EFFECTS OF NICOTINE ON RESPONDING UNDER EXTINCTION IN THE PRESENCE AND ABSENCE OF STIMULI PREVIOUSLY PAIRED WITH SUCROSE

By

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Nicotine increases responding maintained by some moderately reinforcing visual stimuli. Research suggests the drug may serve to enhance the value of these reinforcers (i.e., nicotine may serve as a motivating establishing operation [MEO]). The purpose of the current study was to investigate whether this effect would generalize to a procedure adapted from Files, Branch, and Clody (1989). Rats were exposed to a second-order schedule consisting of contingent visual stimuli occasionally paired with food. Following exposure to this schedule, sessions ended in one of two extinction components: a) standard extinction in which no programmed consequences were available or b) food-paired stimulus extinction in which food was no longer available, but contingent presentation of food-paired stimuli remained available. Rats received acute pre-session subcutaneous injections of 0.03, 0.1, 0.3, and 0.56 mg/kg nicotine and vehicle (Experiment 1) and chronic injections of 0.3 mg/kg nicotine and vehicle (Experiment 2). Nicotine had no effect on responding maintained by food-paired stimuli relative to responding when these stimuli were unavailable. Thus, the ability of nicotine to serve as a MEO either did not generalize to or was undetectable within the experimental context used in the current study. These results reveal that the reinforcement-enhancing effect of nicotine is not as robust as previous research suggests. Results of Experiment 1, however, suggest another potential effect

of nicotine on responding—the drug may interfere with the control some stimuli have over behavior.

CHAPTER 1
INTRODUCTION

Cigarette smoking is the leading cause of preventable death in the United States, resulting in approximately 438,000 deaths each year and costing roughly $167 billion in annual health-related economic losses (Centers for Disease Control and Prevention, 2005). In addition to its devastating impact on the US, smoking is also the leading cause of preventable death in the world (World Health Organization, 2003). Globally, five million deaths are attributed to smoking each year. By 2023, this rate is expected to increase to 10 million deaths annually as the number of smokers in developing countries increases (World Health Organization, 2003).

If there is any good news to emerge from research on the smoking epidemic, it is that 70% of smokers report a desire to quit (Schwartz, 1992). Without treatment intervention, however, only three percent each year are successful and able to maintain abstinence for at least six months (Shiffman, Mason, & Henningfield, 1998). Among the many treatment options available (e.g., pharmacotherapy, behavioral programs, counseling, hypnosis, etc.), the most commonly studied and used is nicotine replacement therapy (NRT). Currently, there are six types of NRT products on the market; yet, despite its prevalence as an over-the-counter treatment alternative, research has shown NRT aids cessation for only about 14% of those who use it (Shiffman, Mason, & Henningfield, 1998).

The limited success of smokers who attempt to quit with the aid of NRT alone suggests that other factors aside from the direct reinforcing effects of nicotine play a role in the maintenance of smoking. Although the exact nature of these other behavioral mechanisms is still unclear, recent research involving intravenous nicotine self-administration procedures in rats suggests that nonpharmacological stimuli play an important role in the acquisition and

maintenance of this behavior (Caggiula et al., 2002b; Chaudhri et al., 2005, 2006a, 2007; Donny et al., 2003; Palmatier et al., 2006, 2007a, 2007b).

The majority of researchers who have successfully demonstrated nicotine self-administration in rats typically paired nonpharmacological stimuli (e.g., light/dark presentation, tone, etc.) with nicotine (e.g., Caggiula et al., 2002b; Donny et al., 2003; DeNoble & Mele, 2005; Harris, Pentel, & LeSage, 2007; O'Dell & Koob, 2007). In fact, very few researchers have shown that rats will respond for contingent nicotine alone. Those who have successfully demonstrated nicotine self-administration in the absence of additional nonpharmacological stimuli found relatively low rates of self-administration (Caggiula et al., 2002b; Chaudhri et al., 2005, 2006a, 2007; Donny et al., 2003; Palmatier et al., 2006). Some studies have even demonstrated lower rates of responding for nicotine than for a light/tone stimulus complex (Chaudhri et al., 2006a; Palmatier et al., 2006); although response rates across all of these studies reliably increased well above rates maintained by either nicotine or nonpharmacological stimuli alone when the two reinforcers were combined. It is important to note, however, that even when nicotine is paired with nonpharmacological stimuli, responding maintained by these reinforcers is relatively low compared to responding maintained by other primary reinforcers including some non-nicotine drugs (e.g., Mierzejewski, Koros, Goldberg, Kostowski, & Stefanaski, 2003).

However low rates of nicotine self-administration may be, the finding that nicotine does, indeed, maintain responding has been reliable across studies (Caggiula et al., 2002b; Chaudhri et al., 2005, 2006a, 2007; DeNoble & Mele, 2005; Donny et al., 2003; Harris et al., 2007; O'Dell & Koob, 2007; Palmatier et al., 2006, 2007a, 2007b; Shoaib et al., 1997). Further, the importance of nonpharmacological stimuli in the acquisition and maintenance of nicotine self-administration has also been clearly demonstrated (Caggiula et al., 2002b; Chaudhri et al., 2005, 2006a, 2007;

Donny et al., 2003; Palmatier et al., 2006, 2007a, 2007b)—the behavioral mechanism responsible for this observation, however, is still unclear.

One possibility is that nicotine simply establishes environmental stimuli as conditioned reinforcers after repeated pairings with the stimuli. Contingent presentation of previously neutral or weakly reinforcing stimuli that have been reliably paired with primary reinforcers will increase responding as a result of Pavlovian conditioning (Fantino, 1977). For this reason, the presentation of environmental stimuli associated with the subjective effects of drugs of abuse can enhance self-administration (Carter & Tiffany, 1999). Nicotine may therefore function to increase the reinforcing properties of the various environmental stimuli present when people smoke (e.g., the sight, smell, and taste of cigarette smoke). If smoking results in the contingent presentation of nicotine as well as those stimuli that have been previously paired with nicotine, then the behavior should be strengthened (Carmody, 1990).

Two recent studies have shown that responding maintained by 0.03 mg/kg and 0.06 mg/kg nicotine infusions in rats increases significantly when the drug is paired with a contingent visual stimulus and decreases when the visual stimulus is removed (Chaudhri et al, 2005; Donny et al., 2003). If the nonpharmacological stimuli used in these studies obtained their value by virtue of repeated pairings with nicotine, a primary albeit weak reinforcer, Pavlovian conditioning could explain these results. However, this behavioral process cannot explain all of the recent findings on the effects of nicotine on responding in the presence of nonpharmacological stimuli. Consequently, alternative hypotheses have been raised to explain the role environmental stimuli play in nicotine self-administration.

