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Nondrug Reinforcement Loss and Relapse to Alcohol Seeking in Another Context

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NONDRTUG REINFORCEMENT LOSS AND RELAPSE TO ALCOHOL SEEKING IN ANOTHER CONTEXT

by

Adam D. Pyszczynski

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

MASTER OF SCIENCE

in

Psychology

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UTAH STATE UNIVERSITY
Logan, Utah
2010
ABSTRACT

Nondrug Reinforcement Loss and Relapse to Alcohol Seeking in Another Context

by

Adam D. Pyszczynski, Master of Science
Utah State University, 2010

Major Professor: Dr. Timothy A. Shahan
Department: Psychology

Extinguished alcohol-maintained responding has been shown to relapse in a resurgence preparation when food-reinforced responding is subsequently extinguished within the same context. However, drug and nondrug reinforcers are often specific to different contexts. Accordingly, the present experiments sought to determine whether loss of an alternative source of nondrug reinforcement in one context could produce relapse to drug seeking in a separate context. In one experiment, rats made topographically different responses for food or alcohol in alternating components of a multiple schedule. Both reinforcers were delivered during baseline, alcohol was withheld during the second phase of the experiment, and finally both reinforcers were withheld during the final phase. Extinguished alcohol-maintained responding increased upon discontinuation of food deliveries, but may have increased due to similarity between the final experimental phase and an initial training phase. In a second experiment, the training phase that complicated interpretation of the elevated responding observed in Experiment 1 was eliminated
altogether. Alcohol seeking again relapsed upon discontinuation of food, suggesting that the training conditions were not the cause of the observed relapse in Experiment 1. Thus, loss of a nondrug reinforcer in one context can produce relapse to drug seeking in another. This procedure may provide a novel model of drug relapse in which loss of context-specific, alternative nondrug reinforcers precipitates relapse to drug seeking in a separate context.

(72 pages)
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Adam D. Pyszczynski
# CONTENTS

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
</table>

**ABSTRACT** .................................................................................................................. iii |

**ACKNOWLEDGMENTS** ....................................................................................................... v |

**LIST OF TABLES** .......................................................................................................... vii |

**LIST OF FIGURES** ......................................................................................................... viii |

**CHAPTER** |

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
</table>

I. **INTRODUCTION** .............................................................................................................. 1 |

II. **LITERATURE REVIEW** ................................................................................................ 5 |

   - Drug Addiction ........................................................................................................... 5 |
   - Drug Self-Administration ........................................................................................... 7 |
   - Animals Models of Relapse ....................................................................................... 8 |
   - Alternative Reinforcers and Drug Self-Administration ........................................... 16 |

III. **STATEMENT OF THE PROBLEM** ............................................................................... 21 |

IV. **EXPERIMENT 1** ......................................................................................................... 22 |

   - Method ...................................................................................................................... 22 |
   - Results and Discussion ............................................................................................. 28 |

V. **EXPERIMENT 2** ......................................................................................................... 35 |

   - Method ...................................................................................................................... 35 |
   - Results and Discussion ............................................................................................. 37 |

VI. **GENERAL DISCUSSION** .......................................................................................... 44 |

   - Behavioral Contrast ................................................................................................. 46 |
   - Limitations and Future Directions .......................................................................... 51 |
   - Conclusion ................................................................................................................ 52 |

**REFERENCES** ............................................................................................................... 53 |
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mean Baseline Response Rates, Reinforcer Rates, and Ethanol Consumption for Rats in Experiment 1</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>Mean Inactive Lever Presses Per Minute Across Conditions for Rats in Experiment 1</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Mean Baseline Response Rates, Reinforcer Rates, and Ethanol Consumption for Rats in Experiment 2</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>Mean Inactive Lever Presses Per Minute Across Conditions for Rats in Experiment 2</td>
<td>42</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lever presses (filled points) and chain pulls (empty points) during the Last five sessions of Baseline (BL), the first and last five sessions of Extinction Alcohol (EXT EtOH), and all five sessions of Extinction Both (EXT Both) for individual rats in Experiment 1. Note that the scale of the y-axis varies across subjects.</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Proportion of baseline lever presses per minute during the last five Sessions of EXT EtOH (mean ±SD) and all five sessions of EXT Both For individual rats in Experiment 1.</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>Schematic of experimental conditions according to reinforce availability and response requirement. Refer to the Multiple Schedule Training (Mult-training) and Extinction Both (EXT Both) phases (bolded and gray). Prior to extinction in the food component in the EXT Both phase, animals experienced extinction alternating with periods of alcohol availability during Mult-training. Upon extinction of previously food-maintained responding during the EXT Both phase, the experimental conditions may have resembled conditions during the Mult-training phase. Thus relapse may have been caused by prior exposure to food extinction during Mult-training rather than loss of an alternative source of reinforcement.</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>Lever presses (filled points) and chain pulls (empty points) during the last five sessions of Baseline (BL), the first and last five sessions of Extinction Alcohol (EXT EtOH), and all five sessions of Extinction Both (EXT Both) for individual rats in Experiment 2. Note that the scale of the y-axis varies across subjects.</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Proportion of baseline lever presses per minute during the last five sessions of EXT EtOH (mean ±SD) and all five sessions of EXT Both for rats in Experiment 2. Note that the scale of the y-axis for rat B1 differs from the other animals.</td>
<td>41</td>
</tr>
</tbody>
</table>
CHAPTER I
INTRODUCTION

Drug addiction and substance abuse are significant and costly issues in the United States. Drug addiction is a chronic, relapsing brain disease characterized by compulsive drug seeking and use (National Institute on Drug Abuse [NIDA], 2007). The diagnostic criteria for substance dependence reflect these same characterizations (American Psychiatric Association [APA], 2000). Examination of the underlying factors that control the persistence of, and relapse to drug seeking is a critical issue in addressing these problems.

Animal models allow a thorough examination of factors related to substance abuse and addiction on behavioral and neurobiological levels (see Gardner, 2000). One such animal model is drug self-administration, in which drug doses are delivered contingent on some arbitrary response and serve as a reinforcer. Drug self-administration can serve as an animal model because drugs function similar to other reinforcers (Johanson, 1978) and because of considerable similarities in self-administration by animals and by humans (Griffiths, Bigelow, & Henningfield, 1980).

Various animal models are used to examine different aspects of drug use including drug taking, abstinence, and relapse. Reinstatement is the most widely used animal model of relapse to drug seeking (see Shaham, Shalev, Lu, de Wit, & Stewart, 2003). The procedure generally consists of three phases. First, a response is maintained by contingent drug deliveries. Second, drug deliveries are discontinued, resulting in
decreased responding. Third, exposure to stimuli such as drug deliveries, drug-related cues, or certain stressors produces relapse to drug seeking (see Shalev, Grimm, & Shaham, 2002). These same events produce relapse in humans after periods of abstinence (NIDA, 2007).

Two other procedures also produce relapse-like phenomena: renewal (Bouton, 2002; Bouton & Bolles, 1979) and resurgence (Leitenberg, Rawson, & Mulick, 1975; Lieving & Lattal, 2003). In operant renewal preparations, some response is first reinforced in the presence of one set of contextual stimuli. That response is then extinguished in the presence of a different set of stimuli and then relapses once the animal is re-exposed to the initial training context. In resurgence preparations, some initial response is reinforced and is then extinguished while at the same time an alternative response is reinforced. The alternative response is then extinguished producing increased levels of the initial response. These procedures have also been used to model relapse to drug taking. While renewal has received more attention as a model of relapse (see Crombag, Bossert, Koya, & Shaham, 2008), just one published study has used the resurgence preparation as a model of relapse (Podlesnik, Jimenez-Gomez, & Shahan, 2006).

With few exceptions, reinstatement and renewal preparations generally rely on the presentation of events and stimuli, while it is the removal of an alternate source of reinforcement that produces relapse in the resurgence preparation. Some evidence from human studies suggests that the removal of rewarding events such as periods of unemployment or divorce can cause increased drug intake and even trigger relapse (Falba, Teng, Sindelar, & Gallo, 2005; Temple et al., 1991). These findings are not
particularly surprising considering that alternative nondrug reinforcers tend to decrease drug self-administration in animals (see Carroll, 1996). Access to nondrug alternatives can impede or prevent acquisition and decrease drug-maintained responding (Carroll, Lac, & Nygaard, 1989), as well as hasten extinction and attenuate relapse (Liu & Grigson, 2005). The removal of such alternatives may also result in increased drug taking (Carroll & Boe, 1982). Despite these findings, few studies have examined the loss of alternative sources of reinforcement as a cause of relapse.

