THE ROLE OF DOPAMINE IN RESISTANCE TO CHANGE OF OPERANT BEHAVIOR

by

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ABSTRACT

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Psychological disorders such as autism, obsessive-compulsive disorder, drug addiction, and attention-deficit/hyperactivity disorder involve atypically persistent behavior and atypical activity of the neurotransmitter dopamine. Behavioral momentum theory states that the persistence of behavior in a context is determined by the reinforcement received previously in that context. Contexts previously associated with higher rates of reinforcement yield greater persistence of behavior than contexts previously associated with lower rates of reinforcement. According to a prominent hypothesis in behavioral neuroscience, dopamine mediates the incentive salience of a stimulus. A synthesis of behavioral momentum theory and the incentive salience hypothesis proposes similar roles for dopamine activity and reinforcement in determining the

persistence of behavior in a context. The aim of this dissertation was to determine the extent to which a history of dopamine modulation in a context affects the subsequent persistence of behavior in extinction and relapse. Three groups of rats were trained to press a lever for food in two alternating contexts of a multiple schedule. Following a stable baseline, rats entered a treatment phase in which they received a drug or saline injection before and after sessions in each context. In the drug context, rats received the indirect dopamine agonist amphetamine, dopamine D_1 antagonist SCH 23390, or a combination of amphetamine and SCH 23390 prior to the session and a saline injection following the session. The injection schedule was reversed for the saline context such that rats received a saline injection prior to each session in the saline context and a drug injection following the session. During an extinction phase, access to food was withheld. Response-independent food was then provided in each context to trigger reinstatement of responding. A history of dopamine agonism in a context increased the relative persistence of behavior, while a history of dopamine antagonism at D_1 receptors and a combination of dopamine agonism and dopamine antagonism had little impact on the relative persistence of behavior. Likewise, reinstatement was relatively greater in a context previously associated with dopamine agonism. This effect was blocked when dopamine agonism was preceded by D_1 antagonism. A history of D_1 antagonism alone did not affect reinstatement. These results suggest that dopamine plays a role in the

persistence of behavior in extinction and relapse, but that different dopamine receptors mediate these effects.

(101 pages)

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INTRODUCTION

Atypically persistent behavior is symptomatic of many psychological disorders including autism, obsessive-compulsive disorder (OCD), drug addiction, and attention deficit hyperactivity disorder (ADHD; American Psychiatric Association, 2000). In each of these disorders, behavior is either excessively persistent or lacks appropriate persistence. For example, persons with autism exhibit highly persistent repetitive behaviors at the exclusion of other more socially appropriate behaviors. In contrast, persons with ADHD often exhibit behavior that is easily disrupted. Regulation of dopamine (DA) activity is an effective treatment for persistent behavioral symptoms for a wide variety of psychological disorders. This suggests that DA may play a crucial role in the persistence of behavior (Previc, 2006). For example, the highly persistent stereotypy that is symptomatic of autism is commonly reduced using drugs that reduce DA activity, called DA antagonists (McDougle et al., 2005). Similar pharmacotherapy has also been suggested for treatment of OCD and drug addiction (Micallef & Blin, 2001; Volkow, Fowler, Wang, & Swanson, 2004). Likewise, drugs that increase DA activity, called DA agonists, are commonly used to increase the persistence of on-task behavior in persons with ADHD (Volkow et al., 2007). Given the comorbidity of atypically persistent behavior and atypical DA activity, it is necessary to better understand the interaction between the environmental and neural events that contribute to the persistence of behavior.

LITERATURE REVIEW

Environmental Determinants of Learning and Behavior

Pavlovian and operant conditioning are two learning processes that influence the behavior of an organism. Pavlovian conditioning produces responding in the presence of once neutral stimuli through association with naturally evocative stimuli in the environment (Pavlov, 1927). In the traditional example of Pavlovian conditioning, a dog is repeatedly exposed to meat powder, an unconditioned stimulus (US), following the ringing of a bell, a conditioned stimulus (CS). Initially, only the meat elicits a salivation response, called the unconditioned response, but, after repeated CS-US pairings, the dog salivates in the presence of the bell alone. In contrast to Pavlovian conditioning, operant conditioning produces responding in the presence of a stimulus as a result of the consequences in the environment for that response (Thorndike, 1927). Operant behavior can be diagrammed using the following three-term contingency

$$S^D : R \rightarrow S \tag{1}$$

where *R* is a response that, when in the presence of a discriminative stimulus (S^D), results in a consequence (*S;* Skinner, 1953). The S^D may represent one stimulus or a combination of stimuli called a context. In a laboratory example, a rat presses a lever, which results in the delivery of a food pellet when a house light is illuminated. When the house light is not illuminated, food is not delivered

for lever presses. Therefore, the house light in this example serves as a discriminative stimulus for the availability of a food consequence for a lever-press response. Consequences that increase or maintain behavior are called reinforcers.

The Matching Law suggests that organisms distribute their behavior in direct proportion to the relative rates of reinforcement available for each behavior (Herrnstein, 1970, 1974). Higher rates of reinforcement engender higher rates of behavior relative to lower rate reinforcement alternatives. For example, a coyote may forage for food in two locations. In one location, the coyote experiences a food payoff less frequently (i.e. 10% of the time) and in the other location it experiences a food payoff more frequently (i.e. 90% of the time). The coyote's foraging behavior in each location will match the rate of food availability in each location (Gilbert-Norton, Shahan, & Shivik, 2009). Traditional views of response strength state that behavior is strengthened by each reinforcing consequence. In combination with the matching law, behavior that is reinforced at a relatively higher rate should be stronger and possibly more persistent than other behaviors. The matching law, however, falls short of predicting the persistence of behavior under conditions of disruption.

Persistence of Behavior

The environmental mechanisms of the persistence of operant behavior have been quantitatively described by behavioral momentum theory (Nevin &

Grace, 2000). This theory states that operant behavior has two separable aspects, the ongoing rate of a behavior, and the persistence of that behavior when disrupted. The response-reinforcer relation, or the relation between the *R* and *S* terms of the three-term contingency, determines the rate of a behavior as predicted by the matching law (Herrnstein, 1970). The Pavlovian stimulus-reinforcer relation, or the relation between the S^D and *R* terms of the three-term contingency, determines the persistence of a behavior. The stimulus-reinforcer relation is strengthened through Pavlovian processes that afford incentive-motivational properties of the reinforcers to stimuli in the environment. This tenet of behavioral momentum theory is similar to the role of Pavlovian processes in incentive motivational theories of behavior.

According to incentive motivational theories of behavior, when a behavior is reinforced in the presence of a stimulus, the incentive motivational properties of the reinforcer are attributed to the stimulus (Bindra, 1974). The acquisition of incentive motivational properties transforms a once neutral stimulus into a cue with some degree of incentive salience. The incentive salience of a cue motivates the organism to respond, making behavior more likely in its presence. When the cue-reinforcer contingency is terminated, or extinguished, cues retain the ability to motivate behavior (Estes, 1943). This ability then decays over time and with repeated presentations of the cue alone. Behavioral momentum theory expands on incentive motivational theories by quantifying the impact of the stimulus-reinforcer relation on the persistence of operant behavior during

disruption. A disruption may result from extinction of the response-reinforcer contingency, reinforcer satiation, or any event that changes the value or availability of the primary reinforcer, or is distracting. During disruption, the persistence of behavior depends on the value of the context, which is determined by the rate of reinforcement received in its presence (Nevin & Grace, 2000).

The impact of the stimulus-reinforcer relation on the persistence of operant behavior can be assessed using procedures common within research on behavioral momentum. Behavioral momentum experiments typically use a two-component multiple schedule of reinforcement. Each component of a multiple schedule contains a different context that signals an independently operating schedule of reinforcement. The effects of reinforcement rate on the persistence of behavior are typically assessed by arranging a higher rate of reinforcement in one context relative to the alternating context. This may be arranged by programming differential rates of response-dependent reinforcement across contexts or by programming equal rates of response-dependent reinforcement in each context and then adding response-independent reinforcement to one context. For example, Harper (1999) arranged a multiple schedule that delivered food on a variable-interval (VI) 30 s schedule in each context. In one context, additional response-independent food was delivered on a variable-time (VT) 30 s schedule. Variable interval schedules deliver a reinforcer for the first response following an average period of time. Variable time schedules deliver a reinforcer following an average period of time independent of responding. Therefore, the

rate of reinforcement in the first context was two per minute and in the second context four per minute. This relative rate of reinforcement could also be achieved by arranging a VI 30 s schedule in the first context and a VI 15 s schedule in the second context. Interval-based schedules are commonly used because they allow the experimenter to control the rate of reinforcement more precisely than other schedules (Ferster & Skinner, 1957).

Following a stable baseline of responding in each context, a disruptive event such as extinction is introduced. The persistence of behavior in each context is then determined by taking the proportion of baseline response rates during each session of disruption. Expressing response rates during disruption as a proportion of baseline response rates normalizes for the preextinction rates of behavior. This transformation of the data allows the dissociation of the impact of the Pavlovian stimulus-reinforcer relation from the impact of the operant response-reinforcer relation, by essentially removing the impact of preexisting response rates from the existing response rates. Thus proportion baseline response rates reflect the direct effect of the manipulation being made. For behavioral momentum theory, proportion baseline response rates reflect the impact of differential rates of reinforcement. These proportions are frequently expressed in logarithmic space to facilitate detection of systematic differences in linear resistance functions, and avoid floor effects (Nevin, 2002; Shull, 1991). The slope of each resistance-to-change function is then compared to assess the relative persistence of behavior in each context (Nevin, Mandel, & Atak, 1983).

Functions with a shallower slope indicate greater persistence of behavior relative to functions with a steeper slope.

In Figure 1, hypothetical data reflect the relative resistance to change of behavior in two contexts, one previously associated with a relatively rich rate of reinforcement and one previously associated with a relatively lean rate of reinforcement. In this example, extinction serves as the disruptor of behavior. Differences in resistance to change can also be assessed using a two-way repeated measure ANOVA with context and phase as within-subjects factors (Quick & Shahan, 2009). Statistical testing may be especially useful for comparing resistance to change functions that deviate from linearity. In such cases, slope analyses may not be appropriate. These procedures have been used to assess the impact of the stimulus-reinforcer relation on the persistence of behavior using a variety of reinforcers, behaviors, and species ranging from humans to fish (Dube & McIlvane, 2002; Igaki & Sakagami, 2004; Mace, Lalli, Shea, & Nevin, 1992; Podlesnik & Shahan, 2008; Shahan & Burke, 2004).

Evidence in Support of Behavioral Momentum Theory

Three key studies demonstrate the utility of behavioral momentum theory in describing the impact of stimulus-reinforcer relations on the persistence of behavior. In one of these studies, Nevin, Tota, Torquato, and Shull (1990, experiment 1) trained pigeons to respond for equal rates of good in two contexts of a multiple schedule signaled by a red or green key light. Additional response-

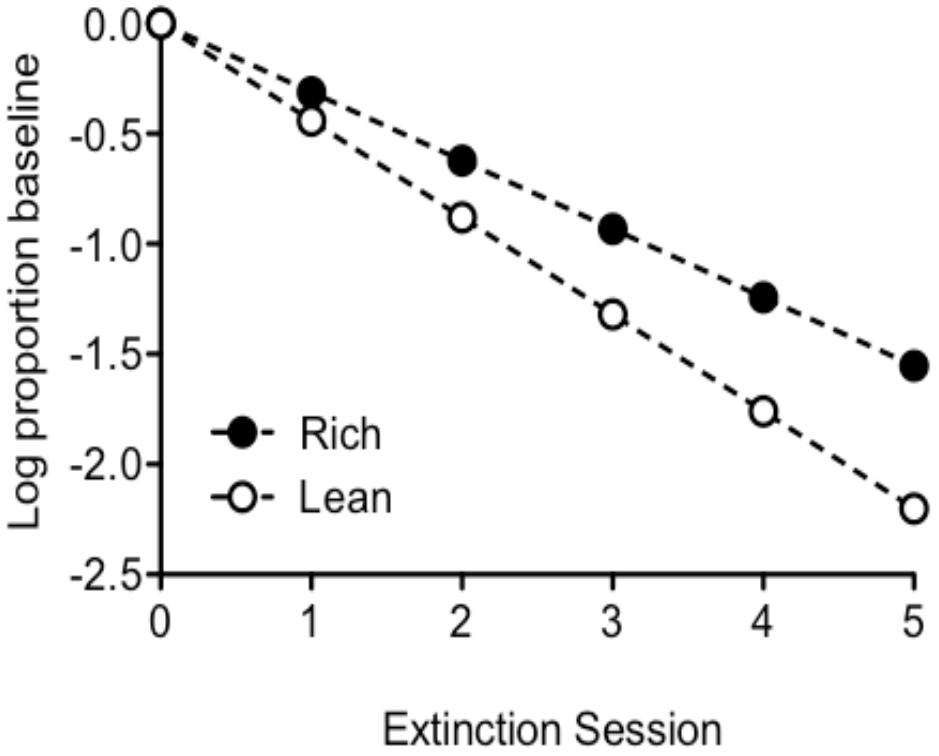

Figure 1. Simulation of relative resistance to change. Behavioral momentum theory predicts that the slope of resistance to change functions is determined by previous rates of reinforcement in context. Resistance to change in a rich context of reinforcement yields a function of shallower slope relative to resistance to change in a lean context of reinforcement.

independent food was also delivered in the red key context. The experiment was divided into seven conditions in which the rate of contingent food and response-independent food in the added food context were varied while the rate of food delivery in the other context was always VI 60 s. In the first, fourth, and seventh condition, food was delivered contingently on a VI 60 s schedule in the added food context without any additional free food. Thus, the overall rate of reinforcement was equal in each context. These conditions served as a control to compare response rates during baseline conditions. In the second and third conditions the rate of contingent food remained on a VI 60 s schedule, but response independent food also was delivered on a VT 120 s schedule in the second condition and on a VT 240 s schedule in the third condition. Thus in these conditions, the overall rate of food was higher in the red key context relative to the green key context. In the fifth and sixth conditions, the overall rate of reinforcement was held constant at one reinforcer per minute in the red and green key contexts. However, in these conditions, the rate of contingent and noncontingent food in the red key context was varied. In the fifth condition, food was delivered contingently on a VI 20 s schedule and noncontingently on a VT 40 s schedule. In the sixth condition, food was delivered contingently on a VI 12 s schedule and noncontingently on a VT 48 s schedule.