Results of numerous studies suggest that nicotine may enhance the reinforcing properties of primary reinforcers through some behavioral process other than, or in addition to, Pavlovian

conditioning. For example, Donny, et al. (2003) found that noncontingent (i.e., response-independent) nicotine administration enhanced responding for visual stimuli. The response-dependent visual stimuli presented in this study and the response-independent nicotine infusions were never reliably paired. Consequently, it is unlikely that the nonpharmacological stimuli became conditioned reinforcers. As a result of these and other similar findings, Caggiula et al. (2002a) hypothesized that nicotine increases responding in the presence of nonpharmacological stimuli through non-associative processes. In other words, the researchers proposed that a contingent relationship between nicotine and weakly reinforcing nonpharmacological stimuli is not required to enhance responding maintained by the stimuli. Chaudhri et al. (2006b) suggested that nicotine enhances the reinforcing efficacy of primary reinforcers—even relatively weak primary reinforcers such as visual stimuli. The pharmacological effects of nicotine may then serve as a motivating establishing operation (MEO) for some unconditioned primary reinforcers. An MEO is any event, operation, or stimulus that enhances the reinforcing efficacy of other environmental stimuli and enhances responding maintained by those stimuli (Laraway, Snycerski, Michael, & Poling, 2003). Thus, if nicotine establishes nonpharmacological stimuli as more efficacious reinforcers, and nicotine self-administration results in access to those reinforcers, then the behavior should be strengthened.

A related hypothesis regarding the function of nicotine self-administration is that the drug enhances the value of conditioned reinforcers that obtain their value by virtue of repeated pairings with other non-nicotine stimuli. In other words, nicotine may serve as an MEO, not for primary reinforcers, but for previously established conditioned reinforcers. Research on the effects of other stimulant drugs suggests that some stimulants (e.g., methylphenidate) may enhance responding maintained by stimuli previously paired with food (Files, Branch, & Clody,

1989). Further, Olausson, Jentsch, and Taylor (2004) demonstrated that, in rats, nicotine enhanced acquisition of a new response maintained by contingent nonpharmacological stimuli previously paired with water. The researchers concluded that nicotine may enhance the value of conditioned reinforcers previously paired with other nonpharmacological primary reinforcers. However, the results of Olausson et al. (2004) may be confounded by the ability of nicotine to enhance the reinforcing properties of weak primary reinforcers regardless of any conditioned reinforcing value. In fact, a study conducted by Chaudhri et al. (2007) demonstrated that nicotine delivered contingently and noncontingently enhanced responding for a nonpharmacological stimulus complex regardless of previous pairings of the stimulus complex with sucrose.

Another explanation that may account for the role nonpharmacological stimuli play in the acquisition and maintenance of nicotine self-administration can be traced to procedural variables. Within-session intravenous nicotine administration is most often the method used in studies examining the effects of the drug on responding maintained by nonpharmacological stimuli. In fact, this was how nicotine was administered in all but two such studies cited above, Olausson et al. (2004) and Palmatier et al. (2007b). One potential limitation of this method is that even nicotine delivered noncontingently within sessions is occasionally administered within close temporal proximity to response-contingent visual stimuli. Consequently, it is possible that responding maintained by nonpharmacological stimuli in previous studies was a result of adventitious reinforcement. When nicotine was delivered noncontingently, occasional pairings of the drug with the contingent nonpharmacological stimulus may have been enough to maintain responding followed by that stimulus—an effect that may have been magnified due to a lack of discrimination as to when the drug was delivered.

Some evidence suggests that the subjective effects of nicotine (especially at lower doses) may not be salient enough for rats to discriminate exactly when the drug is administered. In a study conducted by Chaudhri et al. (2005), for example, responses on an active lever resulted in delivery of either 0.03 or 0.06 mg/kg contingent nicotine (depending on random group assignment), and responses on an inactive lever resulted in no programmed consequences. The results demonstrated that the rats' response rates in both groups on both active and inactive levers were very similar. For another group of rats in the same study, responding on the active lever resulted in the delivery of a comparatively higher dose of nicotine (0.15 mg/kg nicotine infusions). In this group, response rates were much lower on the inactive lever compared to response rates on the inactive lever in the groups in which lower doses of nicotine were the scheduled consequences. Based on the finding that a clear preference for responding on the active lever over the inactive lever developed when a higher dose of nicotine was the consequence, it is not unreasonable to assume that responding maintained by nicotine alone at lower doses might, in fact, occur more frequently if the consequence (i.e., nicotine administration) was simply easier to discriminate. Nonpharmacological stimuli paired with nicotine administration aids in such discrimination.

It therefore stands to reason that the value of environmental stimuli may not be enhanced per se; rather, the stimuli may serve as more salient sensory stimulation than nicotine infusions alone in signaling the delivery of the drug and the subjective effects that follow. Thus, when nicotine is delivered noncontingently within a session, it is reasonable to suggest that responding may be maintained by nonpharmacological stimuli as a result of adventitious reinforcement. That is, responding may be a adventitiously reinforced when the subject is unable to discriminate infusions of low doses of nicotine, but the subject is able to discriminate that the subjective

effects of the drug occasionally follow responses maintained by other more salient nonpharmacological stimuli.

It is possible to investigate the effects of nicotine on responding maintained by nonpharmacological stimuli in rats without delivering the drug within sessions. For example, using an observing-response procedure, Raiff and Dallery (2006) administered pre-session nicotine injections in a study examining the effects of acute and chronic nicotine administration on responding maintained by primary and conditioned reinforcers. The researchers found that nicotine administration resulted in an increase in responding maintained by conditioned reinforcers. Further, Palmatier et al. (2007b) found that pre-session nicotine administration increased responding maintained by the termination of a houselight—a moderate primary reinforcer. Similar to the procedures used by Raiff and Dallery (2006) and Palmatier et al. (2007b), in the current study, nicotine injections were administered prior to experimental sessions in order to avoid coincidental pairings between within-session intravenous nicotine administration and response-contingent nonpharmacological stimulus presentation.

Some researchers have argued that other procedural variables may also account for the finding that nicotine serves as a MEO. Frenk and Dar (2004) suggested that increases in responding maintained by visual stimuli following nicotine administration in the study conducted by Donny et al. (2003) as well as other similar studies may not be attributed to a reinforcement-enhancing effect. The authors argue that nicotine non-specifically activates a variety of behavior, including locomotion. Thus, increases in responding maintained by visual stimuli following nicotine administration may be due to general activation.