One study conducted by Podlesnik et al. (2006) used a resurgence preparation to examine reinforcer loss as a catalyst for relapse to alcohol seeking. Podlesnik et al. observed relapse to alcohol seeking once food reinforcers were withheld for an alternate response; however, this study is limited by the fact that both drug and nondrug reinforcers were delivered and consumed within a single stimulus context. Early studies on conditioned drug effects indicate that drug use may occur repeatedly in the same environment (see Stewart & Eikelboom, 1987; Wikler, 1973). Furthermore, sources of nondrug reinforcement such as jobs or recreational activities may be specific to separate contexts. It remains to be seen whether loss of nondrug reinforcers can induce relapse in instances in which drug and nondrug reinforcers are specific to particular contexts.

Accordingly, the present experiments attempted to determine whether loss of nondrug reinforcers in one context could produce relapse to drug seeking in a separate context. In Experiment 1, rats responded in a multiple schedule in which food and alcohol reinforcers were made available exclusively in separate stimulus contexts. Topographically different responses were associated with each of the two reinforcers.
After baseline, alcohol deliveries were withheld for a series of sessions. Food reinforcers were then also discontinued, resulting in increased alcohol seeking. However, during prior training conditions periods of extinction alternated with periods of alcohol availability. Alcohol seeking may have increased because extinction in the food component served as a cue for alcohol availability in the alternating component. Thus, in Experiment 2, the problematic training conditions were excluded to evaluate whether they contributed to the relapse seen in Experiment 1.

Rats in Experiment 2 were placed directly on the multiple schedule of reinforcement after alcohol self-administration training and were then exposed to the same experimental conditions as in Experiment 1. Even with modified training conditions, responding increased on the lever previously associated with alcohol deliveries when food rewards were removed from the alternating component of the multiple schedule. These results suggest that loss of an alternative source of reinforcement in one context can induce relapse to extinguished drug seeking in a separate context. The procedure used here might provide a useful animal model that is analogous to situations experienced by human drug users in which significant episodes of loss (e.g., divorce or unemployment) precede episodes of relapse.
CHAPTER II
LITERATURE REVIEW

Drug Addiction

Alcohol and illicit drug abuse and addiction are widespread and costly problems in the United States. Results from the National Survey on Drug Use and Health in 2008 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2009) indicate that 20.1 million or 8% of individuals aged 12 or older are illicit drug users (as defined by reported usage within the 30 days prior to administration of the survey). Nearly 23.3% of individuals aged 12 or older reported binge drinking, defined as consuming five or more drinks on a single occasion within the last month. Furthermore, 17.3 million or 6.9% of that same age group reported heavy drinking defined as at least five episodes of binge drinking within the last month. Costs related to drug and alcohol abuse may actually surpass the costs of other chronic diseases (see NIDA, 2008). It is estimated that the direct and indirect costs of illicit drug abuse cost the United States $161 billion per year. When alcohol-related costs are included in this figure, the total jumps to a staggering $346 billion annually. To put these numbers in perspective, the estimated combined yearly costs of diabetes and cancer in the United States is just over $300 billion (see NIDA, 2008).

The National Institute on Drug Abuse (NIDA, 2007) classifies drug addiction as a chronic, relapsing brain disease characterized by compulsive drug seeking and use despite negative consequences. The diagnostic criteria set by the APA (2000) reflect
these same characterizations. Substance dependence is present if three or more of the following criteria are present in an individual within a year. The first criterion is tolerance defined by a need for increased amount of drug to achieve desired effects or by decreased drug effect when repeatedly using the same amount of drug. The second criterion is withdrawal, which may appear as a drug-specific withdrawal syndrome or if a drug is taken in order to avoid withdrawal symptoms. The third is that more of the drug is taken or drug use goes on longer than originally intended. The fourth criterion is repeated attempts to scale back drug use. Fifth is significant time is spent obtaining the drug, consuming it, or recovering from the drug. The sixth is that substance use occurs in lieu of other important activities. Finally, the seventh criterion states that drug use may continue despite adverse effects that are caused or aggravated by the drug. These criteria speak to the persistent nature of drug abuse. According to the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration; SAMHSA, 2009), 22.2 million or 8.9% of individuals aged 12 or older are classified as substance dependent or substance abusers as defined by these criteria.

Speaking to the persistence of substance abuse and addiction, the APA (2000) also outlines remission course specifiers related to the length of time that individuals are free of the diagnostic criteria (Early versus Sustained) and whether or not any of the diagnostic criteria resurface during remission (Partial versus Full). These specifiers can be applied only after individuals are free of all substance dependence diagnostic criteria for at least one month. Continued abstinence during remission is indicative of better outcomes and less risk to relapse. That is, the longer an individual can stay abstinent from
drug use, the more likely they will remain drug free. Collectively, the remission specifiers and the diagnostic criteria outlined earlier highlight the main issues of drug addiction: persistence of drug taking and vulnerability to relapse.

**Drug Self-Administration**

Animal drug self-administration methods were developed as an attempt to model human drug use. In part, the motivations for developing such techniques were based on various limitations of human models (Johanson, 1978). For one, the ethical constraints are far fewer when dealing with animals, allowing experimental questions to be addressed that otherwise could not. Second, drug self-administration procedures allow a well-controlled experimental focus on the behavioral, environmental, and neural mechanisms of drug taking. Overall, animal drug self-administration is a valuable tool for understanding the underlying mechanisms of drug taking.

Drug self-administration methods depend largely on the ability of drugs to function as reinforcers and maintain behavior in operant conditioning paradigms (Johanson, 1978). Responding maintained by drugs is very similar to responding maintained by other reinforcers in terms of schedule-specific patterns of responding. Furthermore, manipulations of reinforcer magnitude and deprivation conditions in drug-maintained behavior produce similar outcomes as behaviors maintained by nondrug reinforcers (Johanson, 1978).

The validity of drug self-administration as an animal model of drug taking also depends on similarities between drug taking in humans and animals (Griffiths et al.,
1980). Many drugs abused by humans, including widely used legal and illegal substances, are readily self-administered by animal subjects. Also, under unrestricted availability, humans and animals self-administer the same drugs under the same characteristic patterns and with similar consequences. Manipulations of dose and response requirement also produce similar patterns across humans and animals. Furthermore, some of the same administration routes employed by humans maintain drug self-administration in animals.

Self-administration techniques show considerable generality across species, response types, and administration routes. These animal models are especially effective in identifying and clarifying underlying factors involved in both drug taking and relapse by allowing rigorous analyses of factors contributing to all phases of drug addiction (Koob, 2000). Adding to the validity of such methods, a variety of self-administration procedures have been reported to map onto the various diagnostic criteria of drug dependence (Shippenberg & Koob, 2002).

Animal Models of Relapse

The primary animal model of relapse is the reinstatement procedure (see Shaham et al., 2003). The typical reinstatement arrangement in drug self-administration begins with the training of an arbitrary response resulting in drug deliveries. Next, drug deliveries are discontinued or replaced with a neutral substance, often just the drug vehicle itself. Finally, while the original response remains on extinction, some external stimulus is presented resulting in the reappearance (i.e., reinstatement) of the response
previously maintained by drug deliveries. These experimental phases may occur within sessions, between sessions, or a combination of the two with little effect on the generality of the outcomes (see Shaham et al., 2003).

There are three primary types of stimuli that produce relapse within this arrangement. First, drug-priming reinstatement refers to reinstatement of extinguished responding occasioned by re-exposure to the previously self-administered drug, typically via noncontingent deliveries. A study conducted by de Wit and Stewart (1981) provided an early demonstration of drug priming reinstatement in rats of responding previously reinforced by cocaine infusions. Rats implanted with jugular catheters pressed a lever to receive cocaine infusions during daily sessions consisting of two components: a self-administration period lasting between 1-2 hours and then an extinction phase lasting 90 min. After 60 min in extinction, rats received a noncontingent cocaine infusion, which resulted in increased lever pressing despite the extinction contingency still being in place.

Drug priming reinstatement shows considerable generality in that it has been reported in a diverse set of abused drugs including heroin, cocaine, alcohol, and nicotine (see Shalev et al., 2002). The priming dose appears to be a key factor in the magnitude of the reinstatement observed in that larger doses produce more reinstated responding and for longer periods of time (de Wit, 1996). Furthermore, delivery of a different drug belonging to the same pharmacological class (de Wit, 1996) or less commonly, from a different pharmacological class (De Vries, Schoffelmeer, Binnekade, & Vanderschuren, 1999), can reinstate extinguished drug seeking.

Second, presentations of various drug-paired cues are also capable of reinstating previously drug-maintained behavior (see Shalev et al., 2002). The nature of the cue and
the manner of presentation appear to mediate the degree of reinstatement (Grimm, Kruzich, & See, 2000; Meil & See, 1996). Cues can either be discrete cues paired with drug deliveries or can be broader contextual stimuli associated with drug availability. Discrete cues will be reviewed here because reinstatement with broader contextual cues and discriminative stimuli appears more similar to a different model of relapse (i.e., renewal) that will be discussed later.