Following a stable baseline of response rates in the second, third, fifth, and six conditions, behavior was disrupted with three disruptors, stimulus compounding, prefeeding, and extinction. These disruptors were presented

successively intermixed with returns to the baseline contingencies. The disruptive impact of stimulus compounding, in which novel stimuli were superimposed onto the red and green keys, was minimal, but prefeeding and extinction produced substantial decreases in behavior over time. Resistance to prefeeding and extinction was relatively greater in the red-key context in the second and third conditions, which arranged an overall higher rate of reinforcement with the addition of free food deliveries. This effect occurred despite having equal rates of response-dependent food in each context. Resistance to prefeeding or extinction was equivalent in the red and green key contexts in conditions 5 and 6, which arranged equal overall rates of reinforcement with different response-reinforcer contingencies. Therefore, as predicted by behavioral momentum theory, resistance to change in a context is determined by the overall rate of reinforcement received in that context and not by the response-reinforcer contingency.

The second key study provided further evidence that the overall rate of reinforcement received in the presence of a stimulus determines the resistance to change of behavior even when qualitatively different reinforcers were used to enhance context value. Using rat subjects, Grimes and Shull (2001) arranged a multiple schedule consisting of two contexts that each arranged food pellet delivery on VI 100 s schedules. In one context, added free milk deliveries were provided on a VT 30 s schedule. Extinction was introduced as a disruptor following a stable baseline of responding in the two contexts. Resistance to

change was greater in the added free milk context relative to resistance to change in the food alone context. This result occurred despite the rate decreasing effects of adding free milk deliveries during baseline. So, resistance to change is dependent on the overall rate of reinforcement in the context independent of the type of reinforcer used.

The third key study extended previous findings on the role of the stimulus reinforcer relation in governing the persistence of behavior to alcohol-maintained behavior. Rats were first trained to press a lever for equal rates of alcohol delivery, random interval (RI) 15 s schedules, in two contexts of a multiple schedule (Shahan & Burke, 2004). Like VI schedules, RI schedules arrange a reinforcer for the first response after an average time period has elapsed. In one of the contexts, rats also received response-independent food deliveries on a random time (RT) 15 s schedule. Random time schedules are similar to VT schedules in that reinforcers are arranged after an average time period has elapsed. Although baseline response rates in the added food context were relatively lower, alcohol seeking was relatively more persistent in the added food context. In each of these experiments, behavioral persistence was greatest in the context that was previously associated with a higher relative rate of reinforcement. Therefore, as predicted by behavioral momentum theory, the persistence of behavior is not dependent on the previous rates of responding in a context, but on the value of the stimulus context acquired through association with primary reinforcement.

Quantitative Models of Behavioral Momentum

A context associated with a higher rate of reinforcement will yield more persistent behavior than a context associated with a lower rate of reinforcement. Thus, it is the relative rate of reinforcement in a context that determines the persistence of a behavior, such that

$$\frac{m_1}{m_2} = \left(\frac{r_1}{r_2}\right)^b \tag{2}$$

where m_1 and m_2 represent the persistence of behavior in the presence of stimulus contexts 1 and 2, r_1 and r_2 are the rates of reinforcement received in those contexts (Nevin, 1992). The parameter *b* represents the organism's sensitivity to the relative rates of reinforcement in the two contexts. The relative assessment of overall persistence in Equation 2 can be modified to assess the impact of disruption on a single behavior using the following equation

$$\log(B_x / B_0) = -x / r^a \tag{3}$$

where the measure of resistance to change, $log(B_x/B_0)$, represents the response rates under disruption conditions (B_x) as a proportion of preextinction response rates (B_0; Nevin & Grace, 2000). As mentioned previously $log(B_x/B_0)$ is commonly used throughout behavioral momentum analyses (Nevin, 2002), but is not appropriate for nonlinear resistance functions. In the right side of Equation 3, *f* represents the force of a disruptor that decelerates the rate of behavior as

determined by the previous rate of reinforcement in training, *r* according to a power function.

Notice that this model does not differentiate between the effects of contingent and noncontingent reinforcement on the stimulus-reinforcer relation. Rather, each reinforcer obtained in the presence of the stimulus enhances the stimulus-reinforcer relation. Relatively higher overall rates of reinforcement yield greater relative resistance to change. Thus, Equation 3 can account for the impact of added free reinforcers in a context on the resistance to change of behavior as exemplified in Nevin et al. (1990), Grimes and Shull (2001), and Shahan and Burke (2004). This assertion has been confirmed in a variety of experimental preparations (Nevin, 2002, 2003; Nevin, Davison, & Shahan, 2005; Nevin & Grace, 2000).

Behavioral Momentum and Extinction

One of the most common disruptions of behavior, extinction, occurs when the reinforcement schedule is suspended. Within the study of extinction behavior there is evidence that behavior is more persistent following intermittent schedules of reinforcement than continuous schedules of reinforcement, an effect termed the Partial Reinforcement Extinction Effect (PREE; see Mackintosh, 1974; Nevin, 1988, for reviews). So, behavior that has been reinforced at a lower rate on an intermittent schedule of reinforcement is more resistant to extinction than behavior that has been reinforced at a higher rate. At first glance, PREE seems

to oppose the tenets of behavior momentum theory, which states that higher relative rates of reinforcement in a context yield relatively greater resistance to change. This apparent contradiction is resolved by capturing the impact of generalization from the baseline context to the extinction context within behavioral momentum theory (Nevin & Grace, 2000). Omitting reinforcers during extinction changes the context relative to baseline, which causes a reduction in behavior called generalization decrement. The degree of generalization decrement from the baseline context to the extinction context is directly proportional to the rate of reinforcement delivered in that context. Thus, the impact of reinforcer omission will be greater for behavior in contexts associated with richer rates of reinforcers than contexts associated with leaner rates of reinforcers. Accordingly, the transition from an intermittent schedule of reinforcement to extinction produces a smaller generalization decrement compared to the transition from continuous reinforcement to extinction.

Quantitatively, the impact of generalization decrement can be accounted for by dividing the impact of extinction into two additive factors, the omission of reinforcers, and termination of the response-reinforcer contingency (Nevin, McLean, & Grace, 2001). Therefore, the model of behavioral persistence requires two terms for describing the impact of extinction on the persistence of behavior. The augmented model of behavioral momentum captures the impact of both reinforcer omission and the change in the response-reinforcer contingency during extinction with the following equation,

$$\log(B_x / B_0) = \frac{-x(c + d\Delta r)}{r^a} \quad (4)$$

where B_x is the response rate at time x in extinction, B_o is the asymptotic response rate of behavior during baseline, c is a parameter that scales the impact of terminating the reinforcement contingency, d is a parameter that scales the impact of generalization decrement associated with omitting reinforcers, r is the rate of reinforcement in baseline, and a is a parameter that represents sensitivity to reinforcement rate (Nevin & Grace, 2000). The parameters c, d, and a are generally free parameters but can have constant values depending on experimental conditions. Equation 4 formally states that the disruptive impact of omitting reinforcers and terminating the response-reinforcer contingency combine additively and will be greater in contexts previously associated with lower relative rates of reinforcement.

Nevin et al. (2001) evaluated the validity of including separate parameters for the omission of reinforcers and terminating the contingency in equation 4 across three experiments. The first experiment examined the effects of terminating the response-reinforcer contingency while leaving the rate of reinforcement received in the contexts intact. This was achieved by establishing a baseline of differential reinforcement rates across two contexts of a multiple schedule. In one context, food was delivered on a VI 60 s schedule, termed the Rich context, and in the alternating context food was delivered on a VI 240 s schedule, termed the Lean context. Then, the contingent reinforcers were omitted in each context and replaced with the same rate of noncontingent, or

free-food. Terminating the response-reinforcer contingency resulted in a decrease in responding that was greater in the Lean component than in the Rich component. When the effect of terminating the response-reinforcer contingency was combined with the effect of reinforcer omission in a typical extinction condition, behavior was equally persistent in the two contexts. These findings suggest that termination of the contingency impacted behavior equally across the two contexts, revealing the differential impact of reinforcer omission across contexts associated with differential rates of reinforcement.

In the second experiment, pigeons were exposed to a baseline multiple schedule consisting of two contexts with equal rates of food delivery. In one context, designated the Rich context, the magnitude of reinforcement was four times higher relative to the alternating Lean context. The magnitude of reinforcement in the two contexts differed by the same ratio as the reinforcer rates in Experiment 1. The response-reinforcer contingency was again terminated by arranging response-independent food in each context at the same rate as in baseline. When the response-reinforcer contingency was suspended, behavior was more persistent in the Rich context than in the Lean context, providing evidence that when suspension of the contingency equally affected behavior under extinction conditions, the effects of reinforcer omission correspond to differential magnitudes of reinforcement under baseline conditions.

While the first two experiments of Nevin et al. (2001) assessed the impact of only suspending the response-reinforcer contingency, Experiment 3 assessed

the impact of simulating the effect of only omitting reinforcers while leaving the response-reinforcer contingency intact. During baseline sessions pigeons responded for food in a two component multiple schedule consisting of a Rich, VI 30 s context, and a Lean, VI 120 s context. Because the omission of reinforcers in extinction is thought to produce a generalization decrement, pigeons were then exposed to extinction and during half of the context presentations a novel flashing light was presented at the same rate in each context. By presenting the novel stimulus at equal rates in the two contexts, the generalization decrement should have been approximately equal across the contexts as well. Response rates were equally persistent in the two contexts when extinction occurred alone, but response rates were more persistent in the Rich context than in the Lean context during novel stimulus presentations when the context was changed. Therefore, reinforcer omission appears to cause a generalization decrement which is similar to changing the context of reinforcement with a novel flashing light. Additionally, when the impact of generalization is roughly equal across contexts, differences in previous reinforcer rates determine the persistence of behavior in extinction. These findings provide support for the hypothesis that the disruptive impact of extinction is due to two separable processes, termination of the response-reinforcer contingency and omission of reinforcement.

So, it is reasonable to conclude that the commonly observed PREE is consistent with the predictions of behavioral momentum's augmented model of extinction, that is, Equation 4. The PREE should not be observed if the *d*

parameter is allowed to differ according to previous rates of reinforcement in a context as described by Equation 4. When comparing resistance functions across contexts previously associated with high and low rates of reinforcement, the *d* parameter should be greater for contexts associated with extremely high rates of reinforcement as in continuous reinforcement schedules as compared to contexts associated with lower rates of reinforcement as in intermittent schedules of reinforcement. Therefore, due to differences in generalization decrement the rate of previous reinforcement in a context may appear to be negatively correlated with resistance to change or have little correlation with resistance to change. Overall, Equation 4 has been used to account for the persistence of behavior in extinction previously maintained by a variety of reinforcers including the indirect DA agonist cocaine (Quick & Shahan, 2009).

Behavior Momentum and Relapse

Behavioral momentum theory can also account for the relapse of behavior after extinction. The relapse of extinguished behavior occurs when some event, such as the introduction of reinforcer-related or novel cues, reduces the impact of the disruptive effects of extinction. Relapse has been studied with a variety of experimental paradigms including reinstatement, resurgence, and renewal. In each of these procedures a baseline of stable responding is established. Extinction conditions are then introduced until behavior is substantially decreased, and then some event occurs that causes behavior to relapse. The

reinstatement procedure uses the same context for baseline and extinction. Following extinction, presenting a small quantity of reinforcement, reinforcer cues, or stress reinstates behavior (Shaham, Shalev, Lu, de Witt & Stewart, 2003). The resurgence procedure is very similar except that during extinction, reinforcement is provided for an alternative behavior. When the alternative behavior is then placed on extinction, behavior relapses (e.g., Podlesnik, Jimenez-Gomez, & Shahan, 2006). Unlike the reinstatement and resurgence procedures, the renewal procedure establishes baseline and extinction in two distinct contexts. Behavior often relapses when the subject is replaced in the baseline context or in some cases when placed in a novel context (see Bouton, 2004, for review). In each of these procedures, behavior relapses as a result of reintroduction of some aspect of the baseline context. Therefore, the value of the context in which the relapse of behavior occurs continues to impact its persistence through extinction and relapse conditions.

The augmented model of behavioral persistence has been modified to include predictions for relapse during extinction. Podlesnik and Shahan (2009) modified Equation 3 to include a parameter *m* that scales a reduction in the impact of extinction on behavior during relapse. The resulting equation,

$$\log\left(\frac{B_t}{B_o}\right) = \frac{-t(mc + mdr)}{r^b} \tag{5}$$

where each of the terms are as in Equation 4, requires that *m* take a value of 1 during extinction. When a relapse event occurs, *m* takes a value less than 1, such that the magnitude of disruption caused by the discontinuation of the

response-reinforcer contingency and the omission of reinforcers are reduced. Thus, Equation 4 predicts greater relapse in a context previously associated with a higher rate of reinforcement relative to a context previously associated with a lower rate of reinforcement. The behavioral momentum model of relapse accounts for data from a number of relapse experiments using the resurgence, renewal and reinstatement procedures (Podlesnik & Shahan, 2010).

While behavioral momentum theory provides a useful theoretical and procedural framework for assessing the impact of the stimulus-reinforcer relation on the persistence of behavior, the neural mechanisms of these effects have not been examined. The comorbid symptoms of atypical DA activity and atypical behavioral persistence, however, suggest that DA may play a role in the persistence of behavior. It is likely that there are several neurotransmitter systems that contribute to behavioral persistence, but this review will focus on the DA system.

Dopamine and Behavior

Dopamine is a neurotransmitter that acts in the central nervous system as well as in the periphery. Within the brain, a system of dopaminergic neurons runs throughout a subregion of the limbic system called the mesolimbic system. The neurons of the mesolimbic system originate in the ventral tegmental area (VTA) and substantia nigra (Hyman, Malenka, & Nestler, 2006). Projections from the VTA extend to the nucleus accumbens (NAcc), amygdala, hippocampus, and the

prefrontal cortex (PFC), while projections from the substantia nigra extend to the dorsal striatum (Figure 2). At the VTA efferents, DA acts at either D_1-like receptors, including D_1 and D_5 subtypes, or D_2-like receptors including, D_2, D_3, and D_4 subtypes (Missale, Nash, Robinson, Jaber & Caron, 1998). Activity at both D_1- and D_2-like DA receptors may mediate locomotor activity and operant behavior.