The purpose of the current study was to further examine the effects of nicotine on responding maintained by visual stimuli previously paired with food. If nicotine establishes

nonpharmacological stimuli as more effective primary or conditioned reinforcers, then pre-session nicotine administration should increase responding maintained by food-paired stimuli. The experimental design is a systematic replication of an experiment conducted by Files, Branch, and Clody (1989). Files et al. examined the effects of methylphenidate on pigeons responding under extinction in the presence and absence of stimuli previously paired with food. At the beginning of each session, key-pecking was maintained by a nonpharmacological stimulus complex occasionally paired with 3 sec access to mixed grain on a second-order RR 2 (VI 30:S) schedule (see Experiment 1 Methods for a description of this schedule). The stimulus complex was comprised of a tone, alterations to key color, and the termination of a houselight. The occasional pairings of the stimulus complex with brief access to grain were utilized so that the food would impart conditioned reinforcing value to the stimulus complex. After a history of training on this schedule, sessions were shortened and followed by one of two extinction components. In the first component, "standard extinction" was in effect. During this component, there were no programmed consequences for key-pecking. In the second component, "conditioned reinforcement extinction" was in effect. During this component, food was no longer available; however, the stimulus complex remained contingent on key-pecking. The researchers found minimal differences between response rates during both types of extinction components prior to drug administration. In other words, response-contingent presentation of stimuli previously paired with food did not maintain higher rates of responding relative to rates of responding in a condition in which no programmed consequences were contingent on responding. Thus, the food-paired stimuli did not appear to function as reinforcers. After methylphenidate was administered however, the drug was shown to increase responding more during the "conditioned reinforcement extinction component" (i.e., when the

food-paired stimuli were still available) than during the "standard extinction component." One interpretation of these results is that the value of the nonpharmacological stimulus complex used in this study was enhanced by methylphenidate. That is, the effects of the drug may have served as an MEO that established the nonpharmacological food-paired stimuli as more effective reinforcers.

Similar procedures were used in the current study; however, the effects of nicotine on lever-pressing in rats were investigated rather than the effects of methylphenidate on key-pecking in pigeons. The procedures used by Files et al. (1989) were adapted to test whether or not the finding that nicotine serves as an MEO for primary or conditioned reinforcers would generalize to this relatively novel experimental design. Experiment 1 was designed to examine the effects of acute nicotine on responding under extinction in the presence versus the absence of food-paired stimuli. Experiment 2 was designed to examine the effects of chronic nicotine on responding under extinction in the presence versus the absence of these stimuli. If nicotine serves as an MEO for nonpharmacological primary or conditioned reinforcers, then pre-session drug administration would be expected to increase responding under extinction when stimuli previously paired with food are available relative to responding under extinction when those stimuli are unavailable.

CHAPTER 2
EXPERIMENT 1

Method

Subjects

Six experimentally naïve adult male Long-Evans hooded rats (Harlan; Indianapolis, IN) approximately 5 months old at the beginning of the experiment were used. Subjects were housed individually in a windowless colony room in clear polycarbonate cages with bedding under a 12/12 hr light/dark cycle (lights on at 8 A.M) maintained between 22 °C and 25 °C. Each rat had free access to water and was maintained at 85% of its free-feeding weight (402-447 g) by post session feeding of Lab Diet® 5001 Rodent Diet delivered as needed immediately after each session.

Apparatus

Sessions were conducted in six 30.5 cm long x 24 cm wide x 29 cm high experimental chambers (MED Associates®; St. Albans, VT). Chambers were enclosed in separate light- and sound-attenuating cubicles. A white-noise generator was located in the laboratory to mask extraneous noise. Each chamber contained a 28 V yellow houselight mounted 1.5 cm below the ceiling on the wall opposite the intelligence panel. Two levers (2 cm long x 4.5 cm wide) requiring approximately 0.3 N of force were located on the intelligence panel 7 cm above the chamber floor. Centered 7 cm above each lever and 0.7 cm apart were three horizontally aligned LEDs. From left to right, the LEDs were colored red, yellow, and green. A food receptacle (5 cm wide x 5 cm high x 3 cm deep) was centered between the two levers (3.5 cm from each lever) 1.5 cm above the chamber floor. The food receptacle was connected to an automated pellet dispenser located outside the experimental chamber. Forty-five mg sucrose pellets (Test Diet®

AIN-76A Rodent Tablet) were dispensed individually. Med-PC hardware and software were used to arrange and record experimental events.

Procedure

Training

Throughout all phases of Experiment 1, sessions were conducted at approximately the same time each day, 7 days per week during the rats' light cycle. Before training began, the right lever was designated as the active lever for subjects 208, 210, and 212, and the left lever was designated as the active lever for subjects 209, 211, and 213. Responses on both levers were recorded; however, throughout all phases of the experiment, programmed consequences were only available on the active levers.

Lever-pressing was shaped by the method of successive approximation and was conducted over the course of two sessions that lasted 30 min each or until subjects earned approximately 40 pellets per session. Throughout all subsequent phases of training, sessions terminated after the delivery of 40 pellets. Following shaping, rats were exposed to 2 sessions of fixed-ratio (FR) 1. Beginning with exposure to FR 1, all sessions were preceded by a 5 min blackout period, during which the chamber remained dark and responses were recorded, but no programmed consequences were in effect. Illumination of the houselight signaled the start of each session. Responses on the active lever resulted in the delivery of one pellet, as well as a stimulus complex consisting of the following: first, the illumination of 3 LEDs directly above the active lever preceded pellet delivery by 0.5 sec; second, an audible click was presented simultaneously with the delivery of the pellet; third, a second audible click, the termination of the 3 LEDs, and the termination of the houselight, followed pellet delivery by 0.5 sec. The houselight remained off for 2 sec, during which responses were recorded, but no programmed

consequences were in effect. Rats were subsequently exposed to 3 sessions of variable-interval (VI) 10 sec, 15 sessions of VI 20 sec, and 45 sessions of VI 30 sec. Twenty VI values based on the Fleshler-Hoffman distribution (Fleshler & Hoffman, 1962) were used.

For the remainder of training (25 sessions), subjects were exposed to a second-order schedule. Under a second-order schedule, the completed requirement of one schedule serves as the unit that is reinforced on another schedule. In Experiment 1, rats were exposed to a random-ratio (RR) 2 of VI 30 sec (denoted RR 2 [VI 30:S]). Food was available on the RR component and the stimulus complex (S) was available on the VI component. In other words, completion of a VI 30:S schedule requirement resulted in the presentation of S, but not necessarily the delivery of a sucrose pellet. Only upon completion of the RR 2 schedule requirement was food delivered, and this component could only be satisfied by completing a VI 30:S schedule requirement. Each completion of a VI 30:S schedule requirement had a 0.5 probability of food reinforcement. Thus, on the RR 2 (VI 30:S), S was available on a VI 30 sec schedule, and approximately 50% of S presentations were paired with food.