In one experiment, de Wit and Stewart (1981) tested whether noncontingent presentations of discrete drug cues reinstate extinguished drug seeking. Two groups of rats responded on a variable ratio (VR) 6 schedule of reinforcement for cocaine infusions. In one group (correlated group), a tone accompanied cocaine infusions, whereas in the other group (uncorrelated group) the tone presentations were yoked to infusions received by a different rat. After self-administration periods lasting 1-2 hours, extinction went into effect and cocaine infusions were no longer delivered. The tone was then activated noncontingently after rats went 30 min without responding during extinction, resulting in weakly reinstated lever pressing.

Meil and See (1996) conducted a similar experiment except that a stimulus light and the sound of the infusion pump (compound stimulus) accompanied cocaine infusions earned during daily sessions. Meil and See reported significant reinstatement after 20 days of extinction with noncontingent presentations of the stimulus light and pump sound. In a separate experiment, Meil and See tested whether the stimulus light alone would reinstate extinguished responding. The light alone failed to reinstate cocaine seeking. The authors speculated that compound stimuli might be necessary for cue-induced reinstatement or that the pump sound may have served as a better cue.
In another study, Grimm et al. (2000) allowed three groups of rats to self-administer cocaine for 14 days, followed by seven days of extinction. During self-administration, a tone and light accompanied cocaine infusions. Subsequent to extinction, rats experienced three days with access to the cocaine-related stimuli, but not cocaine infusions. Presentation of the cocaine-related cues varied between groups: one group received the combination stimulus contingent on lever presses, another noncontingently (time-based schedule), and the third received both contingent and noncontingent cue presentations. Cocaine seeking was reinstated to a greater degree in the group of rats that received contingent presentations of the compound cue than the groups that received noncontingent or mixed presentations. Thus, it appears that compound stimuli presented contingent on responding are most effective in reinstating drug seeking during extinction.

Third, certain stressors are also capable of reinstating drug seeking. Shaham and Stewart (1995) provided an early demonstration of this effect using a brief period of intermittent electric footshock. Rats self-administered heroin intravenously according to a fixed ratio (FR) 1 schedule during baseline and then experienced a number of extinction sessions. Subsequent to extinction, various reinstatement tests were administered in a counterbalanced order across animals: the two relevant to the current discussion are noncontingent drug infusions and 10-min periods of intermittent electric footshock. Both drug infusions and footshock reinstated extinguished heroin seeking, and interestingly, electric footshock reinstated behavior to a greater degree than drug priming.

Footshock stress is frequently used because it shows generality across different drugs and doses, response requirements, shock parameters, and rat strains (see Shaham, Erb, & Stewart, 2000). Footshock also reinstates drug seeking across a variety of drugs.
including heroin, cocaine, alcohol, and nicotine (see Sinha, 2001). Thus, it has become the most widely used stressor in reinstatement experiments. Interestingly, footshock may not reinstate food-maintained behavior suggesting that shock may selectively reinstate drug seeking (Ahmed & Koob, 1997; Buczek, Le, Wang, Stewart, & Shaham, 1999; Le et al., 1998). Although not as common, other stressors also reliably reinstate drug seeking. For instance, injections of corticotropin-releasing factor, which induces a stress-like state, have been used to reinstate drug seeking (Shaham et al., 1997). Acute periods of food deprivation have also been shown to reinstate responding previously maintained by infusions of cocaine (Carroll, 1985; Shalev, Highfield, Yap, & Shaham, 2000) and heroin (Shalev, Marinelli, Baumann, Piazza, & Shaham, 2003).

Thus, re-exposure to the self-administered drug, cues associated with the self-administered drug, and certain stressors reliably reinstate previously drug-maintained responding within the reinstatement procedure. Importantly, these same variables produce relapse in humans after periods of abstinence (NIDA, 2007). The fact that similar variables produce relapse within the reinstatement model and in humans is cited as evidence of the validity of the model (Epstein, Preston, Stewart, & Shaham, 2006).

Relevant to the present study, all forms of reinstatement have been demonstrated within alcohol self-administration. Free deliveries of an ethanol solution produce recovery of extinguished alcohol seeking, effectively demonstrating drug priming-induced reinstatement (Chiamulera, Valerio, & Tessari, 1995). Le et al. (1998) demonstrated stress-induced reinstatement by exposing rats to periods of either 5 or 15 minutes of intermittent footshock prior to self-administration. Le et al. (1998) found that shock produced robust response recovery--greater than priming doses of alcohol, and also
found greater recovery after the longer shock duration. Cue-induced reinstatement of alcohol seeking has been demonstrated with an olfactory cue (Katner, Magalong, & Weiss, 1999) as well as response-contingent presentations of visual discriminative stimuli (Liu & Weiss, 2003).

Before its application to drug self-administration, reinstatement was reported in classical and traditional operant conditioning preparations. In classical conditioning, animals learn to associate a conditioned stimulus (CS; e.g., tone) with an unconditioned stimulus (US; e.g., footshock). The CS is then capable of eliciting fear, which is inferred from suppressed behavior. Extinction occurs with repeated exposure to the CS alone (without footshock). That is, the CS no longer elicits fear and previously suppressed behavior resumes. In classical conditioning, reinstatement refers to the reappearance of a previously extinguished conditioned response after noncontingent presentation to the U.S. Presentation of the U.Ss results in the reinstatement of the extinguished CR (e.g., fear).

In operant conditioning, reinforcers (e.g., food) are presented contingently on some arbitrary response (e.g., lever press); thus, the response-reinforcer relation maintains responding. Extinction of operant conditioning refers to breaking the response-reinforcer relation by withholding the reinforcer (i.e., extinction), and a subsequent decrease in the operant response. In reinstatement of operant conditioning, reinforcers or cues associated with reinforcer delivery are presented independent of responding during extinction. Deliveries of reinforcers (Rescorla & Skucy, 1969) or stimuli associated with reinforcers (Campbell, Phillips, Fixsen, & Crumbaugh, 1968) result in reinstated responding. These phenomena suggest that original learning remains intact after
extinction, and can re-emerge under the right circumstances (Bouton & Swartzentruber, 1991).

Renewal and resurgence are two other extinction-related phenomena from classical and operant conditioning preparations that also support this idea that extinction learning is highly context-specific. Furthermore, both procedures have been used as animal models of relapse. Renewal refers to response recovery produced by a change in context after extinction (Bouton & Bolles, 1979). A common form is ABA renewal in which the subject returns to the original conditioning context after extinction. That is, initial training takes place in one context (context A), extinction in a second context (context B), and then responding is renewed once the subject is returned to the original training context (context A). This type of renewal is observed in both classical and operant conditioning (see Bouton & Swartzentruber, 1991). Exposure to a novel context after extinction (ABC renewal) also produces response recovery in classical conditioning paradigms (Bouton, 2004).

Like reinstatement, renewal has been used as an animal model of relapse (see Crombag et al., 2008). The renewal procedure produces relapse to extinguished drug taking previously maintained by a variety of drugs including heroin (Bossert, Liu, Lu, & Shaham, 2004), cocaine (Crombag, Grimm, & Shaham, 2002), and a mixture of the two drugs (Crombag & Shaham, 2002). It has also been widely reported that relapse to alcohol seeking is susceptible to ABA renewal (Burattini, Gill, Aicardi, & Janak, 2006; Chaudhri, Sahuque, & Janak, 2008; Hamlin, Newby, & McNally, 2007; Marinelli, Funk, Juzytsch, Li, & Le, 2007; Zironi, Burattini, Aicardi, & Janak, 2006). Just as the same stimuli that produce relapse within reinstatement arrangements produce relapse in
humans, renewal-like mechanisms have been implicated in instances of relapse in human drug users (Conklin & Tiffany, 2002).

Resurgence (Epstein & Skinner, 1980; Leitenberg et al., 1975) refers to the reoccurrence of some extinguished response when an alternative response, introduced during extinction of the first response, is also extinguished. Within this procedure some initial response (e.g., lever press) is reinforced. Next, that initial response is extinguished while an alternate response (e.g., alternate lever press or chain pull) is introduced and reinforced. Upon extinction of the new, alternate response, the initial response reappears. Just one published study has used resurgence as a model of drug relapse.

Podlesnik et al. (2006) examined the resurgence procedure as a novel animal model of relapse. Because the procedure uses loss of an alternative source of reinforcement as a catalyst for relapse, Podlesnik et al. reasoned that it might be a good procedure for examining relapse similar to that observed in humans in which some significant loss precedes an episode of relapse. Rats lever pressed for alcohol dippers according to a random-ratio (RR) 25 schedule of reinforcement in 25 30-min sessions. Next, lever pressing was extinguished and a chain was introduced into the chamber. Chain pulls produced 45 mg food pellets according to an RR 10 schedule for 10 sessions. Finally, chain pulls were also extinguished. Podlesnik et al. found that when chain pulls were extinguished, lever pressing increased significantly relative to response rates during the second phase of the experiment. This elevation in responding occurred despite the fact that extinction of lever pressing for alcohol was still in effect. Responding on an inactive lever in the chamber did not increase, suggesting that the increased responding brought on by extinction of the alternate response was not due to some nonspecific
activation. Thus, Podlesnik et al. demonstrated that loss of an alternative, nondrug source of reinforcement could produce relapse of previously drug-maintained behavior.