Due to their activity during reinforcer-maintained operant behavior, the dopaminergic projections from the VTA form what is called the mesolimbic DA reward circuit. Within the mesolimbic DA reward circuit, DA neurons respond to

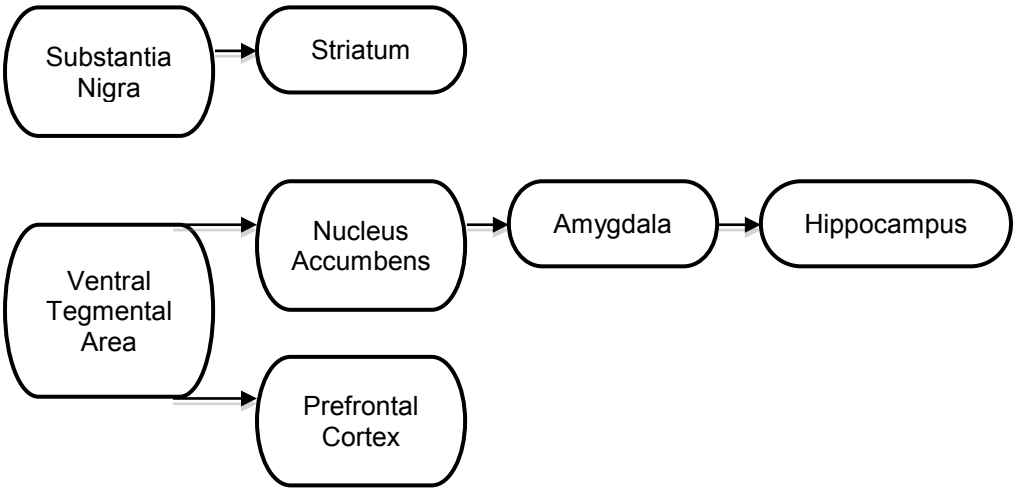

Figure 2. Dopaminergic pathways. Dopaminergic pathways originate in the substantia nigra and ventral tegmental area. Projections from the substantia nigra extend to the striatum. Projections from the ventral tegmental area extend to the nucleus accumbens, amygdala, hippocampus and prefrontal cortex.

multiple types of reinforcers including food, water, sex, electrical brain stimulation, and drugs of abuse (Spanagel & Weiss, 1999). The presentation of a reinforcer causes the dopaminergic neurons to release dopamine from the axon terminal to VTA efferents, such as the NAcc (Hernandez & Hoebel, 1988). After repeated presentation of a reinforcer, DA is no longer released in response to the reinforcer, but in response to the stimuli that come to predict its occurrence (Datla, Ahier, Young, Gray, & Joseph, 2002; O'Doherty, Deichmann, Critchley, & Dolan, 2002). Even when a reinforcer is no longer available, DA may be released in response to stimuli previously associated with that reinforcer. For example, human participants with a history of cocaine use exhibited mesencephalic DA release when reading cocaine related words, but not during neutral words (Goldstein et al., 2009).

The effects of DA agonists and antagonists on behavior further support the role of DA in reinforcement. For example, indirect DA receptor agonists serve as reinforcers for operant behavior. Indirect agonists differ from direct agonists in that they increase the extracellular concentrations of a neurotransmitter but do not act directly on neurotransmitter receptors. For example, systemic injection of the indirect DA agonist, *d*-amphetamine (2mg/kg, IP), has been shown to increase DA concentration in the nucleus accumbens from 3 pg/20 μl to 11 pg/20 μl (Hernandez, Lee, & Hoebel, 1987). Various species will perform a response for intravenous (IV) delivery of drugs that increase extracellular concentrations of DA such as cocaine, *d*-amphetamine, or methamphetamine (mice: Thomsen &

Caine, 2007; rats: Pickens & Thompson, 1968; nonhuman primates: Woolverton, Goldberg, & Ginos, 1984). Animals do not reliably self-administer DA antagonists (Amit & Smith, 1991).

The number of infusions that an organism will obtain within an experimental session appears to be a function of the current level of DA activity. In a study of cocaine-maintained responding, Barrett, Miller, Dohrmann, and Caine (2004) found that presession administration of the indirect DA agonists, *d*-amphetamine, GBR 12909, or the D_2 agonists, 7-OH-DPAT, quinelorane, produced leftward shifts of the dose-response function that represented the number of obtained cocaine reinforcers as a function of drug dose. Presession administration of the direct D_1 agonists, SKF 82958 or R-6-Br-APB, produced an overall flattening of the dose-response function. These shifts in the dose-response curves suggest that presession DA agonism decreases the effectiveness of cocaine as a reinforcer. In contrast, pretreatment with the DA antagonists SCH 39166 or eticlopride produced a rightward shift of the dose-response function, which suggests that DA antagonism increases the effectiveness of cocaine as a reinforcer. Overall, pretreatment with indirect or direct DA agonists decreased the total number of obtained cocaine infusions while DA antagonists increased the total number of obtained cocaine infusions. These results suggest that the fluctuations in DA activity associated with reinforcement mediate the impact of reinforcement on behavior.

Manipulation of DA activity by DA agonists and antagonists also produces changes in operant behavior maintained by food reinforcement. As in DA agonist-maintained behavior, presession administration of an indirect DA agonist, such as *d*-amphetamine, has been shown to decrease the rate of responding maintained by food (Cohen, 1986). The effects of indirect DA agonists, however, have also been shown to be dependent on the baseline rate of behavior (see Kelleher & Morse,1968 for review of rate-dependent drug effects). At low rates of behavior, amphetamine produces dose-dependent increase in response rate. At intermediate rates of behavior, low doses of amphetamine increased response rates and high dose of amphetamine decreased response rates. At high rates of behavior, low doses of amphetamine had no effect behavior and high doses decreased response rates (Clark & Steele, 1966). Dopamine antagonism has also been shown to decrease the rate of responding maintained by food. Beninger et al. (1987) evaluated the effects of DA antagonism on behavior reinforced on a VI 30 s schedule of food. Following a stable baseline, rats were treated with one of the following drugs; saline, pimozide, a D_1/D_2 antagonist, SCH 23390, a D_1antagonist, or metoclopramide, D_2 antagonist. Additionally, a group of rats received no treatment and were exposed to extinction. Treatment with each of the DA antagonists produced a decrease in response rates. The pattern of response rate decline mimicked the pattern of extinction-induced response rate decline, which suggests that the DA antagonists decrease the reinforcing impact of food. The difference between the effect of DA antagonism on food- and DA

agonist-maintained behavior is likely the result of antagonizing different degrees of DA activity. It may also be that the effects of DA antagonism differ across schedules of reinforcement.

The role of DA in operant behavior during steady-state conditions may also contribute to the extent to which behavior persists in extinction. For example, a group of DA transporter (DAT) knockout mice, which have enhanced levels of DA activity, were trained to respond on a progressive ratio schedule of reinforcement, which delivered a food pellet for an increasing number of responses (Hironaka, Ikeda, Sora, Uhl, & Niki, 2004). Progressive ratio schedules measure the effectiveness of a reinforcer by determining the amount of responding an animal will exert to access the reinforcer. The DAT knockout mice, homozygous mice, and wild type controls were equally persistent in obtaining food during the progressive schedule, but, when the mice were placed under extinction conditions, the DAT knockout mice exhibited much greater persistence relative to their control counterparts. There are two possible interpretations of these results. First, the enhanced level of DA activity during extinction could have overshadowed the absence of food-induced DA activation following a lever press. Second, if each reinforcer affords value to the context, as stated by behavioral momentum theory, and DA mediates reinforcement, then an enhancement of DA activity would have the effect of enhancing reinforcement associated with the context. Thus, the DAT knockout mice may have been more persistent under extinction conditions because the context for behavior had

greater value than for the control mice. Further investigation on the impact of DA agonism during baseline conditions on the persistence of behavior is needed to evaluate these possibilities.

In addition to the role of DA in the maintenance and extinction of operant behavior, DA may also contribute to the relapse of extinguished behavior. Odum and Shahan (2004) trained rats to respond for food on a RI 30 s schedule, which delivers a reinforcer for responses an average of every 30 s. One group of rats received saline before and after each session, a second group of rats received 3.0 mg/kg of *d*-amphetamine before each session, and a third group received 3.0 mg/kg *d*-amphetamine after the session. All groups were then exposed to extinction conditions. Following extinction, rats were tested for reinstatement using a presession priming dose of *d*-amphetamine (3.0 mg/kg). Although presession *d*-amphetamine reduced response rates during baseline, rats with a history of presession *d*-amphetamine exhibited the greatest degree of priming induced reinstatement. Therefore, a history of treatment with an indirect DA agonist increased the degree of drug-induced relapse. This effect is likely due to an interaction between enhanced DA levels and the context because rats with a history of postsession amphetamine exposure did not exhibit drug-induced relapse. Alternately, the discriminative stimulus properties of the drug acquired through association with reinforced responding may have occasioned greater reinstatement in the presession *d*-amphetamine group. A within-subjects treatment design may allow a discriminative stimulus explanation to be

addressed further. A discriminative stimulus explanation could also be addressed by testing for reinstatement with either cues or food deliveries. It is unclear whether the effect obtained in Odum and Shahan (2004) is specific to a drug-priming reinstatement test or if relapse would also be greater in response to a free-food reinforcer reinstatement test. Therefore, future research should address the role of DA in the attribution of value to contexts during steady state conditions and the subsequent effect on relapse triggered by free access to the previously response-dependent reinforcer.

Enhancement of DA activity has also been shown to increase cue-induced relapse as measured by Pavlovian Instrumental Transfer (PIT). In this procedure, rats are trained to press a lever for food and then exposed to a series of Pavlovian association sessions that pair food with a cue (Dickinson & Dawson, 1987). The value of the cue is then determined by counting the responses following random presentations of the cue under extinction conditions. Wyvell and Berridge (2000) found that injections of *d*-amphetamine dose-dependently increased cue-induced responding. In a follow-up study, rats were exposed to a treatment period consisting of six daily injections of *d*-amphetamine or vehicle prior to the extinction test sessions. Then during extinction test sessions, amphetamine treated rats exhibited greater cue-induced behavior than rats treated with saline (Wyvell & Berridge, 2001). These results suggest that indirect DA agonism increased the value of the cue independently of the value obtained

during the Pavlovian food pairing sessions. DA antagonism, therefore, should decrease the value of the cues independent of their association with food.

Although not determined with PIT procedures, there is some evidence that DA antagonists that act at D_1 receptors reduce the degree of cue-induced relapse. For example, administration of the D1 DA antagonist, SCH 23390, prior to a renewal test of relapse reduces context-induced renewal of responding previously maintained by several types of rewards (food: Hamlin, Blatchford, & McNally, 2006; alcohol: Hamlin, Newby, & McNally, 2007; cocaine: Crombag, Grimm & Shaham, 2002). Antagonism of DA D_1 receptors also reduces cue-induced relapse in the reinstatement procedure. For example, Allerweireldt, Weber, Kirschner, Bullock, and Neiswander (2002) trained rats to press a lever on a variable ratio (VR) 5 schedule that delivered a cocaine infusion accompanied by a tone and light cue for every fifth response on average. Following extinction, reinstatement of responding was tested with response-dependent access to the cocaine cues. When administered prior to the reinstatement test session, SCH 23390 dose-dependently reduced reinstatement of lever pressing relative to saline treated rats. Although evidence from renewal and reinstatement models of relapse provides further support for the role of DA in context valuation, it is unclear how DA antagonism during steady-state baseline conditions may affect the subsequent relapse of behavior. If DA antagonism reduces the value of the contexts and cues during extinction tests, antagonism during baseline conditions should have the same effect. Behavioral momentum

theory also emphasizes the impact of contextual value on relapse. Therefore, it is reasonable to predict that contexts associated with DA antagonism should induce a relatively lower degree of relapse.

Incentive Salience Hypothesis of DA Action

Within the field of behavioral neuroscience, one of the prominent hypotheses regarding the role of DA in behavior suggests that DA is responsible for the incentive salience of a stimulus (Berridge, 2004). This hypothesis stems from the incentive motivational theories discussed previously in which contexts are thought to acquire the incentive motivational properties of reinforcement received in their presence. The incentive salience of a stimulus or the ability to induce “wanting” of the primary reward, is then measured by assessing the persistence of behavior in its presence. Deficits of DA have been shown to decrease the persistence of behavior while leaving the “liking,” or hedonic value, of a reward intact (see Berridge & Robinson, 2003, for review). This DA hypothesis emphasizes the role of DA in facilitating the Pavlovian relation between a stimulus and a reinforcer. Accordingly, the incentive salience DA hypothesis is capable of explaining the persistence of behavior in the presence of a stimulus when the primary reinforcer is no longer available.

In addition to the DA incentive salience hypothesis, the hedonic value hypothesis, general activation hypothesis, and error prediction hypotheses claim to capture the role of DA in behavior (see Berridge, 2007 for an in-depth review

of DA hypotheses). The hedonic value hypothesis proposes that DA activity corresponds to a degree of pleasurable feelings (Wise, 1982). Organisms will work for a reward to maintain the pleasure mediated by DA. Rather than mediating the hedonic value of reward, the general activation hypothesis proposes that DA is responsible for providing an organism with the motivation to work for a reward (Salamone & Correa, 2002; Salamone, Correa, Mingote, & Weber, 2005). Finally, the reward error prediction hypothesis states that DA activity reflects changes in reward availability as compared to the organism's expectation of reward. When a reward is not expected, DA activity increases, when the reward is predicted there is no change in DA activity, and when a reward was predicted but not received there is a decrease in DA activity (Shultz, 2007). While each of these hypotheses provides a plausible role for DA, they have difficulty accounting for the cue-specific impact of DA modulation as reported by Odum and Shahan (2003), Wyvell and Berridge (2000), and Wyvell and Berridge (2001). Incentive salience hypothesis, however, proposes that DA is responsible for cue valuation, which may explain why in each of these studies, behavior exhibited greater relapse in the presence of cues associated with an elevated level of DA activity.