Baseline

During baseline, all sessions began with the RR 2 (VI 30:S). In 1 out of every 10 sessions, this schedule remained in effect until the end of the session; that is, food was continuously available throughout these sessions until each session terminated following the delivery of 40 sucrose pellets. These sessions will hereafter be referred to as "non-extinction" sessions. All other sessions (i.e., approximately 90% of sessions) were comprised of two components. The first component, the RR 2 (VI 30:S) or "food component," terminated after the delivery of at least 10 but no more than 20 sucrose pellets were delivered (determined randomly by Med-PC software). Following the food component, one of two extinction components went

into effect for 20 min. During the "standard extinction component," the houselight remained on but no scheduled consequences were in effect. During the "food-paired stimulus extinction component," the VI 30:S remained in effect but no food was available; in other words, the same stimulus complex that was presented during the food component was still delivered contingent on responding until the session timed out. Subjects were not exposed to sessions ending in the same extinction component for more than three consecutive sessions.

Acute drug administration

Drug administration began after baseline rates of responding stabilized (i.e., no upward or downward trends in data were apparent; after 52 sessions). Nicotine hydrogen tartrate salt was dissolved in a potassium phosphate (KPO_4) solution (1.13 g/L monobasic KPO_4, 7.33 g/L dibasic KPO_4, 9 g/L NaCl in distilled H_2O) and administered via subcutaneous injection immediately prior to the session. Either vehicle (KPO_4), or 1 of 4 doses of nicotine (0.03, 0.1, 0.3, and 0.56 mg/kg) were administered on designated acute days twice per week if data collected on the previous day (designated control days) met the following criteria: response rates during neither the food component nor the extinction component on the previous session could be outside the range of the food and respective extinction component response rates in the preceding 10 non-acute sessions. Each subject completed approximately 100 sessions on average during the acute administration phase. Subjects received 2 administrations of each dose of nicotine and vehicle in ascending order (208, 209, and 210) or descending order (211, 212, and 213) immediately preceding sessions ending in both types of extinction; therefore, each subject received 4 administrations of each dose and vehicle. Repeated administration of nicotine doses in the same order for each subject allowed within-subject comparison of dose-response functions. Additionally, administration of nicotine doses in two different orders across subjects allowed

between-subject comparison of dose-response functions. This method was used to aid in the detection of any potential order effects.

Results

There were no differences in dose-response functions between those subjects that received doses of nicotine in ascending order relative to those that received doses in descending order. However, for all but one subject (211), response rates obtained during the food component were reliably lower after the first administration of the higher doses of nicotine (i.e., 0.3 and 0.56 mg/kg nicotine) relative to the second administration (data not shown). There was no systematic effect of order of administration within subjects or between subjects on responding under extinction.

Figure 2-1 shows responses per minute as a function of nicotine dose in each session component. The graphs reveal a consistent decrease in response rates in the food component across all subjects at the highest dose of nicotine, 0.56 mg/kg. However, there were no systematic differences in rates of responding under extinction in the presence versus the absence of food-paired stimuli.

Figure 2-2 illustrates responses per minute under each extinction component expressed as a percentage of responses per minute in the preceding food component for those sessions in which 0.3 mg/kg nicotine and vehicle were administered. Extinction response rates were not presented this way for all doses due to the minimal effect of nicotine on responding under extinction at lower doses and due to the rate-suppressing effect of the highest dose of nicotine (i.e., 0.56 mg/kg) on responding in the food component. Figure 2-2 shows that 0.3 mg/kg nicotine increased responding under extinction in the presence and the absence of food-paired stimuli relative to vehicle across all subjects. However, the figure does not show a reliable

increase in rates of responding in the food-paired stimulus extinction component relative to the standard extinction component.

After rats were exposed to sessions ending in extinction, we observed that rates of responding began to decrease in non-extinction sessions (i.e., those sessions in which food was continuously available throughout the session). Figure 2-3 illustrates the average responses per minute for each rat in non-extinction sessions before exposure to sessions ending in extinction (i.e., during the training phase) and after exposure to sessions ending in extinction (i.e., during the baseline and acute administration phases). The figure reveals that response rates decreased for all but one subject (208) after exposure to sessions ending in extinction.

Within-session analysis revealed that rates of responding decreased and became more variable approximately 15 min after the beginning of each non-extinction session—at roughly the same time that the food component would typically end and subjects would be exposed to extinction. Figure 2-4 is two representative cumulative records reproduced from the data collected for subject 209. Panel A, obtained prior to the subject's exposure to sessions ending in extinction, reveals relatively steady and higher rates of responding throughout the non-extinction session. Panel B, obtained following the subject's exposure to sessions ending in extinction, reveals relatively variable and lower rates of responding beginning approximately 15 minutes following the start of the non-extinction session, despite the continued availability of food.

The observed declines in response rates were not only confined to non-extinction sessions. Following a history of exposure to sessions ending in extinction, responding in both extinction components also declined. In addition to inspecting cumulative records, Pearson correlations were calculated to summarize the relationship between each subject's rate of response under extinction and the duration of the preceding food component. Correlations were

-0.44, -0.51, -0.43, -0.45, -0.47, and -0.46 for subjects 208, 209, 210, 211, 212, and 213 respectively. For all subjects, as the length of the food component increased, the rate of responding in both extinction components decreased. This finding reveals that lever-pressing was not strictly under the control of the independent variables of interest (e.g., food availability), but it was also under the control of other variables (e.g., session duration or number of sucrose pellets earned during the food component).

Discussion

The results of Experiment 1 revealed no systematic effect of nicotine on responding under extinction in the presence versus the absence of food-paired stimuli. If nicotine enhances the value of weak primary reinforcers as evidenced by previous research on the behavioral effects of the drug, then pre-session nicotine administration would be expected to increase rates of lever-pressing under extinction when visual stimuli are available. Yet, no reliable differences in rates of responding were observed across extinction components before or after acute nicotine administration.

One potential cause for the lack of effect in the current experiment may be related to the acute drug regimen used in the current study. Many researchers who have demonstrated the effects of nicotine on responding maintained by nonpharmacological stimuli administered a chronic regimen of nicotine (e.g., Caggiula et al., 2002b; Chaudhri et al., 2006a; Donny et al., 1999). Therefore, a history of chronic exposure to nicotine may be necessary for the drug to affect responding maintained by nonpharmacological stimuli. However, the results of Raiff and Dallery (2006, 2008) suggest that acute nicotine administration may increase responding maintained by conditioned reinforcers. Nevertheless, chronic nicotine was administered in Experiment 2 in order to rule out the acute drug regimen as a possible cause for the null effects of Experiment 1.