The majority of studies using reinstatement or renewal arrangements as models of relapse have relied on the presentation of environmental events or stimuli to induce relapse to drug seeking. That is, animals receive drug deliveries, presentations of drug-paired or contextual cues, or are subjected to physical stressors. Unlike reinstatement and renewal, resurgence relies on the loss of some alternative source of reinforcement (i.e., extinction) within the experimental context in order to produce relapse. It is somewhat surprising that models of relapse like resurgence have received so little attention considering a large body of literature considering the effects of alternative nondrug reinforcers on drug self-administration.

**Alternative Reinforcers and Drug Self-Administration**

Environmental enrichment via access to alternative nondrug reinforcers has well-documented effects on reducing drug abuse (see Carroll, 1996). The presence of alternatives is a protective factor during various phases of drug self-administration. For instance, Carroll et al. (1989) examined acquisition and maintenance of cocaine self-administration while an alternative nondrug reinforcer was available. Animals were trained to self-administer cocaine with access to a glucose and saccharin solution or water delivered via a tongue-operated drinking spout. Carroll et al. reported that some rats with concurrent access to the sweetened solution failed to acquire cocaine self-administration. Moreover, rats with access to the sweetened solution that met the acquisition criterion self-administered less drug than rats that had concurrently available water. When water
was substituted for the sweetened solution, cocaine intake increased. Thus, a concurrently available nondrug reinforcer can prevent acquisition of drug self-administration and also decrease ongoing self-administration.

Liu and Grigson (2005) focused on the effects of access to alternatives during extinction and relapse phases of drug taking. Rats responded by licking a spout for cocaine infusions during training and baseline. After a 3-month withdrawal period, matched groups received either 5-min access to water or a solution of glucose and saccharin in their home cages prior to extinction sessions. Rats with access to the sweetened alternative showed significantly reduced cocaine seeking during extinction. With extinction contingencies still in effect, rats were then tested for reinstatement with intraperitoneal (IP) injections of cocaine. Similar to the results observed during extinction, rats that received the palatable alternative did not show reinstated drug seeking whereas the water group did. While not a demonstration of concurrent access to a nondrug alternative because access was given prior to experimental sessions, it appears that even brief exposure to nondrug alternatives has the capacity to hasten extinction and attenuate relapse.

Carroll and Boe (1982) examined drug self-administration during deprivation from a solution of glucose and saccharin while regular rat chow and water were still freely available. Six rats intravenously self-administered etonitazene, a potent analgesic drug, with concurrent access to the glucose and saccharin solution; however, every third day rats were deprived of the palatable solution. Carroll and Boe reported small but reliable increases in etonitazene self-administration on deprivation days.
Other studies have examined drug taking under environmental enrichment via manipulations other than palatable consumables. For instance, Higley, Hasert, Suomi, and Linnoila (1991) examined the long-term effects of early rearing on alcohol consumption in young, nonhuman primates. Young primates were reared by their mothers or by peers until they were 7 months old. After this period, all monkeys were treated identically and lived with a group of same-aged peers. Higley et al. found that the peer-reared primates consumed more alcohol than primates reared by their mothers. When animals reared by their mothers were separated from their peers during social separations, alcohol consumption increased to levels similar to their peer-reared counterparts. In another study, Stairs, Klein, and Bardo (2006) found that housing rats with other rats and novel objects enhanced extinction of amphetamine-maintained behavior and also increased the reinstatement threshold for priming doses of amphetamine (i.e., larger doses were required to reinstate drug seeking in rats housed in the enriched conditions). Theil, Sanabria, Pentkowski, and Neisewander (2009) found that enriched housing conditions enhanced extinction and attenuated cue-induced relapse to cocaine seeking, but had no effect on priming reinstatement. Thus, environmental enrichment via palatable nondrug alternatives, access to novel objects, and contact with conspecifics can act as a protective factor during various phases of drug self-administration.

These results are in accordance with a number of human studies that have established a link between the removal of alternative, reinforcing events and increases in drug intake or instances of relapse after periods of abstinence. For example, Falba et al. (2005) examined data from the Health and Retirement study in order to explore the
relationship between involuntary job loss and smoking intensity as well as relapse in abstinent smokers. Falba et al. found that involuntary job loss contributed significantly to elevated levels of smoking in individuals who already smoked. Furthermore, risk of relapse doubled after job loss in ex-smokers. Gallo, Bradley, Siegel, and Kasl (2001) also analyzed longitudinal data from the Health and Retirement survey. The authors used multivariate models to explore the relationship between involuntary job loss and alcohol use. Involuntary job loss was related to alcohol consumption in that individuals who did not report any alcohol consumption prior to involuntary job loss were twice as likely to initiate drinking after job loss as compared to individuals who remained employed during the same time period. Temple et al. (1991) conducted a meta-analysis of 12 longitudinal studies, which revealed that divorce and unemployment were consistently predictive of increased alcohol consumption. Accordingly, loss of vocational and marital reinforcers appears to be a significant factor in increasing alcohol and nicotine intake, as well as increasing the likelihood of relapse to drinking and smoking in abstinent individuals.

While it has been demonstrated that a variety of stressors increase drug self-administration (see Piazza & Le Moal, 1998), fewer types have been used within models of relapse, and those that have been used are generally physical stressors (e.g., footshock, restraint) as noted above. In human populations, many stressful life events such as job loss and divorce that contribute to increased drug consumption (San Jose, Van Oers, Van De Mheen, Garretsen, & Mackenbach, 2000) and relapse (Brady & Sonne, 1999) appear to be based on significant loss. According to Vuchinich and Tucker (1988) alcohol consumption is dually determined by the direct constraints on access to alcohol as well as availability of other reinforcers and the constraints placed on those other reinforcers.
Alcohol preference varies inversely with presence or amount of other alternatives, and tends to increase with increases in response requirement for alternatives. However, few animal models have explored removal of alternative reinforcers as a means of inducing relapse, and the one published study that has done so (Podlesnik et al., 2006) is limited by the fact that drug and nondrug reinforcers were obtained and consumed within a single experimental context. Studies on conditioned drug effects indicate that through repeated pairings with drug use, neutral stimuli, such as the setting where the drug taking occurs, can come to elicit motivational states similar to those produced by the drug itself (see Stewart & Eikelboom, 1987; Wikler, 1973). Thus, drug taking may have a tendency to occur repeatedly in a particular setting or environment. In addition, vocational, recreational, social, or family reinforcers may also be specific to particular contexts separate from the context where drug use occurs (e.g., workplace, recreational area). Therefore, specific, separate contexts and situations may be associated with certain types of rewarding events.

While some studies have examined food deprivation outside the self-administration context as a stressor in reinstatement arrangements (Carroll, 1985; Shalev et al., 2000), these studies did not examine reinforcer loss as a source of relapse. Podlesnik et al. (2006) demonstrated that extinction of a response reinforced by nondrug alternatives produces relapse in a single context, but there has yet to be a demonstration of relapse produced by extinction of an alternatively reinforced response in a separate context. This raises the question of whether nondrug reinforcer loss in one context can cause relapse to drug seeking in a separate context.
CHAPTER III

STATEMENT OF THE PROBLEM

Drug abuse is a significant problem in human populations, and animal models are useful in examining its underlying mechanisms. While reinstatement is the primary animal model of relapse, renewal and resurgence are two other procedures that have been adapted to serve as models of relapse. Reinstatement and renewal generally rely on the presentation of events and stimuli, whereas extinction of an alternately reinforced response produces relapse in resurgence preparations.

The presence of alternative sources of reinforcement tends to be a protective factor during various phases of drug intake, while their absence has the opposite effect. Only one study has examined loss of nondrug reinforcers as a determinant of relapse in an animal model (Podlesnik et al., 2006). However, there is a limitation to this study in that drug and nondrug reinforcers were delivered and consumed in a single context. In humans the availability of rewarding events, such as vocational reinforcers, or drug taking may be specific to separate contexts. Accordingly, the purpose of the present experiments was to determine whether loss of nondrug reinforcers specific to one context could produce relapse to drug seeking in a separate context.
CHAPTER IV
EXPERIMENT 1: METHOD

Subjects

Six experimentally naïve male Long-Evans rats (Charles River, Portage, Michigan, USA) approximately 90 days old when received were used in the experiment. Two additional rats were eliminated from the experiment because they did not reliably self-administer alcohol. Free-feeding weights were established over a period of approximately 14 days. Subjects were then maintained via supplemental feedings at approximately 80% of their free-feeding weights and housed individually with free access to water in a temperature-controlled room with a 12:12h light/dark cycle (lights on at 7:00 AM). Experimental sessions took place at approximately the same time each day during the light cycle.