The DA incentive salience hypothesis appears to be closely related to the explanations of behavioral persistence within behavioral momentum theory. As in behavioral momentum theory, the incentive salience, or value, of the cue determines the likelihood of behavior in its presence. Behavioral momentum

theory states that the value of a cue is determined by the rate of reinforcement in its presence, while incentive salience hypothesis says that the value of the cue is determined by the degree of DA activity. By synthesizing these assertions, it is plausible that DA levels interact with contextual stimuli to determine the persistence of operant behavior. It seems appropriate, therefore, to approach questions regarding the role of DA in the persistence of behavior using the existing theoretical and procedural framework provided by behavioral momentum.

PURPOSE AND OBJECTIVES

Many psychological disorders such as autism, OCD, drug addiction, and ADHD are characterized by behavior that is either excessively persistent or lacks sufficient persistence. The persistence of behavior has been described using the procedural and theoretical framework of behavioral momentum theory. Behavioral momentum theory states that the persistence of behavior is governed by the value of the context in which behavior occurs. The value of the context is derived from its Pavlovian association with reinforcement. Behavior is more persistent in a context previously associated with a higher rate of reinforcement relative to a context previously associated with a lower rate of reinforcement. So, the rate of reinforcement in a context will determine the future persistence of behavior in its presence.

The proposed role of the Pavlovian stimulus-reinforcer relation is similar to the role of DA proposed by the incentive salience hypothesis, which states that DA is responsible for the attribution of incentive motivational properties from the reinforcer to the surrounding stimuli. A few experiments that assess the effect of enhancing and reducing DA activity on behavior support the incentive salience hypothesis. Specifically, indirect DA agonism has been shown to increase the persistence of cue-induced behavior under extinction conditions. Indirect DA agonism may also augment the degree of relapse of an extinguished response, while DA antagonism at D_1 receptors has been shown to decrease the degree of

relapse. Thus, the incentive salience of a context or cue appears to be determined by the degree of DA activity in its presence.

The predictions of behavioral momentum theory and the DA incentive salience hypothesis, propose a similar role for the rate of reinforcement in a context and the degree of DA activity in a context in determining the value of a context and the persistence of behavior in its presence. So, if DA activity is increased in a context, the Pavlovian stimulus-reinforcer relation should be enhanced, yielding relatively more persistent behavior. If DA activity decreased in a context, the Pavlovian stimulus-reinforcer relation should be diminished, yielding relatively less persistent behavior. Therefore, the aim of the present research is to determine the extent to which modulation of DA activity during steady state conditions alters the resistance to change of behavior during and extinction and relapse. This research aim is addressed within the theoretical and procedural framework of behavioral momentum theory, and includes the following objectives:

1. Assess the direct effect of indirect DA agonism and antagonism on the rate of lever pressing for food in a two-component multiple schedule that arranges two distinct contexts with equal rates of response-dependent food delivery.
2. Assess the relative persistence of lever pressing in a context previously present during treatment with an indirect DA agonist or

antagonist as compared to a context present during treatment with saline.

3. Assess the relative reinstatement of lever pressing in a context previously present during treatment with an indirect DA agonist or antagonist as compared to a context present during treatment with saline.
4. Assess the extent to which pretreatment with a DA antagonist blocks the effect of treatment with an indirect DA agonist during steady-state conditions on the persistence of behavior in extinction and reinstatement.

For the current research, the indirect DA agonist *d*-amphetamine was used to enhance DA activity. D-amphetamine was selected given the extensive previous research in which systemic administration has been shown to increase DA levels within the mesolimbic DA reward pathway (Hernandez et al., 1987). Furthermore previous studies of incentive sensitization have also used *d*-amphetamine to assess the impact of indirect DA agonism on cue reactivity (Wyvell & Berridge, 2000, 2001). Using microdialysis and HPLC, *d*-amphetamine has been shown to dose-dependently increase DA levels in the caudate putamen, which was associated with increases in postsynaptic signal transduction in the nucleus accumbens as measured by increases in cAMP activity (Ren, Xu, Choi, Jenkins, & Chen, 2009). Direct agonism of the DA D_1 receptor has also been correlated with increases in cAMP activity (Traynor &

Neubig, 2005). Therefore, enhancement of extracellular DA concentration may lead to increased activation of DA D_1 receptors. In the current research, this hypothesis was tested using the DA D_1 antagonist SCH 23390 to block DA activity at D_1 receptors alone and in combination with enhanced DA extracellular levels. The current research, however, did not assess extracellular DA levels.

Three groups of rats were trained to press a lever for food in a two-component multiple schedule with components that alternated across days. In each context of the multiple schedule, rats worked for equal rates of food delivery and received a presession and postsession injection of saline or a drug. The injection type depended on the phase of the experiment. During the baseline phase rats acquired lever-pressing for food in each context and received pre- and postsession injections of saline. During the treatment phase, each rat received saline prior to the session and drug following the session in one context. In the second context, each rat received drug prior to the session and saline following the session. Rats in the DA agonist group received *d*-amphetamine as the drug injection, rats in the DA antagonist group received SCH 23390 as the drug injection, and rats in the DA antagonist/agonist group received a pretreatment dose of SCH 23390 followed by *d*-amphetamine as the drug injection. Pre- and postsession injections were given to equalize total drug exposure across days. During extinction, food deliveries were discontinued and all rats were injected with pre- and postsession saline. Responding was reinstated in each component using response independent food deliveries.

METHODS

Subjects

The subjects were 24 experimentally naïve male Long-Evans rats approximately 120 days old. All rats were pair-housed in a climate controlled colony room with a 12hr: 12hr light:dark schedule. All rats were given postsession food in the home cage to maintain their bodyweight at 80% of their adult free-feeding weight. Food restriction in the laboratory allows animals to avoid obesity and maintain body-weights that are comparable to body-weights in the wild (Poling, Nickel, & Alling, 1990). Food restriction is also associated with DA and NMDA neuroadaptations that increase the sensitivity to the rewarding impact of drugs of abuse (Carr, 2007). Twenty-four hours of food deprivation has been associated with an increase in mesocortical DA activity (Carlson, Herrick, Baird, & Glick, 1987). In the present study, rats generally consumed their daily food ration within one hour following the session, which is similar to a 23-hour food deprivation. The use of food-restricted rats, therefore, may allow strong external validity, but comparing the effects of DA modulation in food deprived rats to nonfood deprived rats may be limited. Water access was not restricted. Of these 24 rats, 8 were randomly assigned to the DA agonist group, 8 were assigned to the DA antagonist group, and 8 were assigned to the DA antagonist/agonist group. One rat in the DA antagonist/agonist group died during the treatment phase. His data were removed from the experiment.

Apparatus

All experimental sessions were conducted in four Med Associates® behavioral chambers. Each chamber measured 30 cm long, 24 cm wide, and 21 cm high, and was housed in a sound-attenuating cubicle. The interior of each chamber contained a response panel consisting of two nonretractable levers, two lever lights, an aperture for food delivery, and a houselight. The levers, each illuminable by a lever light, were located on either side of the food aperture approximately 13 cm apart. The house light was located at the top center of the panel above the food aperture. The food aperture was also equipped with a photocell to record head entries into the aperture. All output stimuli and input responses were controlled and monitored by Med Associates® interfacing and software

Drugs

D-Amphetamine (Sigma-Aldrich) was mixed with 0.9% saline to a concentration of 1.7 mg/mL. Odum and Shahan (2003) treated rats with a 3.0 mg/kg dose of *d*-amphetamine, but this dose dramatically suppressed response rates. To minimize the rate decreasing effect, this study used a 1.7mg/ml dose, which was proven effective in pilot tests. SCH 23390 was mixed with 0.9% saline to a concentration of 0.06 mg/mL. The dose of SCH 23390 was selected after finding that the higher dose of 0.1 mg/kg used by Beninger et al. (1987)

dramatically reduced response rates for food in pilot testing. Both drugs were delivered intraperotoneally at a volume of 1ml/1kg.

Methods

Rats experienced daily experimental sessions lasting approximately 30 min each. The experiment consisted of 108 sessions total across all phases of the experiment. In each session, one of two contexts was presented. In one context, the right lever was active and illuminated by the right lever light. In the other context, the left lever was active and illuminated by the left lever light. A flashing house light and tone or a steady house light and tone also differentially signaled these contexts and were counter-balanced across subjects. The two contexts were presented in an alternating order across days. The experiment was divided into five phases of sessions: training, baseline, treatment, extinction, and reinstatement. In each phase rats received a pre- and postsession injection of saline, amphetamine, SCH 23390, or SCH 23390 followed by amphetamine depending on the experimental phase.

Training Phase

Rats were trained to press the left and right levers when active, which was signaled by an illuminated light above the lever. Training sessions arranged an FR 1 schedule of food-pellet delivery in the first session of each component. The required number of responses was increased across sessions up to an FR 8

schedule of pellet delivery in each component. The fixed-ratio schedule in each context was then changed to a RI 30 s schedule of pellet delivery. Training required 5 sessions per context, or 10 sessions total.

Baseline Phase

After the training phase, each rat proceeded to the baseline phase. During baseline, pellets were delivered according to a RI 30 s schedule in both contexts. Additionally, each rat received a presession injection of saline and was then placed immediately into the experimental chamber. As in training, baseline sessions lasted 30 minutes. Then, following the session, rats received a postsession injection of saline. The baseline phase consisted of 15 sessions per context, or 30 sessions total.

Treatment Phase

After completing the baseline phase, rats proceed to the treatment phase. There were 20 treatment sessions per context, or 40 sessions total. For the DA agonist group, one of the contexts was designated the amphetamine context, and the other context was designated the saline context. Designation of context was counter-balanced across rats. On days in which the amphetamine context was presented, rats received a presession injection of amphetamine and a postsession injection of saline. On days in which the saline context was presented, rats received a presession injection of saline and a postsession

injection of amphetamine. For the DA antagonist group, one of the contexts was designated the SCH 23390 context, and the other context was designated the saline context. Again designation of context was counter-balanced across rats. On days in which the SCH 23390 context was presented, rats received a presession injection of SCH 23390 and a postsession injection of saline. On days in which the saline context was presented, rats received a presession injection of saline and a postsession injection of SCH 23390. For the DA antagonist/agonist group, one of the contexts was designated as the SCH 23390-amphetamine context, and the other context was designated the saline context. Designation of context was counter-balanced across rats. On days in which the SCH 23390-amphetamine context was presented, rats received a presession injection of SCH 23390 followed 5 minutes later by an injection of amphetamine and a postsession injection of saline. On days in which the saline context was presented, rats received a pre-session injection of saline and a postsession injection of SCH 23390 followed 5 minutes later by an injection of amphetamine.

Extinction Phase

The extinction phase began the session after the treatment phase was completed. During extinction, all groups experienced extinction conditions in both contexts. Extinction conditions were arranged by withholding food delivery. Also, all groups received a pre- and postsession injection of saline instead of the

previous treatment injections. There were 10 extinction sessions per context, or 20 extinction sessions total.

Reinstatement Phase

Following extinction, the rats were exposed to one session of reinstatement in each context. During reinstatement, response independent food was delivered at the same rate as arranged in baseline and treatment sessions. Thus, in each context food was delivered according to a RT 30 s schedule. All rats continued to receive pre- and postsession injections of saline.

Statistical Methods

Reinforcer rates were calculated as the number of reinforcers per minute. The reinforcer rates in each context were averaged across the last five days for the baseline and treatment phases for each rat. A three-way mixed ANOVA in which context and experimental phase served as within subject factors and drug treatment type served as a between-subjects factor was conducted to test for differences in reinforcer rates in the baseline and treatment phases. A separate two-way mixed ANOVA in which context served as a within subjects factor and drug treatment type served as a between-subjects factor was conducted to test for differences in reinforcer rates during the reinstatement phase. Response rates were calculated as the number of responses per minute. The mean response rates in each context for each rat were averaged across drug treatment

groups for each phase of the experiment. For baseline and treatment phases, response rates were averaged from the last five days of each phase. The effects of drug treatment on relative response rates were first compared to baseline response rates using a three-way mixed ANOVA in which context and experimental phase served as within subjects factors and drug treatment group served as the between subjects factor. Follow-up two-way repeated measures ANOVAs were then conducted for each drug treatment group. Paired *t* tests were then used to compare response rates in each context during the baseline and treatment phases. The persistence of responding across all ten extinction sessions was assessed by comparing absolute response rates in each context for each drug treatment group as well as by comparing the proportion of treatment response rates in each context across drug treatment groups. For both comparisons, separate two-way repeated measures ANOVAs were conducted. Reinstatement of responding also was assessed by comparing absolute response rates in each context during the last day of extinction and the reinstatement test as well as by comparing the proportion treatment response rates in each phase for all drug treatment groups. Follow-up two-way repeated measures ANOVAs were then conducted for each drug treatment group. Paired *t* tests were then used to compare response rates in each context during the extinction and reinstatement phases.

RESULTS

Throughout the baseline, treatment and reinstatement phases, reinforcement rates were held constant in each context at approximately two reinforcers per minute. Equivalent reinforcer rates were obtained in the baseline and treatment phases for each of the drug treatment groups as shown in Table 1. This conclusion is based on a nonsignificant three-way interaction, F (2, 20) = 0.417, p = 0.664. Additionally, there was no significant difference in reinforcer rates across contexts and across the three drug-treatment groups during the reinstatement phase as evidenced by a nonsignificant two-way interaction, F(2, 20) = 2.232, p = 0.133. Thus, the effects of drug treatment in a context were not due to changes in reinforcement rates across contexts, across phases of the experiment, or differences in reinforcer rates across drug treatment groups.

Table 1

Reinforcer Rates

	Mean reinforcers per minute					
	Amphetamine		SCH 23390		COMBO	
PHASE	Drug	Saline	Drug	Saline	Drug	Saline
Baseline	1.94	1.83	1.90	1.86	1.90	1.97
Treatment	1.72	1.93	1.82	1.94	1.58	1.87
Extinction	-	-	-	-	-	-
Reinstatement	1.93	2.04	2.07	1.79	2.11	2.10

Note. Mean reinforcer rates in each context for rats in the amphetamine, SCH 23390, and COMBO treated rats across each phase. Means were first calculated across the last five days of the baseline and treatment phases for each rat.