Another procedural difference between the current study and previous research may account for the discrepant findings. The primary reinforcing value of the visual stimuli used in the current study may not have been high enough for nicotine to have had any effect on responding maintained by the stimuli. Palmatier et al. (2007b) suggested that the reinforcement enhancing effects of nicotine are dependent on the value of the reinforcers earned. In their study, Palmatier et al. demonstrated that nicotine increased rates of responding when responses were maintained by 5 sec termination of a houselight (a stimulus that was found to be a relatively moderate reinforcer during baseline), but not when responses were maintained by 5 sec illumination of a cue light above the active lever (a stimulus that was found to be a relatively weak reinforcer). Palmatier et al. concluded that nicotine enhances the value of moderately reinforcing stimuli, but not weakly reinforcing stimuli. In Experiment 1 of the current study, the visual component of the stimulus complex consisted of the illumination of cue lights above the active lever for 1 sec followed by the termination of the houselight for only 2 sec. It is possible that the reinforcing value of this stimulus complex was simply too low for the effects of nicotine to be revealed.

The absence of any systematic variation in rates of responding under extinction in the presence versus the absence of food-paired stimuli observed in the current study was also contrary to the findings of Files et al. (1989). Of course, the differences between the findings of the current study and those reported by Files et al. may be due to the differences between the two drugs used in these studies (i.e., methylphenidate versus nicotine) or the two species (i.e., pigeons versus rats). Despite these differences, however, the fact that no effect was observed in the current study may have also been partially attributed to several procedural variables. Therefore, several adjustments were made in Experiment 2 to determine whether or not this

procedure could still be used to reveal an effect of nicotine on responding maintained by conditioned reinforcers.

As shown in Figures 2-1 and 2-2, no reliable differences in response rates between the two extinction components were observed after nicotine was administered. Although this finding does not show that the current procedure can be used to demonstrate that nicotine enhances the reinforcing efficacy of nonpharmacological primary reinforcers, it may still be possible for the procedure to reveal whether or not nicotine enhances the value of conditioned reinforcers. It is difficult to conclude that the food-paired stimuli served as conditioned reinforcers in Experiment 1 because the response rates across control, vehicle, and nicotine administration sessions were never consistently higher in the presence of food-paired stimuli for any subject.

Figure 2-2 shows that responding under extinction in the presence of food-paired stimuli relative to the absence of these stimuli was substantially higher following both 0.03 mg/kg nicotine and vehicle administration for only one subject, 213. Further, for subject 208, response rates were considerably higher under extinction in the absence of food-paired stimuli. It is possible that the percentage of pairings between the stimulus complex and food during the first component of the session, 50%, may have simply been insufficient to establish the nonpharmacological stimuli as potent enough conditioned reinforcers to reveal the effects of nicotine on responding. The more consistently the pairings occur between a stimulus complex and food, the more likely the food will impart conditioned reinforcing strength to the less reinforcing stimulus complex (Fantino, 1977). Therefore, the percentage of stimuli paired with food was increased to 67% for Experiment 2. The topography of the stimulus complex and its

temporal proximity to the reinforced response were also altered in order to more effectively establish the stimulus as a conditioned reinforcer (see Experiment 2 Methods for details).

The main purpose of Experiment 1 was to determine whether or not nicotine enhances responding maintained by food-paired stimuli relative to responding in the absence of these stimuli. Although this effect was not observed, interestingly, the results of Experiment 1 revealed an increase in rates of responding in both extinction components following nicotine administration relative to rates of responding under extinction following vehicle administration. This finding did not appear to be due to a general increase in activity following nicotine administration. As indicated by Figure 2-1, lower doses of nicotine had little effect on responding maintained by food. The drug even decreased responding maintained by food following 0.56 mg/kg nicotine administration. Further, there was no increase in responding on inactive levers following nicotine administration (data not shown). Therefore, the results suggest that nicotine increased resistance to extinction.

However, procedural limitations in the experiment make this conclusion premature. Figures 2-3 and 2-4 indicate that after the subjects were exposed to repeated sessions ending in extinction other variables (e.g., session duration) began to control lever-pressing. As session duration increased, rate of responding decreased. Consequently, another explanation that would account for increased responding under extinction following nicotine administration is that the drug disrupted the control that session duration had over responding. Loosely speaking, the subjects' ability to discriminate the length of time that was elapsing within sessions and "predict" when extinction would go into effect may have been weakened by nicotine.

One purpose of Experiment 2 was to elucidate the behavioral mechanisms responsible for the finding that response rates increased under extinction as a function of nicotine dose in

Experiment 1. Therefore, another adjustment we made to the experimental procedures was to increase the frequency of non-extinction sessions from approximately 1 out of every 10 sessions to approximately 5 out of every 7 sessions (i.e., approximately 2 sessions per week ended in extinction). We believed that increasing the number of non-extinction sessions would place the subjects' responding during the latter portions of each session more under the control of the availability of food and the schedule that was in effect and less under the control of the duration of the session.

