change of alcohol-maintained responding was observed when naltrexone was used as a disruptor.

Extinction

In the present experiment, responding in the rich component (VI 15 s) was more resistant to the disruptive effects of extinction than responding in the lean component (VI 45 s). This finding is consistent with the prediction of behavioral momentum theory that resistance to change is determined by the rate of reinforcement delivered in the stimulus context (i.e., stimulus-reinforcer relation; see Nevin, 1992 and Nevin & Grace, 2000, for reviews). Similar results have been obtained when disrupting the behavior of various species under similar experimental arrangements (Cohen, 1986; Mace et al., 1990; McLean & Blampied, 1995; Nevin, 1974; Nevin et al., 1990; Shahan & Burke, 2004). Shahan and Burke found that alcohol-maintained responding was more resistant to extinction in the presence of the stimulus that signaled a higher rate of reinforcement.
(response-dependent ethanol deliveries and response-independent food deliveries) than in the presence of the stimulus that signaled a lower rate of reinforcement (response-dependent ethanol deliveries). The present findings are consistent with the results of Shahan and Burke. The two experiments differed procedurally in that Shahan and Burke delivered alcohol at equal rates across the two components and provided additional response-independent food to enhance the stimulus-reinforcer relation, whereas in the present experiment alcohol deliveries were presented at different rates for each component. Based on the findings of these two experiments, behavioral momentum theory accounts for the resistance to change of ethanol-maintained behavior when extinction is used as a disruptor.

The purpose of the present study was to compare the effects of behavioral and pharmacological disruptors on ethanol-maintained behavior. The importance of this comparison becomes apparent if one considers treatments for alcohol dependence as a form of disruptor of drinking behavior. Therapy programs for people who abuse or are dependent on alcohol can include both behavioral (e.g., therapy) and pharmacological (e.g., naltrexone) components. Thus, a better understanding of the impact of each component on the persistence of alcohol-maintained behavior would allow practitioners to maximize the effects of their interventions.

According to behavioral momentum theory, the persistence of behavior depends on the rate of reinforcement delivered in the stimulus context in which the behavior occurs (see Nevin, 1992 and Nevin & Grace, 2000, for reviews). Similarly, baseline frequency or amount of drug use has been found to be a strong predictor of intervention outcome in human studies (e.g., Preston et al., 1988). Based on the present findings,
behavioral interventions could decrease ethanol-maintained responding and this decrease will depend on the context in which the behavior occurs. Thus, drinking in contexts associated with higher rates of reinforcement will be more resistant to behavioral interventions. In the present experiment, however, extinction was the only behavioral disruptor used. Other behavioral disruptors should be tested under experimental conditions similar to the ones in the present experiment to assess the generality of these findings. For instance, preloading with ethanol before the experimental session (i.e., satiation) or providing an additional source of reinforcement for a behavior that is incompatible with alcohol-seeking behavior could be used as behavioral disruptors of alcohol-maintained behavior.

In terms of the application of these findings, extinction may not always be a plausible or appropriate intervention in the treatment of human alcohol abuse and dependence. Therefore, further study is needed to extend the present findings to the treatment of humans, particularly to evaluate which behavioral interventions for humans may function in a manner analogous to disruptors used in experiments on resistance to change (i.e., to decrease the persistence of behavior). Several behavioral interventions for humans that have been shown to significantly decrease drug-taking behavior are consistent with behavioral momentum theory (e.g., provide additional reinforcers in another context or for another behavior; see Higgins, Heil, & Lussier, 2004, for a review).
In the present experiment, response rates decreased dose-dependently when naltrexone was used as a disruptor of alcohol-maintained responding. Contrary to the predictions of behavioral momentum theory, however, the rate of alcohol delivered in the components did not determine the resistance to change of alcohol-maintained responding to disruption by naltrexone.

Based on previous findings, an alternative potential result was for responding in the rich component to be less resistant to the disruptive effects of naltrexone. Williams and Woods (1999) trained monkeys on a choice procedure that delivered water for one alternative and an ethanol solution for the other alternative. As the ethanol concentration increased, the number of ethanol deliveries decreased and the number of water deliveries increased. That is, the ethanol concentration determined which fluid was more preferred. When the monkeys received naltrexone (0.1 mg/kg, im), responding decreased more for the fluid that maintained the most behavior (i.e., preferred alternative). Preference and resistance to change have been found to positively correlate in a variety of procedures (Grace & Nevin, 1997; Grace, Schwendiman, & Nevin, 1998; see Nevin & Grace, 2000, for a review). Based on this relation between preference and resistance to change, one might predict that naltrexone would disrupt responding more in the rich component of a multiple schedule. This result, however, was not obtained in the present experiment. The difference between the results in the Williams and Woods study and the present experiment may be due to methodological differences. Williams and Woods did not directly manipulate rate of reinforcement delivered by each alternative, instead the
reinforcers delivered were determined by the monkey’s allocation of behavior that changed as ethanol concentration increased. This interdependence between rate of reinforcement and response rate may be responsible for their results. The use of VI schedules of reinforcement in the present study eliminated such interdependence between dependent and independent variables.