Responses per minute in each context across the baseline and treatment phases for the amphetamine-, SCH 23390-, and combination-treated rats are shown in Figure 3. Overall, response rates differed in each context across the baseline and treatment phases depending on the drug administered prior to experimental sessions in the drug context, which was supported by a significant three-way interaction, $F(2, 20) = 3.880$, $p < .05$. Although baseline response rates were equal in each context, treatment with amphetamine in one context decreased response rates relative to saline treatment, $F(1, 7) = 15.518$, $p < .01$ (top panel). Likewise, baseline response rates were similar in the drug and saline contexts but then differed during the treatment phase when SCH 23390 was administered prior to sessions in the drug context, $F(1, 7) = 24.126$, $p < .01$ (middle panel). As compared to baseline levels, treatment with SCH 23390 decreased response rates in the SCH 23390 context, $t(7) = 2.514$, $p < .05$, and increased response rates in the saline context, $t(7) = -5.453$, $p < .05$. Baseline response rates did not differ in the combo and saline contexts, but the combination of pretreatment with SCH 23390 and treatment with amphetamine prior to sessions in the drug context produced differential response rates across the two contexts, $F(1, 6) = 11.140$, $p < .05$ (bottom panel).

Response rates in the drug contexts did not differ reliably across the treatment groups during the treatment phase, $F(2, 20) = 1.004$, $p = 384$, but, response rates in the sale contexts were significantly different, $F(2, 20) = 3.895$, $p < .037$. As supported by a Bonferroni post hoc analysis, this effect was

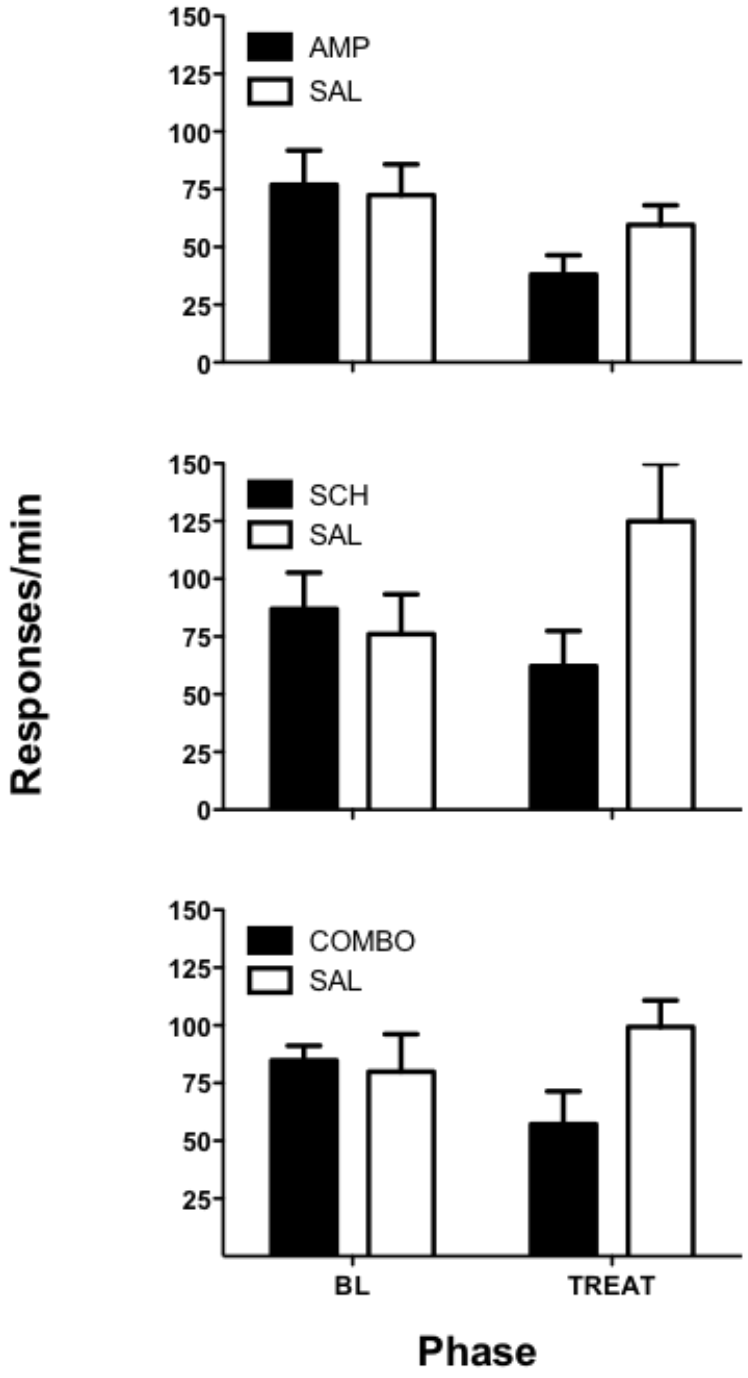

Figure 3. Baseline and treatment response rates. Mean response rates in the drug and saline contexts for rats treated with amphetamine (top panel), SCH 23390 (middle panel), SCH 23390 and amphetamine (bottom panel).

primarily due to higher response rates in the saline context of the SCH 23390-treated group relative to response rates in the saline context of the amphetamine-treated group. Thus, amphetamine treatment produced context specific decreases in response rates, while SCH 23390 treatment produced context-specific response rate decreases as well as an enhancement of response rates in the alternating saline context.

In Figure 4, the persistence of behavior during extinction is analyzed in two ways. First, the mean response rate in each context is graphed as a function of extinction session for each of the groups treated with amphetamine, SCH 23390, or a combination of amphetamine preceded by SCH 23390 in column a. Response rates in extinction decreased at a faster rate in the context previously associated with amphetamine relative to the context previously associated with saline as evidenced by a significant context by session interaction, $F(10, 70) = 10.582$, $p < .05$. Response rates also decreased at a relatively faster rate in contexts previously associated with SCH 23390 treatment, $F(10, 70) = 7.994$, $p < .05$, or a combination of SCH 23390 and amphetamine, $F(10, 60) = 7.759$. In absolute terms, therefore, a history of indirect DA agonism or direct DA antagonism in a context accelerated the subsequent extinction of behavior in that context. It is important to note, however, that response rates were significantly lower in each of the drug contexts than in the saline contexts. When response rates are lower in one context than in the alternating context, the persistence of behavior appears to be greater in the context that had higher response rates

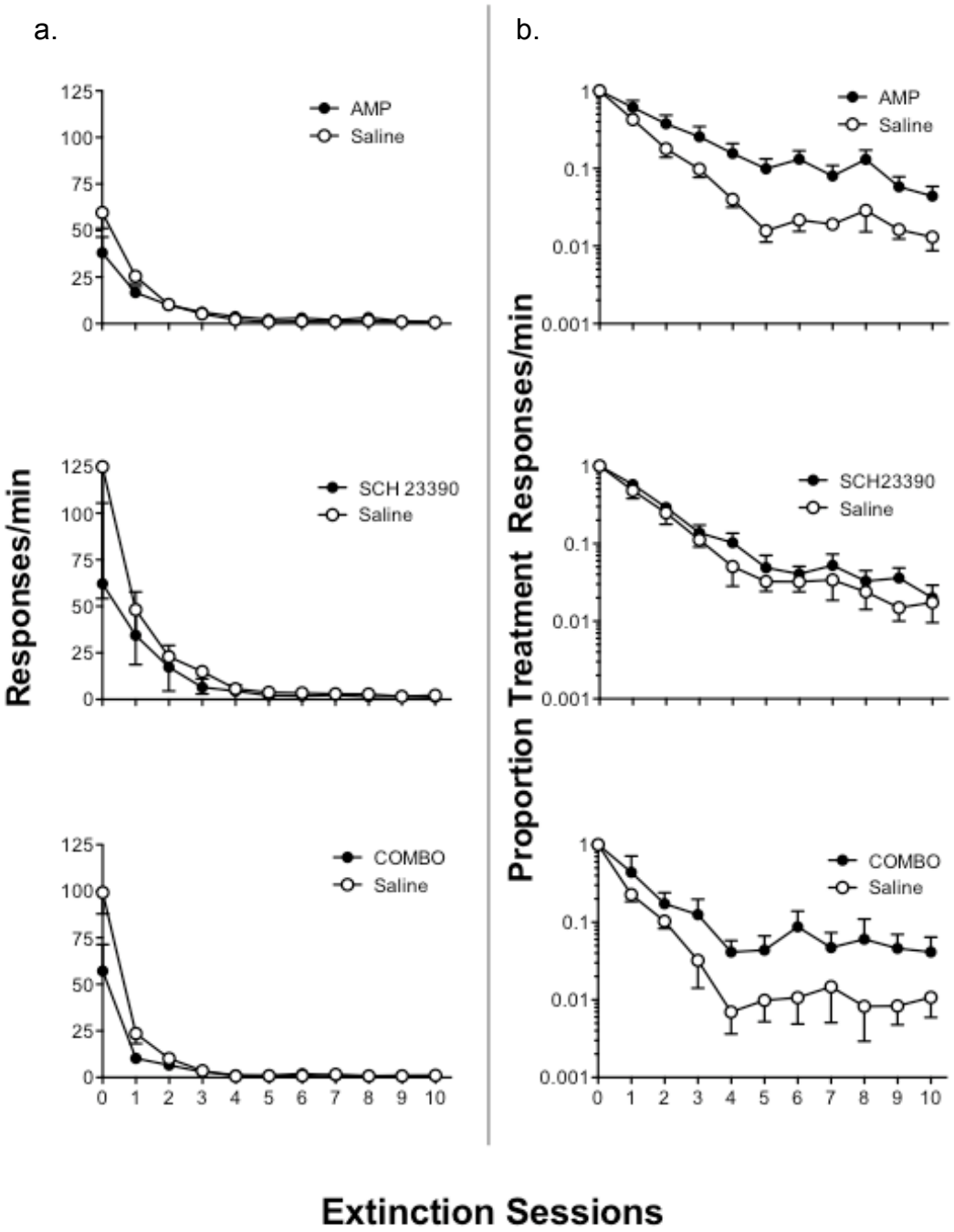

Figure 4. Extinction response rates. Column a. Mean responses per minute in the drug and saline contexts for the amphetamine (top panel), SCH 23390 (middle panel), Combo (bottom panel) treated rats. Column b. Mean responses per minute in the drug and saline contexts expressed as a proportion of treatment response rates for amphetamine (top panel), SCH 23390 (middle panel), Combo (bottom panel) treated rats and plotted on a logarithmic y-axis.

because the rates had a higher relative starting point. Accordingly, from the perspective of behavioral momentum theory, it is necessary to normalize the response rates in each context during extinction to accurately interpret the relative persistence of behavior.

Behavioral momentum analyses use normalized response rates such that response rates in extinction are expressed as a proportion of preextinction response rates (Nevin & Grace, 2000). Larger proportions indicate greater resistance to change relative to smaller proportions. A resistance to change analysis of the response rates in each context is presented for each treatment group in column b of Figure 4. In this column, extinction response rates are expressed as a proportion of treatment response rates and plotted on a logarithmic y-axis. Treatment response rates were calculated as the mean of response rates in the last 5 days of each context for individual subjects. Given the biphasic nature of the functions, statistical testing was used to detect differences in the resistance to change in each context. Response rates in the context previously associated with amphetamine were more resistant to extinction relative to the response rates in the context previously associated with saline (top panel). This conclusion is supported by a repeated measures ANOVA test showing a significant session by context interaction, $F(10, 70) = 3.968$, $p < .05$, as well as significant main effects of extinction session, $F(10, 70) = 69.337$, $p < .05$, and context, $F(1, 7) = 15.046$, $p < .05$. Response rates in the context associated with administration of SCH 23390 and the context associated with

saline declined at a similar rate across extinction sessions as evidenced by a nonsignificant interaction between context and extinction session, $F(10, 70) = 1.001$, $p = .451$, and a significant main effect of extinction session, $F(10, 70) = 78.91$, $p < .05$ (middle panel). As in rats treated with amphetamine, rats that received both SCH 23390 and amphetamine exhibited relatively more persistent responding in the drug associated context, which is supported by a significant session by context interaction, $F(10, 60) = 3.809$, $p < .05$, and significant main effects of context, $F(1, 6) = 11.798$, $p < .05$, and extinction session, $F(10, 60) = 41.613$, $p < .05$(bottom panel). Thus, indirect DA agonism in a context enhanced the relative persistence of behavior in that context, while DA antagonism at D_1-like receptors in a context had little impact on the relative persistence of behavior.