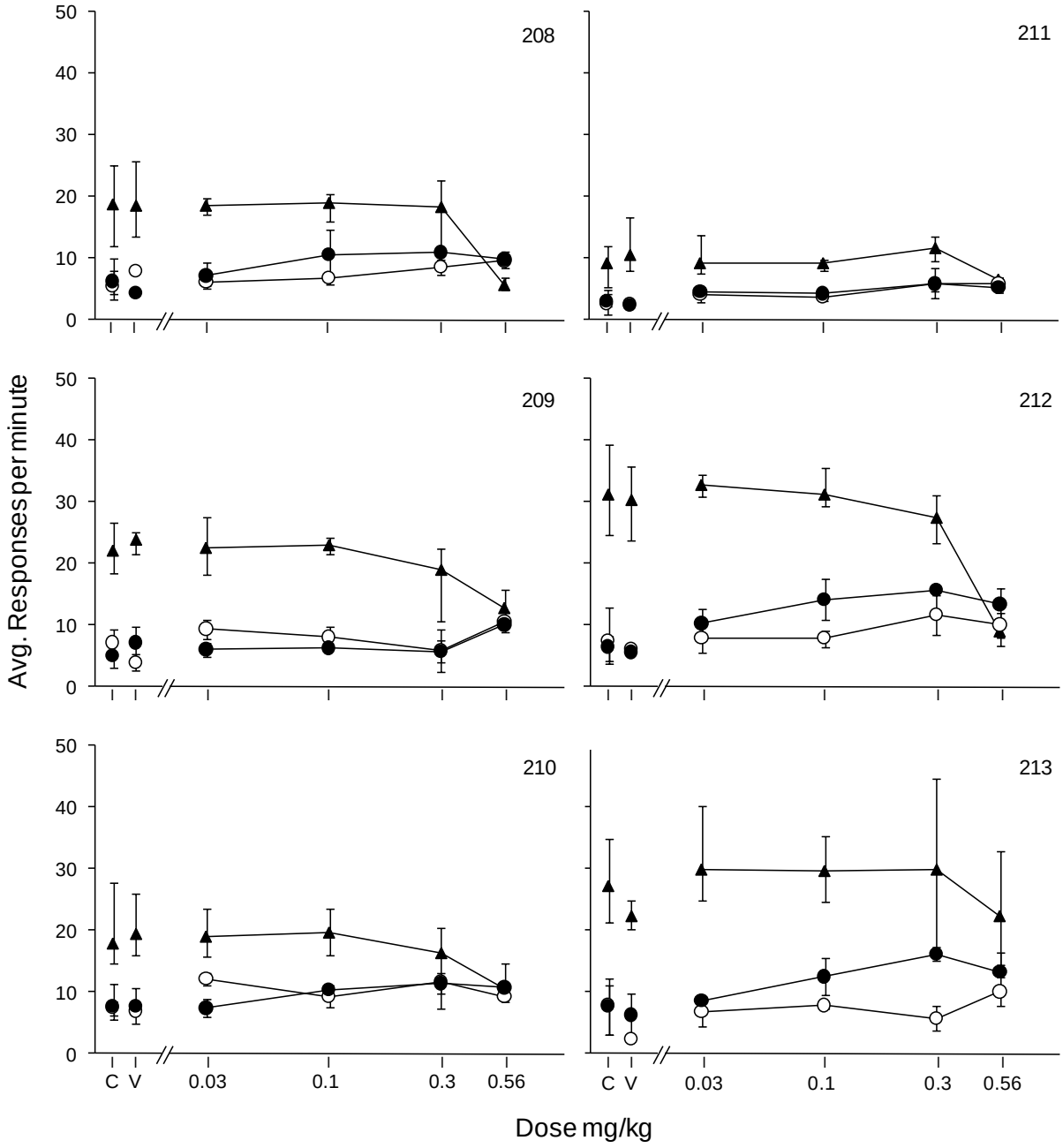

Figure 2-1. Average responses per minute when food is available (triangles) and under extinction when visual stimuli are present (solid circles) and absent (open circles) expressed as a function of control, vehicle, and nicotine sessions. Error bars are ranges. Control and vehicle sessions are located above the "C" and "V" labels, respectively. Nicotine doses in ascending order are 0.03, 0.1, 0.3, and 0.56 mg/kg nicotine. Each panel represents data collected from an individual subject (208, 209, 210, 211, 212, and 213). Note the increase in the maximum value of the y-axes for subjects 212 and 213.

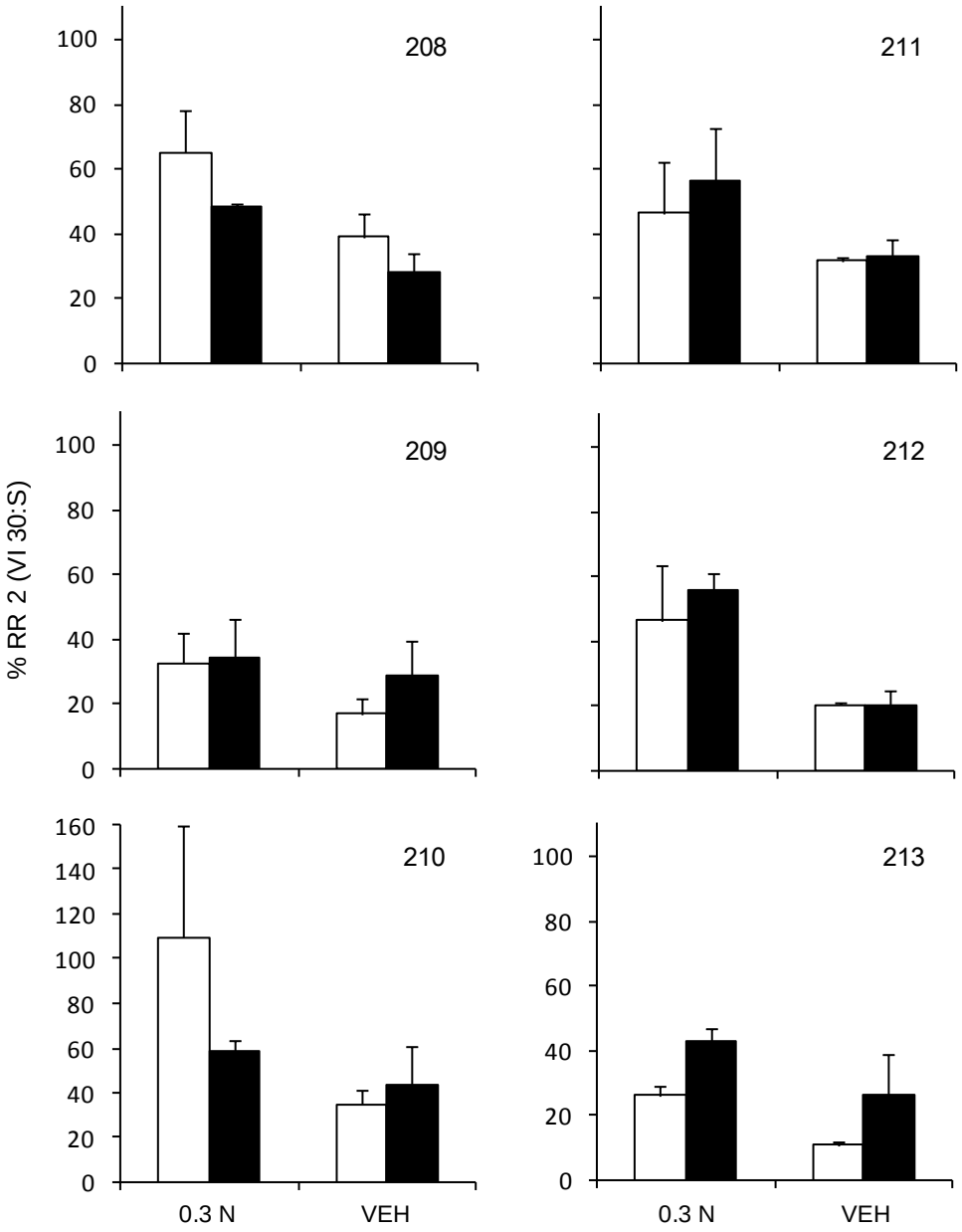

Figure 2-2. Average responses per minute under extinction when stimuli are present (solid bars) and absent (open bars) expressed as a percentage of responses per minute in the preceding RR 2 (VI 30:S), or food, component. Values are displayed as a function of sessions preceded by 0.3 mg/kg nicotine and vehicle administration. Each error bar represents one standard deviation from the mean. Each panel represents data collected from an individual subject (208, 209, 210, 211, 212, and 213). Note the increase in the maximum value of the y-axis for subject 210.