Apparatus

Four Coulbourn operant chambers (29 × 24 × 29 cm) housed in sound-attenuating enclosures were used. A ventilation fan and white noise masked outside noise. Each chamber was equipped with two levers centered 13 cm apart on the front wall of the chamber. Above each lever was a series of three colored LEDs (red, yellow, green). Each chamber was also equipped with a 28-V DC houselight and sonalert (2900 ± 500 Hz, 75-85 dB) centered above the levers. A rectangular aperture (6.5 × 4.2 cm) centered between the levers, also lit by a single 28-V DC feeder light, provided access to both food and alcohol rewards. A solenoid-operated dipper provided 3-s access to 0.1 ml fluid on the
left side of the aperture, and a tube dispensed 45-mg food pellets on the right. An audible click accompanied each pellet delivery. Each chamber was also equipped with a chain that could be inserted into the chamber through the center of the ceiling panel. Distilled water, table sugar, and 95% stock ethanol were used to prepare solutions. MED-Associates (1999) programming and interface controlled experimental events and data recording.

Procedure

Magazine Training

Rats received one 30-min session of magazine training in which food pellets were delivered according to a variable time (VT) 60-s schedule of reinforcement. The chamber remained dark during this session and a brief flash of the feeder light accompanied food pellet deliveries.

Alcohol Self-Administration Training

Rats were trained to self-administer alcohol according to a modified sucrose fading procedure (see Samson, 1986), as described by Shahan (2002). Rats were initially exposed to at least one 30-min session in which 0.1 ml dippers of a 2% ethanol (vol/vol), 10% sucrose (weight/vol) solution were delivered on a concurrent VT 60-s, FR 1 schedule of reinforcement. Responses to the right lever produced alcohol deliveries. Most rats began pressing the lever for the dippers within a single 30-min session. Rats that did not begin pressing the lever remained on the concurrent VT, FR schedule until pressing occurred regularly. Once rats begin reliably pressing the lever for deliveries of the ethanol/sucrose solution, the VT portion of the schedule was removed, and thereafter, the
FR requirement was gradually increased within and between sessions until rats responded reliably on an FR 5. After rats received 200 dippers within a session according to the FR 5 requirement, the schedule was changed to a RR 3 schedule of reinforcement for the following session. Over approximately 30 days the RR requirement was increased between sessions until a terminal value of RR 25 was achieved. During the same time period, the ethanol concentration of the solution was gradually increased, between sessions, from 2% to 10%. Rats responded on the final response requirement of RR 25, and for a solution of 10% ethanol, 10% sucrose for approximately 30 days. Sucrose was then gradually faded from the solution between sessions over another period of approximately 30 days until no sucrose remained and rats responded for only diluted ethanol. Alcohol training lasted until rats responded reliably for the 10% solution of ethanol for a minimum of 10 days. During all training sessions, the lights above the right lever and the houselight were lit. Only the feeder light was lit during the 3-s alcohol deliveries.

Multiple Schedule Training

Once alcohol self-administration had been reliably acquired, rats were moved to a multiple RR 25, extinction (EXT) schedule. This intermediate training phase was included over concerns that introduction of food reinforcers into the multiple schedule might decrease alcohol self-administration (see Carroll, 1996). Differential stimuli signaled the two components of the multiple schedule and these stimuli were counterbalanced across subjects. The houselight and a tone remained on in one component, while turning on and off every 0.5-s in the other. The LED lamps above the right lever were lit during components in which alcohol was available. All stimuli were
turned off during dipper deliveries, with the exception of the feeder light, which remained lit for the 3-s dipper duration.

Each session consisted of 30 alternating multiple schedule components separated by 15-s intercomponent intervals (ICIs) in which responses had no programmed consequences and all stimuli in the chamber were turned off. Sessions always began with an EXT component. Strict alternation of the two components followed for the remainder of each session. Each component lasted 60-s, timed exclusive of reinforcement. This schedule remained in effect until the mean discrimination index (active lever presses in alcohol component divided by total number of active lever presses in both components × 100%) met or exceeded 90% for all animals. Even though some animals reached this criterion within the first week of training, multiple schedule training lasted until all rats had met the criterion to equate exposure to this phase across animals. This phase lasted 55 days for all animals.

**Baseline**

Once the discrimination criterion was met, a chain was inserted into each operant chamber prior to experimental sessions and rats responded on a multiple schedule RR 25 (lever - alcohol) FR 1 (chain - food). The chain hung down from the center of the chamber’s ceiling panel, so rats initiated contact with it almost immediately. The response requirement for food pellets was increased across successive days until rats responded on an RR 10, resulting in a final schedule of RR 25 (lever - alcohol), RR 10 (chain - food).

The multiple schedule stimuli remained as they were during multiple schedule training. The lamps above the right lever remained lit during components in which
alcohol was available, but no additional stimuli accompanied components in which chain pulls produced food pellets. All stimuli were turned off during dipper and pellet deliveries, with the exception of the feeder light, which remained lit for 3-s. Sessions now began with the food component so that all alcohol components were preceded by a food component, thus ensuring that all alcohol components within each session were affected by manipulations to the food component that occurred in subsequent experimental phases.

Baseline consisted of daily sessions in the multiple schedule just described - RR 25 (lever - 0.1 ml 10% ethanol) RR 10 (chain – 45 mg food pellet). Responses to the left lever were recorded but had no programmed consequences. Baseline lasted 35 sessions for each rat.

**Extinction Alcohol**

This phase was identical to the previous phase except that lever presses were extinguished in the alcohol component and no longer produced alcohol deliveries. The food-related contingencies from the previous condition remained in effect in that component of the multiple schedule (i.e., multiple EXT, RR 10 [chain – food] schedule). The lights above the active lever remained on in the alcohol component, but lever presses no longer produced any stimuli associated with reinforcement. Dipper trays were filled with the 10% ethanol solution and were loaded into the area that held the trays outside of the operant chamber as they were in the previous conditions. This phase remained in effect for 20 sessions for all animals.
Extinction Both

Responses in both alcohol and food components were extinguished during this phase (i.e., multiple EXT, EXT schedule). Stimuli related to the two contexts continued to alternate with the components, but lever presses and chain pulls did not produce food or alcohol deliveries. This phase remained in effect for 5 sessions because this was the length of the resurgence phase in the Podlesnik et al. (2006) experiment. Rats were fed additional chow during supplemental feedings to approximate the mean number of pellets obtained during the last five sessions of the previous phase.

Measures

Responses per minute on the active lever (right), inactive lever (left), and chain were the primary dependent measures of this experiment. Responses and time during reinforcer deliveries and ICIs were excluded from calculations of response rate. The inactive lever served as a control, so elevated response rates on the active lever could be interpreted as alcohol seeking rather than general activation. The primary comparison of interest in the present study was between lever pressing at the end of the EXT alcohol condition and during each session of the EXT both condition. Proportion of baseline measures were used in an attempt to normalize data across subjects. Mean response rates over the last five sessions of Baseline (see Table 1) were used in calculations of proportion baseline.
Results and Discussion

Baseline

Table 1 displays mean response rates, reinforcer rates, and g/kg ethanol consumed over the final five sessions of baseline. The left panels of the graphs in Figure 1 shows responses per minute on the active lever and chain during the alcohol and food components, respectively, in the last five sessions of baseline for individual subjects. The relationship between the response rates in the two components varied across animals with two rats responding more for alcohol (A3 and A6), three responding more for food (A1, A4, and A5), and one rat responding nondifferentially in the two components (A2). Table 2 shows that rats made few responses to the inactive lever.

Table 1

Mean Baseline Response Rates, Reinforcer Rates, and Ethanol Consumption for Rats in Experiment 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Alcohol component</th>
<th>Food component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active lever (resp/min)</td>
<td>Inactive lever (Resp/min)</td>
</tr>
<tr>
<td>A1</td>
<td>Mean 25.68</td>
<td>SD 4.48</td>
</tr>
<tr>
<td>A2</td>
<td>Mean 109.09</td>
<td>SD 14.25</td>
</tr>
<tr>
<td>A3</td>
<td>Mean 152.60</td>
<td>SD 6.82</td>
</tr>
<tr>
<td>A4</td>
<td>Mean 80.13</td>
<td>SD 5.53</td>
</tr>
<tr>
<td>A5</td>
<td>Mean 39.88</td>
<td>SD 9.40</td>
</tr>
<tr>
<td>A6</td>
<td>Mean 165.53</td>
<td>SD 10.40</td>
</tr>
</tbody>
</table>
Figure 1. Lever presses (filled points) and chain pulls (empty points) during the last five sessions of Baseline (BL), the first and last five sessions of Extinction Alcohol (EXT EtOH), and all five sessions of Extinction Both (EXT Both) for individual rats in Experiment 1. Note that the scale of the y-axis varies across subjects.
Table 2

*Mean Inactive Lever Presses Per Minute Across Conditions for Rates in Experiment 1*