A possible explanation for the similar resistance to change of responding in the two components of the present experiment is that naltrexone affected stimulus control. If stimulus control was degraded, discriminating the two components from one another would have been more difficult. Stimulus control can be understood in terms of the organism discriminating the different stimulus-reinforcer relations and responding accordingly in each stimulus context (Nevin, 1973). In other words, the occurrence of a behavior is controlled by the stimulus differentially correlated with reinforcement availability. As such, stimulus control is a requirement for the effects of differential stimulus-reinforcer relations to be observed in the organism’s behavior. As a result of a breakdown in stimulus control, the rate of responding in the present experiment could have been more similar for the two components during naltrexone sessions. For instance, Cohen (1986) and Harper (1999b) found no consistent difference in resistance to change when food-maintained responding was disrupted with d-amphetamine. Cohen suggested that the direct effects of the drugs might have confounded the resistance to change results by degrading stimulus control. In the present experiment, however, response rates following naltrexone were consistently higher in the rich component (see Figure 3), suggesting that the subjects accurately discriminated which component was active. This
finding is consistent with previous studies showing that opioid antagonists have no effects on stimulus control (e.g., Grilly & Gowans, 1988; Tang & Franklin, 1983).

Having established that in the present experiment stimulus control was intact after naltrexone treatment, another explanation is needed. One possibility is that the incentive-motivational properties of the alcohol-associated stimuli may have been degraded by naltrexone. Stimuli can arouse or modulate operant behavior as a result of Pavlovian contingencies (e.g., Bindra, 1969, 1974; Killeen, 1979; Morse & Skinner, 1958; Rescorla & Solomon, 1967). According to Rescorla and Solomon's two-process learning theory, an operant response (e.g., lever press) is acquired and maintained by the response-reinforcer contingency, and the capacity of a stimulus to elicit the operant response is acquired and maintained by the Pavlovian stimulus-reinforcer contingency. Through Pavlovian stimulus-reinforcer associations, stimuli that previously signaled the availability of a reinforcer (i.e., discriminative stimuli) acquire some of its "incentive" properties. According to Bindra (1969), the main effect of reinforcement as traditionally conceptualized is "the creation of a motivational state that influences a wide variety of subsequent behavior" (p. 7). The central motivational state proposed by Bindra (1974) is a hypothetical set of processes that lead to goal-directed behavior in relation to incentive stimuli. Thus, in the presence of incentive stimuli, the central motivational state is aroused and as a result the organism emits a response. It has been suggested that stimuli that accompany the delivery or consumption of drugs acquire incentive properties, and are closely related to compulsive drug use (Bindra, 1974; Di Chiara, 1999; Robinson & Berridge, 1993, 2000; Stewart, de Wit, & Eikelboom, 1984).
The incentive-motivational properties of drug-associated stimuli refer to a conditioned arousal state that mimics aspects of the effects produced by a self-administered drug. Incentive-motivational properties increase the effectiveness of drug-associated stimuli in evoking drug-seeking behavior (Stewart et al., 1984). More specifically, stimuli become generators of motivational states that elicit drug seeking. Stewart et al. argue that the incentive-motivational properties of stimuli associated with a drug play a central role in the maintenance and persistence of drug taking. Similarly, the incentive-motivational properties of drug-associated stimuli have an important role in drug craving and relapse (e.g., Wikler, 1948). For instance, Volpicelli et al. (1992) found that when alcohol dependent human subjects were treated with naltrexone they were less likely to relapse and reported less craving than subjects in the placebo group. O’Malley (1996) suggested that a possible explanation for the Volpicelli et al. results may be that naltrexone attenuated the incentive-motivational properties of alcohol-associated stimuli that evoke craving.

The standard method in the study of the incentive-motivational properties of drug-associated stimuli has been the reinstatement model (Shalev, Grimm, & Shaham, 2002; Stewart & de Wit, 1987). In this procedure, reinstatement of drug-seeking behavior by exposure to drugs or drug-associated stimuli is examined after the behavior has been extinguished (Stewart & de Wit, 1987). When exposure to drug-associated stimuli has been used to evoke responding, the rate of responding during the reinstatement sessions has been considered indicative of the incentive-motivational properties of the stimuli. Several studies have assessed the effects of opioid antagonists on reinstatement of drug-

Cunningham, Dickinson, and Okorn (1995) also proposed that the endogenous opioid system might be implicated in the maintenance of conditioned reinforcement produced by stimuli previously associated with ethanol. Based on their findings, Cunningham et al. specifically suggested that naloxone reduced the incentive-motivational properties of the stimulus paired with ethanol by blocking the effects of conditioned release of endogenous opioids. Based on the findings of these studies, opioid receptors may be involved in mediating the incentive-motivational properties of alcohol and alcohol-associated stimuli. Because naltrexone blocks the reinforcing properties of alcohol and the incentive-motivational effects of alcohol-associated stimuli, it could decrease the likelihood of relapse by reducing the subjective feelings of craving ("wanting"; see Robinson & Berridge, 1993, 2000).