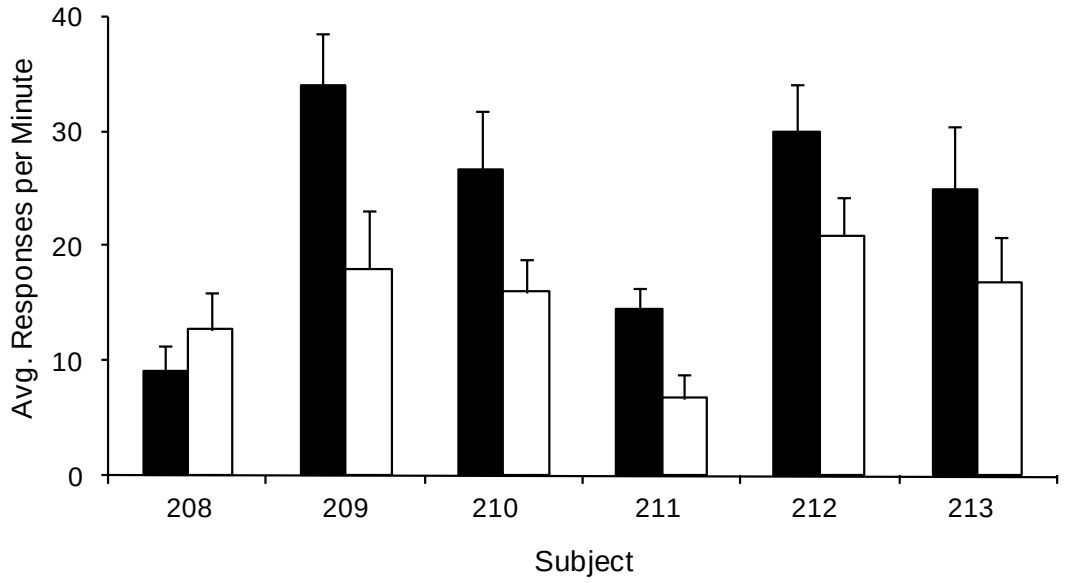

Figure 2-3. Average responses per minute for each subject (208, 209, 210, 211, 212, and 213) in all sessions with continuous availability of food (i.e., non-extinction sessions) before exposure to sessions ending in extinction (solid bars) and after exposure to sessions ending in extinction (open bars). Each error bar represents one standard deviation from the mean.

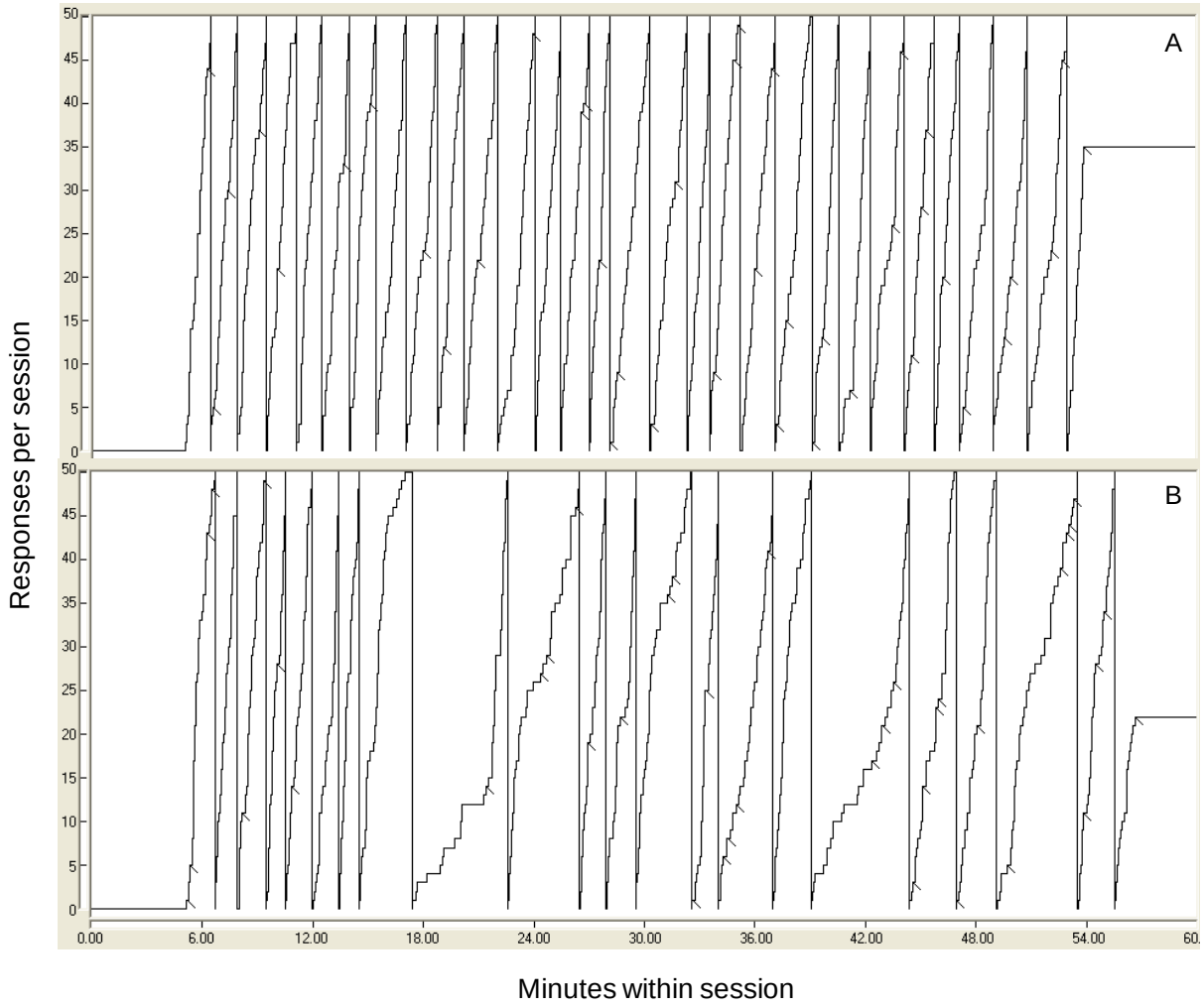

Figure 2-4. Two cumulative records of within-session responding for subject 209. Cumulative number of responses are expressed as a function of time within the session (approximately 60 min). Following 50 responses, the record resets (vertical lines). Short tick marks protruding diagonally from record indicate delivery of a sucrose pellet (sessions terminated following delivery of 40 sucrose pellets). The slope of the line indicates rate of response—as the slope increases, so does the rate. Horizontal segments of the record indicate no responding. Panel A is taken from a non-extinction session prior to exposure to sessions ending in extinction. Panel B is taken from a non-extinction session following exposure to sessions ending in extinction.