<table>
<thead>
<tr>
<th></th>
<th>Alcohol component</th>
<th></th>
<th></th>
<th>Food component</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>EXT</td>
<td>EXT</td>
<td>both</td>
<td>Baseline</td>
<td>EXT</td>
</tr>
<tr>
<td>A1</td>
<td>0.00</td>
<td>0.01</td>
<td>0.24</td>
<td>0.00</td>
<td>0.00</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.03</td>
<td>0.38</td>
<td>0.00</td>
<td>0.00</td>
<td>0.11</td>
</tr>
<tr>
<td>A2</td>
<td>0.03</td>
<td>0.00</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>0.04</td>
<td>0.00</td>
<td>0.04</td>
<td>0.00</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>A3</td>
<td>0.65</td>
<td>1.04</td>
<td>0.69</td>
<td>0.00</td>
<td>0.00</td>
<td>0.17</td>
</tr>
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<td></td>
<td>0.44</td>
<td>0.26</td>
<td>0.64</td>
<td>0.00</td>
<td>0.00</td>
<td>0.25</td>
</tr>
<tr>
<td>A4</td>
<td>0.00</td>
<td>0.03</td>
<td>0.04</td>
<td>0.00</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.04</td>
<td>0.06</td>
<td>0.00</td>
<td>0.00</td>
<td>0.15</td>
</tr>
<tr>
<td>A5</td>
<td>0.01</td>
<td>0.07</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>0.07</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>A6</td>
<td>0.20</td>
<td>0.09</td>
<td>0.55</td>
<td>0.00</td>
<td>0.00</td>
<td>0.55</td>
</tr>
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<td></td>
<td>0.23</td>
<td>0.10</td>
<td>0.43</td>
<td>0.00</td>
<td>0.00</td>
<td>0.53</td>
</tr>
</tbody>
</table>

**Extinction Alcohol**

The center panels of the graphs in Figure 1 show response rates on the active lever and chain during the first and last five sessions of EXT alcohol for individual subjects. The extinction contingencies introduced in the alcohol component were effective as evidenced by decreased responding on the active lever for all animals. The effect of the extinction contingency in the alcohol component had mixed effects on the rate of chain pulling in the food component: chain pulling increased for three rats (A1, A4, and A5), decreased slightly for one rat (A2), and remained roughly the same for two rats (A3 and A6). Note that the relationship between response rates across components during baseline was predictive of changes (or lack thereof) in rate of chain pulling during the EXT alcohol condition. More specifically, chain pulling increased for rats that
responded more for food during baseline, decreased for the rat that responded nondifferentially, and remained the same for rats that responded more for alcohol. Table 2 shows that inactive lever presses remained relatively low for most rats during this condition.

Extinction Both

The right panels of the graphs in Figure 1 show responses per minute on the active lever and chain during all five sessions of the EXT both condition for individual subjects. The extinction contingencies in the food component were effective for all animals as can be seen in the decreased chain pulling across sessions. More importantly, lever pressing increased during this condition despite alcohol remaining unavailable. Figure 2 provides a more detailed look at these data displaying mean proportion baseline lever rate during the last five sessions of EXT alcohol and proportion baseline response rate across all five sessions in EXT both. With the exception of rat A2, all rats showed greater response output on the alcohol lever during EXT both when pellet delivery was discontinued in the food component.

The course of relapse over the five sessions varied across animals. For instance, rat A1’s lever pressing increased only modestly over the first two sessions while increasing considerably over the third, while rat A4 responded fairly consistently over all EXT both sessions. As seen in Table 2, inactive lever pressing decreased or remained constant for four of six rats, suggesting that the increased output on the alcohol lever is indicative of drug seeking rather than general activation.
Figure 2. Proportion of baseline lever presses per minute during the last five sessions of EXT EtOH (mean ± SD) and all five sessions of EXT both for individual rats in Experiment 1.
Discussion

The results of Experiment 1 suggest that removal of nondrug alternative reinforcement in one context can generate relapse to drug seeking in a separate context. However, these results cannot be interpreted unambiguously. As shown in Figure 3, periods of extinction alternated with periods of alcohol availability during multiple schedule training. As noted earlier, multiple schedule training was carried out over concerns that introducing food into the multiple schedules would decrease alcohol self-administration (see Carroll, 1996). During multiple schedule training, rats received substantial exposure (55 days) to the eventual food-paired stimuli paired with extinction contingencies in place. Refer again to Figure 3, which shows that upon elimination of food reinforcers during the EXT both phase, experimental conditions may have resembled multiple schedule training when alcohol was still available. Therefore, relapse to alcohol seeking may not have occurred because of discontinuing an alternate source of nondrug reinforcement per se, but because the EXT both phase may have resembled the multiple schedule training conditions. This type of response recovery could be interpreted as some form of contextual renewal.

Multiple studies have demonstrated that relapse to alcohol seeking is susceptible to ABA renewal (Burattini et al., 2006; Chaudhri et al., 2008; Hamlin et al., 2007; Marinelli et al., 2007; Zironi et al., 2006). That is, a change of context during extinction, and then subsequent return to initial training conditions produces relapse to alcohol seeking. Exposure to the EXT both phase after substantial exposure to multiple schedule training may have produced context-induced relapse similar to renewal. Therefore, it was necessary to examine the role of the multiple schedule training phase in the relapse seen
Multiple schedule components & Experimental phases & 

<table>
<thead>
<tr>
<th>Food component</th>
<th>Multi-training</th>
<th>Baseline</th>
<th>Extinction alcohol</th>
<th>Extinction Both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EXT</td>
<td>Food available</td>
<td>Food available</td>
<td>EXT</td>
</tr>
<tr>
<td>Alcohol component</td>
<td>Alcohol available</td>
<td>Alcohol available</td>
<td>EXT</td>
<td>EXT</td>
</tr>
</tbody>
</table>

**Figure 3.** Schematic of experimental conditions according to reinforcer availability and response requirement. Refer to the Multiple Schedule Training (Multi-training) and Extinction Both (EXT Both) phases (bolded and gray). Prior to extinction in the food component in the EXT Both phase, animals experienced extinction alternating with periods of alcohol availability during Multi-training. Upon extinction of previously food-maintained responding during the EXT Both phase, the experimental conditions may have resembled conditions during the Multi-training phase. Thus, relapse may have been caused by prior exposure to food extinction during Multi-training rather than loss of an alternative source of reinforcement.

in Experiment 1, thus clarifying the role of losing a source of alternative, nondrug reinforcement in the reappearance of alcohol seeking.

Experiment 2 replicated Experiment 1 with two exceptions. First, the multiple schedule training phase was eliminated altogether. This change was made to address concerns over a renewal-like relapse operation occurring in the experiment. Second, a more stringent extinction criterion was used. This change was made to ensure low response rates prior to the relapse phase.
CHAPTER V
EXPERIMENT 2: METHOD

Subjects

Seven experimentally naïve male Long-Evans rats (Charles River, Portage, Michigan, USA) approximately 90 days old at the start of the experiment were used. An eighth rat was eliminated from the experiment because it did not reliably self-administer alcohol. Feeding and housing conditions were identical to those in Experiment 1.

Apparatus

The equipment used in the Experiment 2 was the same as that used in Experiment 1.

Procedure

Magazine Training

Magazine training was conducted as described in Experiment 1.

Alcohol Self-Administration Training

Alcohol self-administration training was the same as in Experiment 1, with one exception: during all training sessions, only the lights above the right lever were lit. In Experiment 1, the houselight remained on during training sessions. The rats in Experiment 2 were trained without the houselight to minimize overlap between the alcohol self-administration training context and the contextual stimuli used in the baseline multiple schedule.
Baseline

The multiple schedule training used in Experiment 1 was excluded in Experiment 2. Once responding for alcohol was established, a chain was inserted into each operant chamber prior to experimental sessions and animals were placed directly on a multiple RR 25 (lever - alcohol), FR 1 (chain - food) schedule. The response requirement for food pellets was increased from FR 1 across successive days until rats responded on an RR 10, resulting in a final schedule of RR 25 (lever - alcohol), RR 10 (chain - food). As in Experiment 1, differential stimuli signaled the multiple schedule components and these stimuli were counterbalanced across subjects. Baseline lasted 35 sessions for each rat.

Extinction Alcohol

This condition was identical to the extinction phase as it was described in Experiment 1. However, slightly different extinction criteria were used: this phase remained in effect for at least 20 sessions for all animals, with additional criteria that the mean response rate on the alcohol lever over the final five sessions be less than 10% of the mean response rate over the final five sessions of baseline. No maximum number of sessions was allotted to reach this criterion. In Experiment 1, five of six rats met these criteria within 20 days.

Extinction Both

This phase was identical to that described in Experiment 1.
Measures

The dependent measures were the same as those described in Experiment 1, but refer to Table 3 for baseline response rates used to calculate proportion baseline.