Following extinction, lever pressing was reinstated using response independent food deliveries. The rate of lever pressing in each context during the last day of extinction is presented in two ways in Figure 5. In column a., response rates in each context from the last day of extinction and reinstatement are shown for each of the three treatment groups. A three-way repeated measures ANOVA revealed a significant main effect of experimental phase, $F(1, 20) = 74.05$, $p < .01$, which suggests that response independent food deliveries resulted an increase in response rates in both saline and drug contexts. Additionally, this conclusion was further supported by three two-way repeated measures ANOVA analyses performed for each treatment group. Rats treated with amphetamine

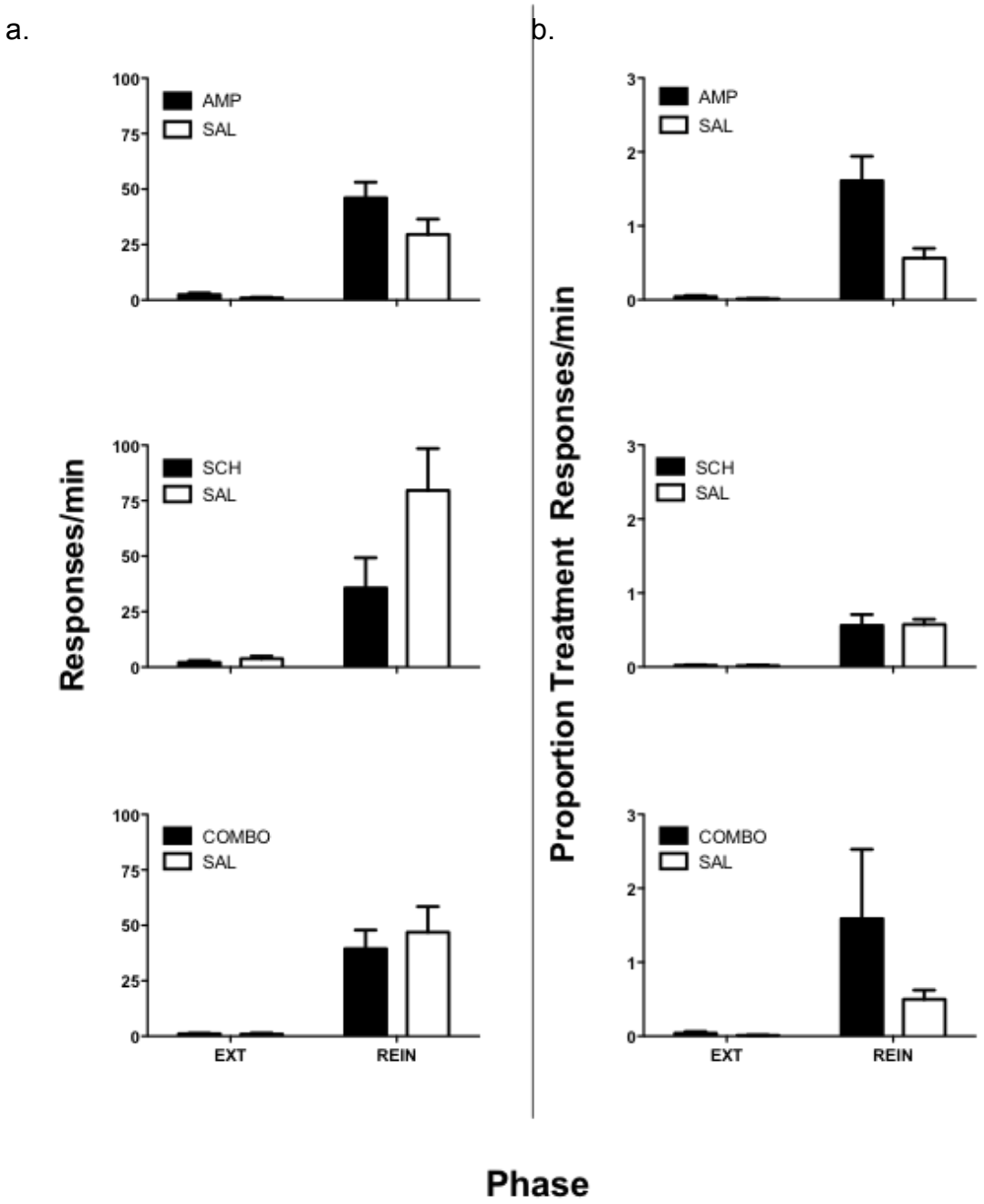

Figure 5. Reinstatement response rates. Column a. Mean responses per minute in the drug and saline contexts for the amphetamine (top panel), SCH 23390 (middle panel), Combo (bottom panel) treated rats. Column b. Mean response per minute in the drug and saline contexts expressed as a proportion of treatment response rates for amphetamine (top panel), SCH 23390 (middle panel), Combo (bottom panel) treated rats.

exhibited higher response rates in the amphetamine context relative to the saline context across the extinction and reinstatement phases, $F(1, 7) = 8.227$, $p < .05$ (top panel). Response rates in each context were higher in the reinstatement phase than in the extinction phase, $F(1, 7) = 30.929$, $p < .01$, but response rates in the amphetamine context increased to a greater degree than response rates in the saline context, $F(1, 7) = 5.904$, $p < .05$. This effect occurred despite the fact that response rates were lower in the amphetamine context than in the saline context during treatment.

Rats treated with SCH 23390 exhibited approximately equal response rates in the saline and SCH 23390 associated contexts during reinstatement, $F(1, 7) = 4.299$, $p = .077$ (middle panel). The rate of responding in reinstatement was significantly greater during the reinstatement test than on the last day of extinction, but the degree of reinstatement did not differ reliably across contexts. This conclusion is evidenced by a significant main effect of phase, $F(1, 7) = 19.789$, $p < .001$] and a nonsignificant interaction, $F(1, 7) = 4.281$, $p = .077$. Therefore, DA antagonism in a context did not affect the reinstatement of responding in that context.

While response rates in the saline and combo contexts were higher in the reinstatement condition than in the extinction condition, $F(1, 6) = 56.143$, $p < .01$, there was no significant difference in response rates between the saline and combo contexts, F (1, 6) =.180, p=.687 (bottom panel). Thus, a history of

combined SCH 23390and amphetamine treatment in a context did not enhance the reinstatement of responding in that context.

Again, an analysis of the effects of DA agonism, DA antagonism and a combination of DA agonism and antagonism on the relative relapse of behavior is skewed without assessing the degree of relapse in relation to preextinction treatment response rates. As with resistance to extinctions, behavioral momentum theory suggests that expressing response rates in reinstatement as a proportion of preextinction response rates are the appropriate measure of relative relapse (Podlesnik & Shahan, 2009, 2010).

In part b of Figure 5, response rates are expressed as a proportion of the preextinction treatment response rates. A three-way repeated measures ANOVA of the within-subjects factors phase and context and the between-subjects factor drug type, revealed significant main effects of context, $F(1 ,2) = 6.038$, $p < .03$, and phase, $F(1, 2) = 27.482$, $p < 0.01$, as well as a significant context by phase interaction, $F(1, 2) = 5.924$, $p < .03$. This analysis suggests that while response rates were different in each context across the extinction and reinstatement phase, these response rates were approximately equal across drug treatment groups. Follow-up two-way repeated measures ANOVAs comparing response rates in each context across the extinction and reinstatement phases for each drug treatment group support this conclusion.

As shown in the top graph, response rates in the amphetamine- and saline contexts were approximately equal on the last day of extinction but then

increased differentially during the reinstatement test, such that response rates were higher in the amphetamine-associated context than in the saline-associated context, $F(1, 7) = 12.657$, $p < .02$. In contrast, response rates in the SCH 23390-associated context and the saline-associated context were approximately equal in both the extinction and reinstatement phases despite a significant increase in response rates overall, $F(1, 7) = 47.517$, $p < .01$. Response rates were not significantly different across the contexts previously associated with saline and with a combination of SCH 23390 and amphetamine in either the extinction or reinstatement contexts, $F(1, 6) = 1.551$, $p = .259$.

DISCUSSION

Overall, this dissertation research begins to address the role of DA within behavioral momentum theory. Behavioral Momentum Theory predicts that contexts associated with a higher rate of reinforcement yield more persistent behavior relative to contexts associated with lower rates of reinforcement (Nevin & Grace, 2000). In this experiment however, the arranged rates of reinforcement were equal across the two contexts and one context was associated with DA agonism, antagonism, or a combination of DA agonism and antagonism. Therefore, differential persistence and relapse in each context may result from dopaminergic modulation.

In the present experiment, the extent to which the neurotransmitter DA plays a role in the resistance to change of operant behavior during extinction and relapse was assessed within four main objectives. The first objective was to assess the effects of DA modulation on response rates when food was still available for lever pressing. Increasing DA activity with the indirect DA agonist *d*-amphetamine decreased response rates in the drug context while leaving response rates in the saline context unaffected. This behavioral effect is similar to the effect of adding response independent reinforcers in one component of a multiple schedule relative to a second component (e.g., Nevin et al., 1990; Shahan & Burke, 2004). Although the effect of DA agonism is similar to enhancing the rate of reinforcement, the effect may have occurred due to a general disruption of the behavior rather than the drug's impact on reinforcement

(Cohen, 1986). The latter interpretation is supported by the response rate decreases observed in the drug context during treatment with the DA D_1 antagonist SCH 23390. The decrease in responding for food as a result of SCH 23390 treatment is consistent with the rate decreasing effects of SCH 23390 on behavior maintained by VI 30s schedules of food reinforcement (Beninger et al., 1987). Additionally, SCH 23390 has been shown to decrease responding during relapse manipulations (Allerweireldt et al., 2002; Crombag et al., 2002; Hamlin et al., 2006, 2007). Systemic administration of SCH 23390, therefore, may serve to suppress behavior independently of the behavioral contingencies.

While treatment with amphetamine in the drug context had no impact on response rates in the alternating saline context, treatment with SCH 23390 in the drug context increased response rates in the alternating saline context. Similar effects have been reported in studies of behavioral contrast in which changing the reinforcement schedule in one component of a multiple schedule changes the response rates in that component (Reynolds, 1961). Response rates in a second component exhibit an opposing change in rate. For example, a multiple schedule initially arranges two components with equal RI 30 components. Then the reinforcement schedule is changed to extinction in one component. Going to an extinction schedule produces response rate decreases in that component, while response rates increase in the second component. Thus, treatment with SCH 23390 in one context acted similarly to decreasing the rate of reinforcement in an alternating context of a multiple schedule.

Alternatively, the enhancement of response rates in the saline context for SCH 23390 treated rats may have been due to the chronic effects of the drug. Previous research has shown that acute systemic injections of SCH 23390 decreased locomotor activity in rats (Hoffman & Beninger, 1985). Chronic treatment with SCH 23390, however, resulted in enhanced locomotor activity, which was correlated with an upregulation of D_1 receptors (Hess, Albers, Le, & Creese, 1986). So, the long-term exposure to SCH 23390 and possible upregulation of D_1 receptors may have contributed to the enhancement of response rates in the saline context. It is unclear how an upregulation of D_1 receptors would also result in a response rate decrease in the drug context following SCH 23390 treatment. The current experiment did not assess D_1 receptor expression or locomotor activity, so it is unclear if the neural effects of chronic SCH 23390 treatment produced the observed behavioral effect. Future studies should address the relationship between changes in D_1 expression and the behavioral effects of SCH 23390 in a multiple schedule of reinforcement.

The second objective of this experiment was to assess the extent to which a history of indirect DA agonism or DA D_1 antagonism in a context modulated the persistence of behavior that context. While the absolute rate of behavior was higher across extinction sessions in the saline context, this effect is an artifact of the difference in response rates at the end of treatment. When expressed as the proportion of treatment response rates, as is appropriate according to behavioral momentum theory, the resistance to extinction of responding was greater in a

context previously associated with indirect DA agonism. Indirect DA agonism in a context produced a behavioral effect that is similar to enhancing the rate of reinforcement in a context. As discussed previously, Nevin et al. (1990) demonstrated that enhancing the overall rate of reinforcement in a context with free alternative reinforcers increased the persistence of behavior in that context. Thus, the indirect DA agonist *d*-amphetamine may have acted to enhance the Pavlovian stimulus-reinforcer relation by enhancing the overall rate or magnitude of reinforcement in the drug context relative to the saline context. The effect of indirect DA agonism on the ability of a context to yield greater behavioral persistence suggests that, as hypothesized, DA activity plays a role in the persistence of operant behavior.

Although DA activity plays a role in the persistence of operant behavior, the mechanisms by which this occurs is unclear. Dopamine may act indirectly by modulating glutamate activity in the NAcc and PFC. Using microdialysis, indirect DA agonists cocaine (15 and 30 mg/kg, i.p.) and *d*-amphetamine (2.0 mg/kg, i.p.) have been shown to increase glutamate and aspartate levels in the NAcc and PFC (Reid, Hsu, & Berger, 1997). Systemic pretreatment with SCH 23390 (0.02 mg/kg, i.p.), haloperidol, a D_2 antagonist, and raclopride, a D_2 antagonist, blocked cocaine induced glutamate in the NAcc. Only SCH 22390 blocked cocaine induced glutamate release in the PFC. So, the *d*-amphetamine enhanced resistance to extinction observed in this experiment may have been due to enhanced activity at both D_1 and D_2 receptors sites, which in turn

stimulated glutamate release in mesolimbic DA regions of the brain. Activation of DA D_1 receptors and glutamate NMDA receptors has also been shown to increase the number of glutamate AMPA receptors in medium spiny neurons of the NAcc, which suggests that chronic DA agonism may facilitate neural plasticity (Sun, Milovanovic, Zhao, & Wolf, 2008). Therefore, *d*-amphetamine induced enhancement of behavioral persistence is likely due to synaptic plasticity in the limbic system, especially in the NAcc.

According to the synthesis of behavioral momentum theory and the incentive salience hypothesis of DA, antagonizing DA receptors in a context should decrease the relative persistence of behavior in that context. The results from specifically antagonizing DA D_1 receptors do not support this hypothesis. When expressed in absolute terms, response rates in the context previously associated with SCH 23390 treatment were lower than behavior in the context previously associated with saline treatment. Again, this result was confounded by the difference in response rates at the end of the treatment phase. When expressed as a proportion of treatment response rates, the relative persistence of behavior was unaffected by a history of DA D_1 antagonism. This suggests that the persistence of behavior is not mediated by activity at D_1 receptors alone. Dickinson, Smith, and Mirenowicz (2000) found that DA D2 antagonists reduced the Pavlovian instrumental transfer with food. Since *d*-amphetamine acts at both D_1 and D2 receptors, it is possible that activity at D2 receptors mediates behavioral persistence rather than activity at D_1 receptors.

The third objective of the current experiment was to assess the extent to which DA modulation in a context affects the degree of relapse in that context. The reinstatement of behavior was greater in a context previously associated with amphetamine treatment than in a saline context. This effect was observed in both absolute response rates and normalized response rates, suggesting that enhancement of DA activity in a context makes behavior in that context more susceptible to relapse. These results are consistent with Odum and Shahan (2004), who demonstrated that the amphetamine-induced reinstatement of food-seeking behavior was greater for rats that had previously received amphetamine while responding for food. In the current experiment, however, the direct behavioral effect of amphetamine was omitted from the reinstatement phase, suggesting that the context, through association with indirect DA agonism, rather than the discriminative stimulus properties of amphetamine, mediated reinstatement of food seeking.