The role of incentive-motivational modulation of responding is consistent with the stimulus-reinforcer relation account of resistance to change provided by behavioral momentum theory. An interpretation of the stimulus-reinforcer relation is that observed differences in resistance to change are a result of the incentive-motivational effects of the
stimuli in the presence of which a behavior occurs (see Nevin et al., 1990, for discussion). The stimulus-reinforcer relation, as proposed by behavioral momentum theory, is a Pavlovian association between the stimulus context and the reinforcers that are delivered in that context (Nevin et al., 1983). As a result of this association, the stimulus acquires value (i.e., incentive-motivational property) that will depend on the rate of reinforcement that was delivered in that stimulus context. In resistance to change experiments, the incentive-motivational effects of the stimulus-reinforcer relation are measured by decreases in response rates during disruption relative to baseline. According to behavioral momentum theory, differences in resistance to change will be due in part to the sensitivity to differential rates of reinforcement (i.e., incentive-motivational effects)

\[
\frac{m_1}{m_2} = \left( \frac{R_1}{R_2} \right)^a
\]

(1)

where ratio of \( m_1 \) and \( m_2 \) is the resistance to change of responding, \( R_1 \) and \( R_2 \) are the reinforcement rates for each component of the multiple schedule, and \( a \) is the sensitivity to the reinforcer ratio (Nevin, 1992). Thus, \( a \) will determine how sensitive relative resistance to disruption is to relative reinforcement rates.

In the present experiment rats’ responding for an ethanol solution decreased dose-dependently as a function of naltrexone dose, and responding was equally resistant to change for the components providing different rates of alcohol deliveries. Thus, although absolute response rates in the two components were consistently different, decreases in response rates in the two components were proportionally similar as a result of disruption with naltrexone. The explanation suggested by O’Malley (1996) that naltrexone
diminished the incentive-motivational properties of ethanol-associated stimuli may explain why the decrease in responding for both components of the multiple schedule was proportionally the same in the present experiment. This explanation is consistent with behavioral momentum theory in the sense that naltrexone may have decreased sensitivity to the reinforcer ratio (i.e., \( a \) in Equation 1), thereby eliminating the difference in resistance to change. The present findings could suggest that the effects of incentive-motivational properties of alcohol-associated stimuli on persistence of drinking can be reversed or weakened with pharmacological treatments. In order to make a conclusive statement, however, further research is needed to corroborate this hypothesis.

An interesting extension of the present findings would be to further test the hypothesis that naltrexone degrades the incentive-motivational properties of alcohol-associated stimuli. One way to do this is by assessing the impact of naltrexone on disruption by extinction. The results of several studies suggest that naltrexone facilitates extinction of food-maintained responding (e.g., Benton, Dalrymple-Alford, McAllister, Brain, & Brain, 1984). If the effects observed in the present study of disruption by naltrexone were due to a degradation of the incentive-motivational properties of the stimulus contexts, then naltrexone administered during extinction should result in an elimination of the reinforcement rate dependent disruption produced by extinction. Future studies could also assess the role of the endogenous opioid system in mediating the incentive-motivational properties of alcohol and alcohol-associated stimuli. For instance, subjects that are genetically different in terms of their opioid system (e.g., NEP-deficient mice; Fischer et al., 2000; Lu et al., 1995) could be compared using procedures
comparable to those used in the present study. Another possibility would be to use other drugs that have the opposite effect of naltrexone on opioid receptors (e.g., morphine) and compare their separate and combined effects on resistance to change. Naltrexone (an opioid antagonist) dose-dependently decreases alcohol consumption, whereas low doses of morphine (an opioid agonist) increases it (Hubbell et al., 1986). Therefore, when administered together, their effects on differential resistance to change during extinction should counteract each other if they exert their effects through the same mechanism (cf. Neisewander, Pierce, & Bardo, 1990). Such studies would further help clarify the mechanisms through which naltrexone decreases alcohol consumption.

Conclusion

The present experiment found that ethanol-maintained responding was more resistant to extinction when the behavior occurred in a component that provided a higher rate of alcohol delivery (VI 15 s) than in a component that provided a lower rate of alcohol delivery (VI 45 s). When responding was disrupted with naltrexone, however, the decrease in responding was proportionally equivalent for the two components of the multiple schedule. These findings suggest that behavioral and pharmacological disruptors of ethanol-maintained responding may function differently. The resistance to change of responding in the face of a behavioral disruptor such as extinction depends on the stimulus-reinforcer relation, as proposed by behavioral momentum theory. Naltrexone may affect the incentive-motivational properties of the stimuli associated with ethanol. Further experiments should directly assess the hypothesis that naltrexone eliminates the
incentive-motivational properties of alcohol-associated stimuli. Specifically, future studies could assess how naltrexone modulates the incentive-motivational effects of reinforcers in the face of behavioral disruption (e.g., effects of naltrexone on alcohol-maintained responding under extinction conditions). The results of various studies have shown that the endogenous opioid system is directly involved in the control of consummatory behavior and in mediating the hedonic effects of reinforcement (see Gianoulakis & de Waele, 1994, for a review). Therefore, future experiments should also investigate the role of the endogenous opioid system in resistance to change of both food- and drug-maintained behavior.
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