Results and Discussion

Baseline

Table 3 displays mean response rates, reinforcer rates, and alcohol consumed over the final five sessions of baseline. The left panels of the individual subject graphs in Figure 3 show lever presses and chain pulls per minute in the multiple schedule components during the last five sessions of Baseline. As in Experiment 1, there was considerable variability in response output as well as the relationship between the two responses within animals. Rats B1, B2, and B3 were essentially non-differential whereas rats B4, B5, B6, and B7 responded more on the alcohol lever than on the chain. Although these rats did not receive multiple schedule training, the mean discrimination index (right lever presses in alcohol component divided by total number of right lever presses in both components × 100%) for all rats over the last five sessions of baseline exceeded 95%. Table 4 shows that inactive lever pressing was relatively low across animals, although somewhat higher than the rats in Experiment 1. It is not clear why this group of rats made more inactive lever presses, but it could be attributable to the lack of multiple schedule training.

Extinction Alcohol

The center panels of Figure 3 show lever and chain response rates in the two components during the first and last five days of EXT alcohol. Just as in Experiment 1,
Table 3

*Mean Baseline Response Rates, Reinforcer Rates, and Ethanol Consumption for Rats in Experiment 2*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Alcohol component</th>
<th>Food component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active lever (resp/min)</td>
<td>Inactive lever (Resp/min)</td>
</tr>
<tr>
<td>B1</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>28.68</td>
<td>7.91</td>
</tr>
<tr>
<td>B2</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>B3</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>B4</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>B5</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>B6</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>B7</td>
<td>Mean</td>
<td>SD</td>
</tr>
</tbody>
</table>

the extinction contingencies were effective in reducing lever pressing in all animals.

There were also mixed effects on chain pulling in the alternating component: rats B1, B2, and B6 showed clear increases in chain pulling whereas the other animals showed no clear change. Within these animals there was no apparent relationship between response rates during baseline and EXT alcohol. Table 2 shows that with the exception of rats B2 and B4, inactive lever pressing remained relatively low.

In Experiment 1, all rats were exposed to 20 days of the extinction phase and the mean response rate on the alcohol lever was less than 10% of the baseline mean for five of six rats. In the present experiment, four of seven rats met the extinction criterion.
within 20 days. B4, B6, and B7 took 35, 69, and 30 days, respectively, to meet the more stringent extinction criterion.

**Extinction Both**

The right panels of the graphs in Figure 4 show response rates across sessions of the EXT both condition. Again, the extinction contingencies were effective in decreasing chain pulling across all subjects. Figure 5 shows lever pressing in terms of mean proportion baseline during the last five sessions of the EXT alcohol condition and proportion baseline lever rates across all five EXT both sessions. As in Experiment 1 lever pressing increased for most rats during EXT both relative to EXT alcohol despite the continued absence of alcohol in the alcohol component. All rats except B4 showed increases on the lever previously associated with alcohol deliveries upon discontinuation of food reinforcers in the other multiple schedule component. These rats also showed difference with regard to the course of relapse over the sessions in this condition. For instance rat B3 showed a marked increase in the first session of EXT both and then steadily decreased across subsequent days. Rat B1 showed a more variable pattern, peaking during the second and fifth sessions. Showing a different pattern, rats B2 and B6 showed slight increases across all sessions. Table 2 shows that inactive lever pressing decreased in four of seven rats relative to the previous phase. As in Experiment 1, these
Figure 4. Lever presses (filled points) and chain pulls (empty points) during the last five sessions of Baseline (BL), the first and last five sessions of Extinction Alcohol (EXT EtOH), and all five sessions of Extinction Both (EXT Both) for individual rats in Experiment 2. Note that the Scale of the y-axis varies across subjects.
Figure 5. Proportion of baseline lever presses per minute during the last five sessions of EXT EtOH (mean ±SD) and all five sessions of EXT Both for rats in Experiment 2. Note that the scale of the y-axis for rate B1 differs from the other animals.
Table 4

Mean Inactive Lever Presses Per Minute Across Conditions for Rats in Experiment 2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Alcohol component</th>
<th>Food component</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>EXT EtOH</td>
<td>EXT Both</td>
<td>Baseline</td>
<td>EXT EtOH</td>
</tr>
<tr>
<td>B1</td>
<td>Mean</td>
<td>0.03</td>
<td>0.21</td>
<td>0.11</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.04</td>
<td>0.14</td>
<td>0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>B2</td>
<td>Mean</td>
<td>0.64</td>
<td>1.19</td>
<td>1.01</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.46</td>
<td>0.44</td>
<td>0.80</td>
<td>0.00</td>
</tr>
<tr>
<td>B3</td>
<td>Mean</td>
<td>0.05</td>
<td>0.08</td>
<td>0.47</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.12</td>
<td>0.09</td>
<td>0.24</td>
<td>0.00</td>
</tr>
<tr>
<td>B4</td>
<td>Mean</td>
<td>0.21</td>
<td>2.28</td>
<td>1.49</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.14</td>
<td>0.76</td>
<td>0.29</td>
<td>0.00</td>
</tr>
<tr>
<td>B5</td>
<td>Mean</td>
<td>2.17</td>
<td>1.75</td>
<td>0.67</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.10</td>
<td>0.24</td>
<td>0.36</td>
<td>0.03</td>
</tr>
<tr>
<td>B6</td>
<td>Mean</td>
<td>0.65</td>
<td>0.32</td>
<td>1.01</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.33</td>
<td>0.32</td>
<td>0.76</td>
<td>0.03</td>
</tr>
<tr>
<td>B7</td>
<td>Mean</td>
<td>2.83</td>
<td>0.83</td>
<td>1.37</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.53</td>
<td>0.21</td>
<td>0.44</td>
<td>0.00</td>
</tr>
</tbody>
</table>

results are indicative of increased alcohol lever pressing due to alcohol seeking and not general activation.

Discussion

Despite the exclusion of the multiple schedule training phase used in Experiment 1, extinguished alcohol seeking relapsed similarly in Experiment 2 upon discontinuation of nondrug reinforcers in the food component of the multiple schedule. Thus, it appears that the training conditions consisting of extinction components alternating with alcohol availability did not play a critical role in the relapse observed in
Experiment 1. The present experiments provide a demonstration of relapse induced by loss of nondrug reinforcement in a separate context.
CHAPTER VI
GENERAL DISCUSSION

Podlesnik et al. (2006) demonstrated that loss of an alternative source of nondrug reinforcement within a stimulus context could produce relapse to alcohol seeking in that context. The present experiments explored nondrug reinforcer loss in a context separate from the drug self-administration stimulus context as a means of producing relapse to extinguished drug seeking. In Experiment 1, rats responded for food or alcohol in different contexts arranged by alternating components of a multiple schedule. Both reinforcers were available during baseline, alcohol deliveries were withheld during the EXT alcohol phase, and both food and alcohol were withheld during the EXT both phase. Responses on the lever previously associated with alcohol deliveries increased during EXT both sessions relative to the last five sessions of EXT alcohol. Inactive lever pressing during alcohol components did not consistently or substantially increase, suggesting that rats were seeking alcohol and the increased lever pressing was not the result of nonspecific, general activation. Relapse to alcohol seeking appeared to have been brought on by discontinuation of food reinforcers in the alternating component. However, early training conditions complicated this interpretation of increased lever pressing: during multiple schedule training, periods of extinction alternated with alcohol availability, so extinction in the food component during the EXT both phase may have served as a cue for alcohol availability in the other component resulting in elevated lever pressing. Thus, the role of these training conditions was examined in a second experiment.
Experiment 2 replicated Experiment 1 except that the problematic training conditions were removed from the procedure and a more stringent extinction criterion was used. These rats experienced the same baseline, EXT alcohol, and EXT both phases and again, lever pressing increased during the EXT both phase relative to the end of the EXT alcohol phase. Like Experiment 1, output on the inactive lever during alcohol components did not increase in the same manner as the active lever. Therefore, it appears that in Experiment 1 extinction in the food component serving as a cue for alcohol availability was not the sole cause of the observed relapse to alcohol seeking. The results of Experiment 2 suggest that it was the loss of food reinforcers in the alternating multiple schedule component that induced relapse to alcohol seeking in the alcohol component.

Collectively, the present experiments provide a demonstration that loss of nondrug reinforcers in one context can reinstate extinguished alcohol seeking in a separate context. The procedure used in Experiments 1 and 2 provides what may be a novel model of relapse analogous to situations that produce relapse in humans in which positive, context-specific events are discontinued (Falba et al., 2005; Temple et al., 1991). This new model may prove useful in developing new forms of treatment and exploring the parameters (e.g., variations in the rate of alternative reinforcement) necessary to produce relapse via discontinuation of reinforcement specific to a context different than the drug-taking context.