In contrast to the effects of indirect DA agonism, reinstatement of behavior was lesser in the context previously associated with DA D_1 antagonism as compared to reinstatement of behavior in the saline context. Analysis of reinstatement as a proportion of treatment response rate suggests that the difference in reinstatement across the contexts was not due to modulation of DA activity but due to differences in response rates during treatment. This result may appear contradictory to previous reports that indicate treatment with SCH 23390 blocks relapse of behavior (Allerweireldt et al., 2002; Crombag et al., 2002;

Hamlin et al., 2006, 2007). The present experiment differed from these reports in two main ways. First, in the previous reports, SCH 23390 was administered just prior to the reinstatement test, whereas SCH 23390 was delivered during the treatment phase of the present experiment and not during the reinstatement phase. It may be that SCH 23390 acts to block reinstatement through its direct effects on behavior rather than through devaluation of contextual stimuli. Second, in the previous report, SCH 23390 was delivered subcutaneously and at a lower dose than in the present experiment, which administered SCH 23390 intraperotoneally at a dose of 0.06 mg/kg. Thus, the lack of differential reinstatement in the saline SCH 23390 contexts may be due to route of administration and dose of the drug.

The magnitude of reinforcer-induced reinstatement also may be affected by the discriminative stimulus properties of the reinforcer. Franks and Lattal (1976), trained rats to respond for food on a schedule that engendered high response rates or a schedule that engendered low response rates. Following extinction, responding was reinstated with response independent food deliveries. Despite equal rates of response independent food, the magnitude of reinstatement was greater when following a baseline of high rate behavior than a baseline of low rate behavior. The authors concluded that the reinforcer gained discriminative stimulus properties of the baseline schedule and that resulting differences in reinstatement of responding were due to differential discriminative stimulus properties of the reinforcer. So, it may be that in the present experiment,

the food reinforcer in each context gained discriminative stimulus properties through association with the rate of responding in that context. Food in the amphetamine or SCH 23390 contexts would be discriminative of low rate behavior whereas food in the saline contexts would be discriminative of high rate behavior. Thus, if the magnitude of reinstatement is dependent on the discriminative stimulus properties of the reinforcer, then the rate of behavior should be higher in both the amphetamine and SCH 23390 contexts relative to the rates of behavior in the saline contexts. While this prediction was true for the amphetamine treated rats, SCH 23390 treated rats exhibited nondifferential reinstatement across the drug and saline contexts. Therefore, in the present experiment the discriminative stimulus properties of the reinforcer do not appear to account for the magnitude of reinstatement.

The fourth objective of this experiment was to assess the extent to which pretreatment with a D_1 antagonist blocks the effects of DA agonism on the persistence of behavior in extinction and reinstatement. During treatment, a combination of SCH 23390 and amphetamine decreased response rates in the drug context while leaving response rates in the saline context intact. The suppression of response rates in the combined drug context was similar to the effects of treatment with *d*-amphetamine alone. Therefore, pretreatment with SCH 23390 did not block the response rate decreasing effect of treatment with *d*-amphetamine. Rats in each of the drug treatment groups also exhibited response rate decreases in the drug context, which suggests that one of the effects of drug

treatment is a general disruption of behavior. The overall disruptive impact of drug treatment may be due to the effects of the drugs on the response-reinforcer contingency, the Pavlovian stimulus-reinforcer relation or the stimulus-response relation. If these treatments impacted the stimulus-reinforcer relation then they should yield differential persistence of behavior in extinction. This effect was not observed across the *d*-amphetamine and SCH 23390 groups, so the persistence of behavior does not appear to be dependent on the extent of disruption during treatment.

When food maintained responding was extinguished, a history of SCH 23390 pretreatment had no effect on the *d*-amphetamine-enhanced behavioral persistence in the drug context expressed in absolute or relative terms. So, despite the disruptive impact of drug treatment, SCH 23390 did not block the impact of *d*-amphetamine on the stimulus-reinforcer relation. SCH 23390 acts primarily to block binding at DA D_1 receptors. Therefore, the differential persistence of behavior in the combo treated group was not due to activity at DA D_1 receptors during steady state baseline conditions. While D_1 receptors may have been blocked with SCH 23390 pretreatment, other receptors were unaffected by SCH 23390 pretreatment. *D*-amphetamine has been shown to dose dependently enhance extracellular DA concentration, serotonin concentration, and norepinephrine concentration when administered systemically (Kuczenski & Segal, 1989; Kuczenski, Segal, Cho, & Melega, 1995). Future studies should pursue the role of activity at DA D_2 –like, serotonin, and

norepinephrine receptors in context valuation during baseline conditions and subsequent behavioral persistence.

While pretreatment with SCH 23390 did not affect the *d*-amphetamine enhanced relative persistence, pretreatment with SCH 23390 blocked the amphetamine-enhanced relative reinstatement of food-seeking. Treatment with SCH 23390 alone had no impact on the relative reinstatement of behavior. Thus, SCH 23390 appears to have impacted reinstatement only when given in combination with *d*-amphetamine-specific actions on relapse. Previous research has shown similar findings in which the direct effect of treatment with SCH 23390 blocked context-induced recovery of extinguished responding while having no direct impact on extinguished responding (Hamlin et al., 2006). In the present experiment, however, SCH 23390 was administered in conjunction with *d*-amphetamine during a discrete treatment period. Therefore, the current results suggest that in addition to the direct effects of SCH 23390 on relapse, a history of DA D_1 receptor antagonism also impacts the differential relapse of food-seeking.

Behavioral momentum theory states that both the persistence of behavior under conditions of disruption and the subsequent degree of relapse are context-dependent. Contexts obtain their value through association with rates of reinforcement received in their presence. The results from the present experiment suggest that like the rate of reinforcement, treatment with d-amphetamine in a context yields more persistent behavior in extinction and a greater degree of relapse. The impact of *d*-amphetamine on the persistence of

behavior in extinction is likely due to enhanced activity at DA D_2 receptors, but enhanced activity at norepinephrine and serotonin receptors may also play a contributing role. The effect of *d*-amphetamine on DA levels at DA D_1 receptors appears to be more important for the relapse of behavior. Therefore, extracellular DA levels in the presence of a stimulus contribute to the persistence of behavior.

Within behavioral momentum theory, the persistence of behavior in extinction and relapse is described using the augmented model of extinction and relapse, that is, Equation 5 (Nevin & Grace, 2000). Figure 6 shows a least-squares regression fit of Equation 5 to the mean extinction and reinstatement data in the saline and drug-associated contexts for the *d*-amphetamine, SCH 23390 and combination treatment groups. The data are presented as log proportions of treatment response rates in the drug and saline contexts during the first five successive sessions of extinction and the single session of reinstatement. For each group, mean data from the drug and saline contexts were fit simultaneously with independent values of the free parameters *c*, *d, a* and *m* in the two contexts using Microsoft Excel Solver. The initial value for *c* was 1.0, *d* was 0.001, *a* was 0.5, and *m* was 0. The initial values for *c*, *d,* and *a* were chosen based on commonly obtained values, where as the initial values of *m* was chosen based on the theoretical predictions of Podlesnik and Shahan (2009). Additionally, the value of *r* was allowed to vary from the initial obtained reinforcer rates in the two contexts, but the initial and obtained values of *r* did not differ among contexts or treatment groups. Obtained reinforcer rates in the two

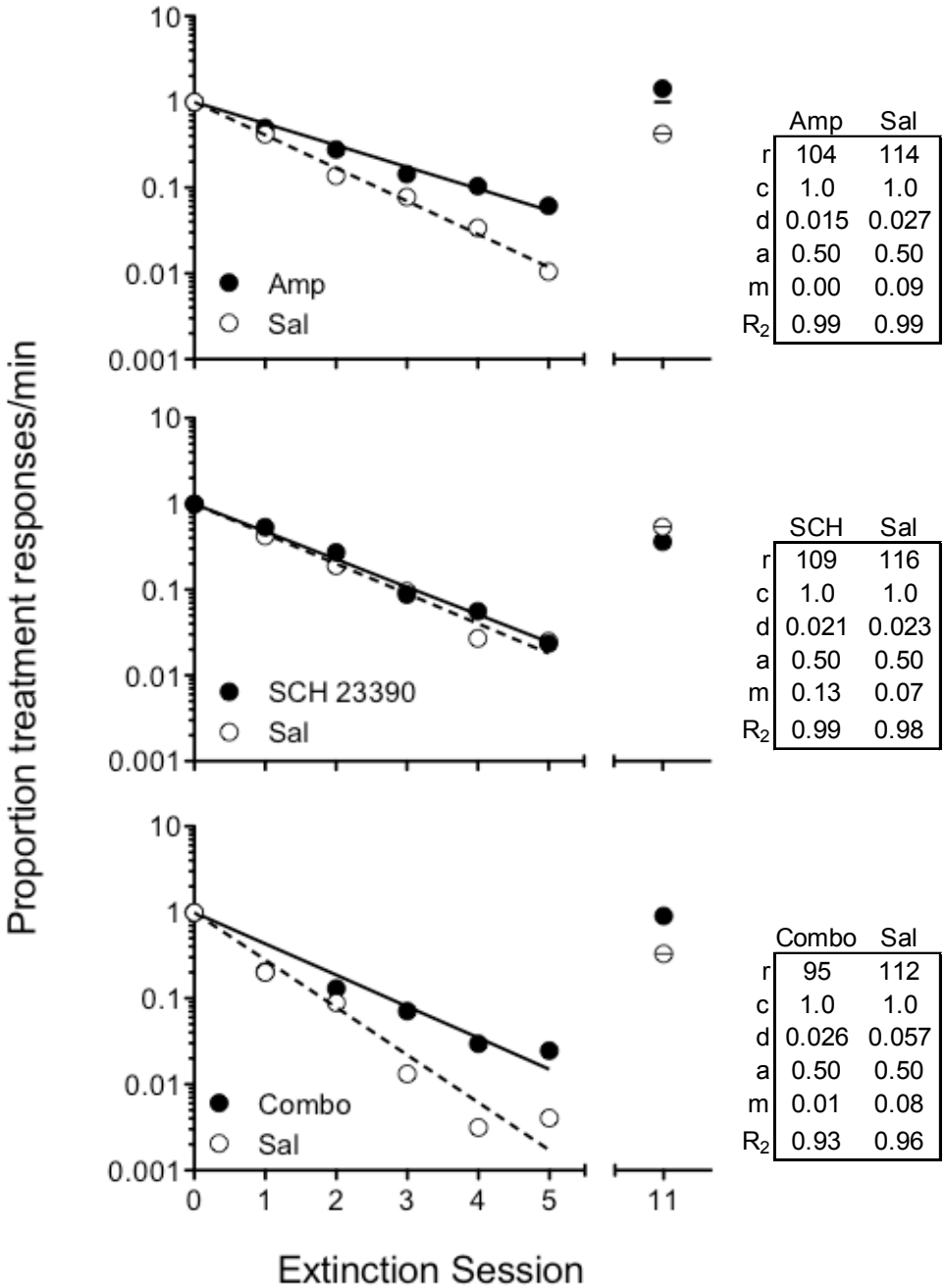

Figure 6. Model Fits to Mean Resistance to Change in Drug Treatment Groups. Fit of the augmented behavioral momentum model of resistance to extinction and relapse (i.e., Equation 5) to mean data from the drug and saline-associated contexts for the Amp, SCH 23390, and Combo drug treatment groups. Obtained parameter values and variance accounted for are also shown. See text for details.

contexts (i.e., *r*) were scaled as the number of food deliveries per hour (i.e., Amp group: Drug = 1.73/min = 104/hour, Saline = 1.90/min = 114/hour; SCH 23390 group: Drug = 1.82/min = 109/hour, Saline = 1.94/min = 116/hour; Combo group: Drug = 1.58/min, 95/hour, Saline = 1.87/min = 112/hour).

Thus, with four free parameters (i.e., *c*, *d, b, and m*), Equation 5 accounted for 99% of the variance in the drug and saline contexts for the amphetamine treatment group. For the SCH 23390 group, Equation 5 accounted for 99% of the variance in the drug context and 98% of the variance in the saline context. For the combo group, Equation 5 accounted for 93% of the variance in the drug context and 96% of the variance in the saline context. Overall, Equation 5 appears to provide a good account of the effects of indirect DA agonism, DA D_1 antagonism and a combination of DA D_1 antagonism and indirect DA agonism in a context on the persistence and relapse of food seeking. The obtained parameter values of *c* and *a* are also consistent with previously obtained values in the behavioral momentum analysis of food-maintained behavior (Nevin, 2002). The obtained values of *m* seem to be much less than the obtained values of *m* in the most recent analyses of the behavioral momentum of relapse (Podlesnik & Shahan, 2009, 2010). Smaller *m* values suggest a greater release from the impact of extinction during the reinstatement test. This difference likely stems from the difference in the type of reinstatement test used. In the present experiment, reinstatement was triggered by presenting noncontingent food deliveries at the same rate as in baseline and treatment. Most reinstatement

tests, however, use a much lower rate of reinforcement to trigger relapse. In many cases, reinstatement is triggered with a few free food deliveries at the session onset.

Interestingly, comparison of parameter estimates among the three groups reveal some suggestion for the mechanism by which DA manipulations may interact with the environmental determinants of behavioral momentum. The main differences observed in these fits are in the *d* parameter estimates. As discussed previously, the *d* parameter represents the scaled impact of omitting reinforcers, which reflects generalization decrement from baseline to extinction conditions. In the present experiment, the *d* parameter is roughly 1.8 times greater for the saline context relative to the amphetamine context and 1.7 times greater for the saline context relative to the combo context. The *d* parameter estimates did not differ across the SCH 23390 and saline contexts. In general, greater *d* values indicate greater disruption due to reinforcer omission.

One possible interpretation is that treatment with *d*-amphetamine decreased the impact of reinforcer omission in the drug context, which may be a result of the shift to more habitual stimulus-driven behavior. So, although the actual reinforcer rates were similar across contexts, the perceived reinforcer rate was greater in the saline context relative to the contexts associated with *d*-amphetamine. This interpretation corresponds to the effect of *d*-amphetamine on endogenous levels of DA in the brain. The brain regularly emits DA in a tonic firing pattern, when a reward or reward-related cue is presented there is a phasic

spike in DA activity. The tonic level of DA may affect the way in which phasic signals are interpreted (Robbins & Everitt, 1992). High tonic levels of DA may mask phasic DA signals in response to reward. Shifts in tonic DA levels may correspond to the shift from goal-directed to habit-directed behaviors (Everitt & Robbins, 2005). Therefore, the *d*-amphetamine enhanced behavioral persistence observed here appears to depend on differences in the impact of reinforcer omission, which may correspond with differences in DA tone. Further research is needed, however, to pursue precise quantifications of DA levels and activity to validate the correlations with *d* parameter values.