Although it appears that we have ruled out an account of the observed relapse based on ABA renewal-like effects, another form of renewal may still provide an explanation for the observed relapse. According to an interpretation of resurgence made by Bouton and Swartzentruber (1991), all instances of operant resurgence may be forms
of ABC renewal. As noted earlier, ABC renewal is a form of renewal in which rats are trained in one context (context A), experience extinction in a second context (context B), and then the trained behavior returns when the animal is exposed to a novel context (context C). If reinforcer availability during the various experimental phases contributed to the overall context of the present experiments, then it could be argued that initial training took place while both reinforcers were available (context A), extinction of alcohol responding took place while just food was available (context B), and then alcohol seeking recovered when food reinforcers were no longer available (context C). However, some studies suggest that an ABC renewal account of the present results is unlikely. For instance, in conditioned suppression paradigms, ABC renewal has been reported to be weaker than ABA renewal (Harris, Jones, Bailey, & Westbrook, 2000). Furthermore, there has been little evidence to support ABC renewal in operant conditioning paradigms, and more importantly, Zironi et al. (2006) failed to find ABC renewal with rats self-administering alcohol. Thus, responding maintained by alcohol deliveries, or operant responding in general, may not be affected by ABC renewal, further supporting the argument that the response recovery observed in present experiments can be attributed to loss of a response-dependent, nondrug source of reinforcement.

**Behavioral Contrast**

Another phenomenon that may inform the present experiments is behavioral contrast. Behavioral contrast refers to an inverse relationship between the response rate in a multiple schedule component associated with a steady rate of reinforcement and a variable reinforcement rate associated with an alternating component (Reynolds, 1961;
see Williams, 2002). For example, a high reinforcement rate in the variable component typically results in a lower response rate in the steady reinforcer rate component, and vice versa. These changes in response rate occur despite no direct changes to the contingencies controlling that response. The present experiments can be classified as instances of behavioral contrast in that responding in the alcohol component of the multiple schedule remains on extinction, yet responding increases as a result of changes to the contingencies in the alternating food component.

In fact, a previous experiment has explored the possibility that behavioral contrast could serve as model of alcohol consumption (McSweeney, Melville, & Higa, 1988). McSweeney et al. noted that alcohol consumption may increase despite no changes to contingencies related to alcohol consumption. They reasoned that these fluctuations in alcohol consumption could be attributed to the contingencies related to alternative reinforcers. Thus, McSweeney et al. examined behavioral contrast in multiple and concurrent schedules in which rats received both food and alcohol reinforcers. They reported increased responding for alcohol in concurrent, but not multiple schedules when a food-maintained response was placed on extinction. It is not entirely clear why they failed to observe increased responding for alcohol in the multiple schedule in light of the results of the present experiments. However, McSweeney et al. examined ongoing alcohol self-administration whereas the present experiments examined relapse of extinguished alcohol self-administration. There are some instances in which variables that initiate relapse do not increase ongoing drug self-administration. For example, although footshock reliably produces relapse to alcohol seeking in reinstatement paradigms (Le et al., 1998) it has mixed effects on ongoing alcohol consumption.
Footshock has reportedly increased (Anisman & Waller, 1974; Volpicelli & Ulm, 1990), decreased (Van Erp, Sheffield, & Miczek, 1994), or not affected alcohol consumption (Fidler & Lolordo, 1996). It could also be that extinction provides a more sensitive baseline to measure contrast effects. Regardless of the McSweeney et al. (1988) results, I will consider some of the mechanisms of behavioral contrast as they might apply to the present experiments.

One account of behavioral contrast posits that changes in response rate result from the matching law (Herrnstein, 1970). Matching in multiple schedules is based on allocating behavior to the components according to relative rates of reinforcement, and is described by the following equation,

\[ P_1 = \frac{kR_1}{R_1 + mR_2 + R_0} \]

in which \( P_1 \) refers to the behavior occurring in one component, \( R_1 \) and \( R_2 \) are the number of reinforcers received in each component, \( R_0 \) is unscheduled reinforcements (e.g., grooming or exploring the operant chamber), which according to Herrnstein (1970) should take a value close to zero, \( k \) is the asymptotic response rate, and \( m \) characterizes the interaction between the two components (varies from 0-1). Thus, the equation predicts contrast if \( R_2 \) drops to zero because the denominator becomes smaller resulting in an increase in \( P_1 \). This account cannot explain the increase of behavior observed in the relapse phase of Experiments 1 and 2 in that reinforcement rate drops to zero in both components of the multiple schedule. If \( R_1 \) were also to drop to zero, then the equation predicts no behavior at all (i.e., \( P_1 = 0 \)).

Other accounts of contrast may be able to account for the effect observed in the present experiments. According to McLean (1995) behavioral contrast occurs because of
the reallocation of extraneous reinforcement. In short, an organism directs most behavior toward the programmed contingencies during an experimental session and the remaining behavior toward other activities maintained by naturally occurring, reinforcing activities (e.g., grooming). Different reinforcement rates in components of a multiple schedule allow for different amounts of behavior maintained by nonexperimenter-controlled contingencies to occur in the components. That is, if one component is associated with a higher rate of reinforcement than an alternating component, less behavior maintained by extraneous reinforcement will occur in the component with the higher reinforcement rate.

In the present experiments during the extinction phase, most extraneously reinforced behavior is presumably occurring in the alcohol component because most of the time in the alternating component is spent responding for food. Once chain pulling is extinguished, less chain pulling occurs in the food component allowing for more extraneously reinforced behavior to occur in that component. Because more extraneously reinforced behavior occurs in the food component, less occurs in the alcohol component and more time can be directed toward the alcohol lever. The present experiments do not allow for assessment of this account.

Amsel (1971) attributed increases in responding observed in behavioral contrast experiments to a frustration effect. Amsel (1958) defines frustration as “a conceptualization of a hypothetical, implicit reaction elicited by nonreward after a number of prior rewards.” Although this account offers little in the way of explanation of the relapse observed in the present experiments, some frustration research might be helpful in pinning down an underlying mechanism. The relevant frustration research has
centered on behavioral and neurochemical changes accompanying situations of nonreward.

Multiple studies have demonstrated increases in stress hormones resulting from frustrative nonreward, specifically corticosterone (Lyons, Fong, Schrieken & Levine, 2000; Romero, Levine, & Sapolsky, 1995). Corticosterone levels also increase during extinction of operant behavior (Coover, Goldman, & Levine, 1971; De Boer, De Beun, Slangen, & Van Der Gugten, 1990) and increase in a dose-dependent manner when rats are subjected to periods of electric shock varying in duration (Friedman, Ader, Grota, & Larson, 1967). While the results of these studies suggest that frustration and shock-induced stress share the same underlying mechanism, there is evidence that stress-induced relapse is not dependent on corticosterone, but rather corticotropin-releasing factor (CRF). This finding generalizes across shock-induced reinstatement of cocaine- (Erb, Shaham, & Stewart, 1998), heroin- (Shaham et al., 1997), and alcohol-seeking (Le et al., 2000). To my knowledge, no studies have examined the role of CRF in situations of frustrative reward or extinction. Thus, it remains to be seen whether stress and frustration are similarly controlled. A future extension of the present study might explore CRF antagonism as a means of blocking relapse produced via loss of reinforcers delivered in a single context, as in resurgence preparations, or in a separate context, as in the present arrangement. Successfully blocking relapse in either case would provide evidence of a common mechanism controlling relapse produced via reinforcer loss and exposure to shock.
Limitations and Future Directions

While the present experimental design appears to address some instances of reinforcer loss, which may be more analogous to human situations, it does have some limitations. For instance, cessation of alcohol consumption in the present experiments was involuntary because responding for alcohol was placed on extinction. Future studies may employ means other than extinction to decrease alcohol-maintained responding.

Interpretation of the current experiments may also be complicated by the fact that the alternative nondrug reinforcer was food. One limitation of using food is that it is a source of calories. At present, it is unclear whether relapse to alcohol seeking occurred as a result of calorie seeking or drug seeking. A similar preparation using intravenous self-administration of a drug without calories (e.g., cocaine) could address these concerns. An additional limitation to the use of food as a reinforcer is that people experience a variety of nondrug reinforcers besides food. Leisure activities or familial interactions are unquestionably reinforcing, but are qualitatively different than food. As noted earlier, some studies have examined the effects of enriched housing conditions consisting of access to nonspecifics and novel objects on drug self-administration and relapse. Enriched housing has shown to be a protective factor during those phases of drug self-administration (Stairs et al., 2006; Theil et al., 2009). Another potential direction to take this research, and make further improvements to the model, is inducing relapse via loss of those enriched housing conditions.
Conclusion

The present experiments provide a demonstration of what may be a novel animal model of relapse, which may inform drug self-administration literature about the potential for loss of context-specific reinforcement to induce relapse. Situations in which context-specific reinforcement is lost may be similar to situations such as job loss or divorce, which sometimes induce episodes of relapse in human drug takers (Gallo et al., 2001; Temple et al., 1991). The present experimental arrangement extends the face validity of animal models in general by creating circumstances more like those experienced by people, and may also enhance predictive validity if neurobiological measures translated from the animal model can help predict vulnerability in humans (see Shippenberg & Koob, 2002). Furthermore, investigation of blocking the type of relapse produced in this model with behavioral or pharmacological manipulations may lead to advances in pharmacological and clinical treatments in human populations.