Limitations

As in any experiment, there are a few limitations that should be considered when interpreting the results of this experiment. The first limitation was that the injection procedure for the combo treatment group may have served as a signal for which context was in effect. Specifically, rats in the combo groups received an injection of SCH 23390 and then an injection of *d*-amphetamine for each drug treatment. The rats only received one saline injection for each saline treatment. Therefore, two injections may have served as an extra cue for drug effects. Future studies should include the same number of injections for treatment across contexts. This could be achieved by mixing the SCH 23390 and *d*-amphetamine into one syringe or by adding a second saline injection prior to the saline context.

Another possible limitation is the arrangement of multiple schedule components across days rather than within a session. One of the strengths of behavioral momentum theory is that the theory includes a procedural framework for assessing the impact of the Pavlovian stimulus-reinforcer relation on the relative persistence of behavior. Most commonly, behavioral momentum research uses a multiple schedule of reinforcement in which contexts alternate within a session. For example, Nevin et al. (1983) used a two-component multiple schedule in which contexts alternated 30 times within the session. Resistance to change analyses, however, are not restricted to the use of a two-component multiple schedule with contexts that alternate repeatedly within a session. In many cases the multiple schedule is modified in order to address aspects of the research question.

In this dissertation, multiple schedule components were alternated across days rather than within a session. Alternating components across days may be subjectively more similar to a single schedule of reinforcement than a multiple schedule of reinforcement. The similarity to single schedules of reinforcement may change the variables that determine the persistence of behavior. In multiple schedule arrangements, contexts associated with higher rates of reinforcement yield greater relative resistance to extinction whereas in single schedule arrangements, however, higher rates of reinforcement yield lesser relative resistance to extinction (Shull & Grimes, 2006). The inverse relation between

relative reinforcement rate and relative resistance to extinction has been likened to the PREE.

As discussed previously, PREE refers to the commonly observed result in which behavior is more persistent following intermittent reinforcement than following continuous reinforcement (see Mackintosh, 1974; Nevin, 1988, for reviews). At first glance, PREE seems to be contradictory to the tenets of behavior momentum theory because intermittent schedules of reinforcement would yield a lower rate of reinforcement than continuous schedules of reinforcement. The augmented model of extinction, as shown in Equation 4, accounts for the partial reinforcement extinction effect by including two separate parameters for the effects of extinction on behavior (Nevin & Grace, 2000). The parameter *c* represents the disruptive impact of suspending the response-reinforcer contingency while the *d* parameter represents the disruptive impact of omitting reinforcers. The *d* parameter is, therefore, capable of adjusting the disruptive impact of generalization decrement from baseline to extinction conditions. Generalization decrement from baseline to extinction is greater for continuous schedules of reinforcement relative to intermittent schedules of reinforcement because the switch to extinction is more discriminable following continuous schedules of reinforcement. So, in Equation 4, continuous schedules of reinforcement would have larger *d* values than intermittent schedules of reinforcement, which increases the numerator value and yields greater behavioral persistence.

Equation 4 has been successfully fit to a variety of data sets exhibiting PREE. For example, Shull and Grimes (2006) used Equation 4 to reconcile the inverse relation between reinforcement rate and resistance to extinction found in single schedules of reinforcement with behavioral momentum theory. In the first experiment, single VI schedules were arranged in blocks of twenty sessions. Each block was followed by a single extinction session. Resistance to extinction was higher in VI blocks that arranged lower rates of reinforcement, which is consistent with the PREE. The obtained PREE was well described by Equation 4. Equation 4 also accounted for the resistance to change functions found in the second experiment. In the second experiment, resistance to extinction was found to be a positive function of the magnitude of reinforcement in single schedules of reinforcement. Therefore, the augmented model of extinction accounts for the resistance to extinction of behavior in both single and multiple schedules of reinforcement. The multiple schedule with components that alternate across days used in this experiment may be perceived as experience in two single schedules of reinforcement. This perception, however, should not affect the ability of behavioral momentum theory to account for the data given precedence of the theory accounting for the persistence of behavior regardless of schedule type. Although this dissertation was the first to test behavioral momentum predictions by arranging a multiple schedule that alternates across days, this arrangement is predicted to yield results that can be well described by the augmented model of extinction and relapse. As discussed previously, Equation 4 provides a good

description of the resistance to extinction and relapse of food seeking in the drug and saline contexts in each of the drug treatment groups.

A third limitation of this dissertation is that modulation of the dopaminergic system may affect other neurotransmitter systems as well. As discussed briefly above, *d*-amphetamine modulates dopaminergic, serotonergic, and adrenergic activity. The primary action of *d*-amphetamine appears to be in the mesolimbic reward circuitry. *D*-amphetamine induced DA release in the ventral striatum, for example, is highly correlated with the euphoric effects of the drug (Drevets et al., 2001). There is some evidence however, that norepinephrine (NE) may also contribute to the subjective effects of *d*-amphetamine (Rothman et al., 2001). Despite contribution to the subjective effects of norepinephrine, lesions to the locus coeruleus, which results in depletion of NE levels, have been shown to increase resistance to extinction of a Pavlovian conditioned nictitating membrane response in rabbits (McCormick & Thompson, 1982). Additionally, administration of the autoinhibitory α_2-receptor agonists, yohimbine, which enhances NE levels, facilitated the extinction of cue and context conditioned responses in mice (Cain, Blouin, & Barad, 2004). These previous findings conflict with the present results indicting that a history of *d*-amphetamine treatment, which may increase norepinephrine levels, enhanced resistance to extinction. Thus, it may be that norepinephrine plays an opposing role to DA during extinction conditions. These studies assessed the direct effect of adrenergic manipulations rather than the long-term effects of a history of adrenergic manipulations. Further research is

needed to dissociate the impact of a history of norepinephrine and DA manipulations on the persistence of behavior.

Future studies may provide more information regarding the role of DA and norepinephrine by using the methodology in this study to assess the impact of a direct DA agonist on the persistence of behavior in one group of animals and compare to the impact of an autoinhibitory α_2-receptor agonist on the persistence of behavior. Results from previous studies in combination with the present experiment would suggest that a history of elevated DA levels would enhance the relative persistence of behavior, whereas a history of elevated NE levels would diminish the relative persistence of behavior. Another way to determine the impact of adrenergic activity would be to treat rats with a combination of *d*-amphetamine and a β-receptor antagonist. The persistence of behavior in the presence of the combination treatment associated context could then be compared to a within subject saline context as well as a group treated with *d*-amphetamine alone. If adrenergic activity facilitates extinction of responding then behavior should be relatively less persistent in a context associated with *d*-amphetamine alone than a context associated with *d*-amphetamine and a β-receptor antagonist.

Conclusion

In conclusion, the present experiment is the first attempt to incorporate the neural and behavioral mechanisms of the persistence of behavior using

behavioral momentum theory. The results from this study allow behavioral momentum theory to incorporate the impact of the neurotransmitter DA on the stimulus-reinforcer relation into explanations of behavioral persistence. The persistence of behavior in a context may then be predicted based on the known rates of reward and DA activity associated with that context. The results of this dissertation provide several directions for future research. These results allow us to begin to address the neural mechanisms of the resistance to change of behavior. Future studies may pursue the impact of site-specific DA agonism and antagonism in various areas of the mesolimbic circuit including the accumbens, VTA, amygdala, and prefrontal cortex. These procedures may also be useful for understanding the role of other neurotransmitters including, norepinephrine, glutamate, and GABA in determining the persistence of behavior. The present results also provide support for the utility of behavioral momentum theory in studying the interaction between neural and environmental determinants of the persistence of behavior. The ability to make precise quantifications of neurotransmitter impact may be possible through in-vivo recording of neurotransmitter activity during baseline, treatment, extinction and relapse of behavior. In conjunction with the present results, future studies will allow for precise localization and quantification of the neural and environmental determinants of the persistence of behavior and may prove useful for understanding the persistence of behavior in a variety of psychological disorders.

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Wyvell, C. L., & Berridge, K. C. (2001). ncentive sensitization by previous amphetamine exposure: Increased cue-triggered "wanting" for sucrose reward. *The Journal of Neuroscience*, *21*(19), 7831-7840.

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EDUCATION

2010 (May) Ph.D., Psychology (Behavior Analysis Emphasis)

Utah State University

Advisor: Timothy A. Shahan, Ph.D.

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2005 M.A., Psychology

Queens College of the City University of New York

Advisor: Robert Ranaldi, Ph.D.

2003 B.S., Psychology

University of Florida

AWARDS

2010 Graduate Research Assistant of the Year

Emma Eccles Jones College of Education and Human Services, Utah State University

2009 1st Place Poster: College of Education and Human Services

11th Annual Intermountain Graduate Research Symposium

2008 Walter R. Borg Scholarship

Psychology Department, Emma Eccles Jones College of Education and Human Services, Utah State University

2003 Science Fellowship

Graduate Center at City University of New York

2002 University Scholar's Program Award

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PROFESSIONAL ACTIVITIES

Research Positions

2009-2010 Research assistant, Behavioral Momentum of Cocaine Self-Administration.

Department of Psychology, Utah State University.

Principal investigator: Timothy A. Shahan, Ph.D.
Extending behavioral momentum theory and methods to cocaine self-administration in rats.

2007-2008 Research assistant, Resistance to Change of Methamphetamine Self-Administration.

Department of Psychology, Utah State University.

Principal investigator: Timothy A. Shahan, Ph.D.
Extending behavioral momentum theory and methods to methamphetamine self-administration in rats.

2005-2006 Research assistant, Divided Attention and Reinforcement Variables

Department of Psychology, Utah State University.

Principal investigator: Timothy A. Shahan, Ph.D.
Assessing the impact of reinforcement on divided attention performance in pigeons.

2003-2005 Research Assistant, Neuroscience of Learning and Motivation.

Department of Neuroscience, Queens College at the City University of New York.
Principal Investigator: Robert Ranaldi, Ph.D.

Assessing the role of the VTA in behavior maintained by cocaine, heroin, or food.

2002-2003 University Scholar, Interresponse Times and Fixed-Ratio Schedules.

Co-investigator: Marc N. Branch, Ph.D.

Investigating a novel procedure to enhance performance on fixed-ratio schedule behavior in pigeons.

Organizational Service

Student Representative: EAPS subprogram, Psychology Department. Utah State University

GRANTS

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Utah State University, Graduate Student Senate

Project Dates 8/24/09 – 4/30/10

Total Costs $1,000

PUBLICATIONS

Quick, S. L., & Shahan, T. A. (2009). Behavioral momentum of cocaine self-administration: effects of frequency of reinforcement on resistance to extinction. *Behavioral Pharmacology,* 20(4), 337-334.

Lee, D. Y., Guttilla, M., Fung, K. D., **McFeron, S.**, Yan, J., & Ranaldi, R. (2007). Rostral-caudal differences in the effects of intra-VTA muscimol on cocaine self-administration. *Pharmacology, Biochemistry & Behavior,* 86*,* 542-549.

CONFERENCE PRESENTATIONS

Quick, S. L. & Shahan, T. A. (2009, May). *Behavioral Momentum of Cocaine Self-Administration: Effects of Frequency of Reinforcement on Resistance to Extinction.* Poster presented at Society for Quantitative Analysis of Behavior Convention, Phoenix, AZ.

Quick, S. L. & Shahan, T. A. (2009, March). Behavioral Momentum of Cocaine Self-Administration: Effects of Frequency of Reinforcement on Resistance to Extinction. Poster presented at 12th annual *Intermountain Graduate Research* Symposium. Logan, UT

Quick, S. L. & Shahan, T. A. (2008, May). *Context Valuation: The Effects of d-Amphetamine on the Persistence of Behavior Previously Maintained by Food.* Poster presented at the 34th annual Association of Behavior Analysis International Convention, Chicago, IL.

Quick, S. L. & Shahan, T. A. (2008, March). *Cocaine Cues and the Persistence of Drug Seeking.* Symposium talk at the 11th annual *Intermountain Graduate Research* Symposium. Logan, UT.

Quick. S. L., Jiminez-Gomez, C., & Shahan, T. A. (2007, May). *Behavioral momentum of cocaine self-adminsitration.* Symposium talk at the 33rd annual Association of Behavior Analysis International Convention, San Diego, CA.

Lee, D. Y., Gutilla, M., **McFeron, S. L.**, Yan, J. & Ranaldi, R. R. (2005, November). *Microinjections of muscimol in the ventral tegmental area decrease rate of intravenous cocaine self-administration in rats.* Poster presented at the 35th annual meeting of the Neuroscience conference, Washington, D.C.

McFeron, S. L., & Ranaldi, R. R. (2005, April). MK-801, an NMDA receptor antagonist, fails to block behavioral sensitization to cocaine. Poster presented at the 9th annual meeting of the NEURON Conference, New York, New York.

Quick, S. L., Branch, M., Yoon, Jin. (2002, November) An Automated Shaping Procedure. University of Florida. Poster Session at the 2002 Southeastern Association of Behavioral Analysis Conference, Charleston, South Carolina.

TEACHING EXPERIENCE

2010 (Spring)	Instructor, Physiological Psychology (Psyc 3460). Utah State University
2008-2009 (Fall-Spring)	Instructor, Research Methods and Scientific Thinking (Psyc 3500). Utah State University

2008 (Summer)	Instructor, Analysis of Behavior: Basic and Lab (Psyc 1400, online). Utah State University
2005 (Summer)	Instructor, Developmental Psychology: Aging and Older Adulthood (Psy 216). Queens College at the City University of New York

PROFESSIONAL MEMBERSHIPS

2007-Present	Member of Society for Quantitative Analysis of Behavior
2002-Present	Member of Association for Behavioral Analysis
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