CHAPTER 3
EXPERIMENT 2

Method

Subjects

The same subjects that were used in Experiment 1 were also used in Experiment 2. The rats were approximately 15 months old at the beginning of the experiment. Housing and maintenance practices remained the same as those described above.

Apparatus

The apparatus were the same in Experiment 2 as those used in Experiment 1.

Procedure

Training

Before training for Experiment 2 began, the designated active levers were switched for each subject. For example, for subjects 208, 210, and 212, the right lever was designated as the active lever during Experiment 1, and the left lever was designated as the active lever during Experiment 2. Due to the subjects' experimental history, no shaping was required in Experiment 2. Subjects were exposed to an RR 1.5 (VI 30:S) throughout the training phase. This schedule was similar to the RR 2 (VI 30:S) used in Experiment 1, but provided a richer schedule of food reinforcement. Under an RR 1.5 (VI 30:S), each completion of a VI 30:S schedule requirement had a 0.67 probability of food reinforcement. Sessions terminated after the delivery of 40 sucrose pellets.

The stimulus complex available on the VI 30:S component was altered for Experiment 2. The stimulus consisted of the onset of the 3 LEDs above the active lever simultaneously accompanied by an audible click. The LEDs remained on for 2 sec. Upon their termination, a second audible click accompanied the delivery of a sucrose pellet (pellets were only delivered if

the RR schedule requirement was satisfied). Unlike the stimulus complex presented during Experiment 1, no part of the stimulus complex presented during Experiment 2 followed sucrose delivery, nor was the houselight terminated at any point.

Subjects were exposed to 100 training sessions before chronic vehicle or nicotine administration began. In contrast to Experiment 2, stable responding was not reached before drug administration began. By this stage in the study, the advanced age of the subjects limited the length of time researchers were able to wait for stability.

Chronic drug administration

Nicotine and vehicle administration procedures were similar to those described during the acute drug administration phase in Experiment 1. In Experiment 2, however, nicotine and vehicle were administered daily during the chronic drug administration phase and only one dose, 0.3 mg/kg nicotine, was used. The 0.3 mg/kg nicotine dose was chosen because it had the greatest effect on response rates under extinction in Experiment 1 without the dose-suppressive effect on response rates in the food component (see Figure 2-1). Subjects 211, 212, and 213 were exposed to three conditions consisting of an ABA chronic regimen of vehicle, nicotine, and vehicle administration. Subjects 208, 209, and 210 were exposed to three conditions consisting of a BAB chronic regimen of nicotine, vehicle, and nicotine administration.

At the beginning of each condition, subjects were exposed to approximately 10 non-extinction sessions preceded by nicotine or vehicle administration in which the RR 1.5 (VI 30:S) remained in effect until the end of the session. Following this initial exposure to each condition, subjects were exposed to sessions ending in either standard or food-paired stimulus extinction components approximately 2 out of every 7 sessions (i.e., twice per week). Subjects remained in

each chronic nicotine or vehicle condition until they were exposed to at least three sessions ending in each type of extinction component (87 sessions for each subject).

Results

Figure 3-1 illustrates the average response rates for each subject under the standard and food-paired stimulus extinction components expressed as percentages of response rates in the preceding food component in both conditions (i.e., either chronic nicotine or vehicle). Any change in this measure would indicate a change in the rate of responding under extinction relative to the rate of responding in the preceding food component. Figure 3-1 shows chronic 0.3 mg/kg nicotine administration did not increase rates of responding under extinction in either extinction component relative to rates of responding following chronic vehicle administration. The figure also shows no systematic effect of the drug on responding under extinction in the presence relative to the absence of food-paired stimuli. However, Figure 3-1 does reveal that rates of responding under extinction were consistently higher in the presence of food-paired stimuli for subjects 208, 209, and 211 across chronic vehicle and nicotine conditions. For no subject were rates reliably higher in the absence of food-paired stimuli across both conditions.

Discussion

The results of Experiment 2 revealed higher rates of responding under extinction in the food-paired stimulus component across both chronic nicotine and vehicle conditions for several subjects (208, 209, and 211). This finding is contrary to the results of Experiment 1 and indicates that adjustments made to the procedures in Experiment 2 may have successfully established the food-paired stimuli as conditioned reinforcers for at least these subjects. By increasing the frequency of pairings between sucrose and the stimulus complex from 50% to 67% and adjusting the temporal contiguity between these stimuli, it appears that the sucrose imparted conditioned reinforcing strength to the stimulus complex. Given this finding, if

nicotine enhances the value of conditioned reinforcers that gain their strength from nonpharmacological primary reinforcers such as sucrose, it would be expected that responding maintained by these stimuli would have increased following nicotine administration. Chronic pre-session nicotine administration, however, did not increase responding under extinction in the presence of food-paired stimuli relative to responding in the absence of these stimuli. Thus, the results of Experiment 2 provided no evidence in support of the hypothesis that nicotine enhances the value of conditioned reinforcers.

Increasing the frequency of non-extinction sessions from approximately 10% of all sessions in Experiment 1 to approximately 71% of all sessions in Experiment 2 also appeared to affect the subjects' behavior by returning control over responding back to the independent variables of interest (e.g., food availability). Within- and between-session analyses (data not shown) confirmed that session duration had much less control over responding in Experiment 2 than in Experiment 1. Within-session data revealed that response rates were much more stable throughout non-extinction sessions than they were prior to the procedural change. Overall, as evidenced by the general downward trends in the graphs in Figure 3-1, for several subjects (most notably 210, 212, and 213) response rates did still decline during extinction after repeated exposure to sessions ending in extinction; however, this decline in responding was not observed in non-extinction sessions.

Unlike the results of Experiment 1, the results of Experiment 2 revealed no increases in rates of responding under extinction in either extinction component following nicotine administration relative to vehicle administration. In other words, nicotine did not appear to increase resistance to extinction. It is important to note the possibility that acute pre-session nicotine administration increased resistance to extinction in Experiment 1. Following chronic

exposure to the drug in Experiment 2, tolerance to the effects of nicotine on responding under extinction may have developed; thus, resulting in decreased resistance to extinction in Experiment 2 following nicotine administration. This interpretation could account for the observed differences in responding under extinction in Experiments 1 and 2. A more reasonable interpretation of this finding, however, is that nicotine interfered with the control other variables, such as session duration, exerted over responding under extinction in Experiment 1. Once the procedural adjustments were made to Experiment 2, control over responding returned to the experimenter controlled variables (e.g., food availability) and, consequently, the effect of nicotine on responding under extinction was no longer observed.

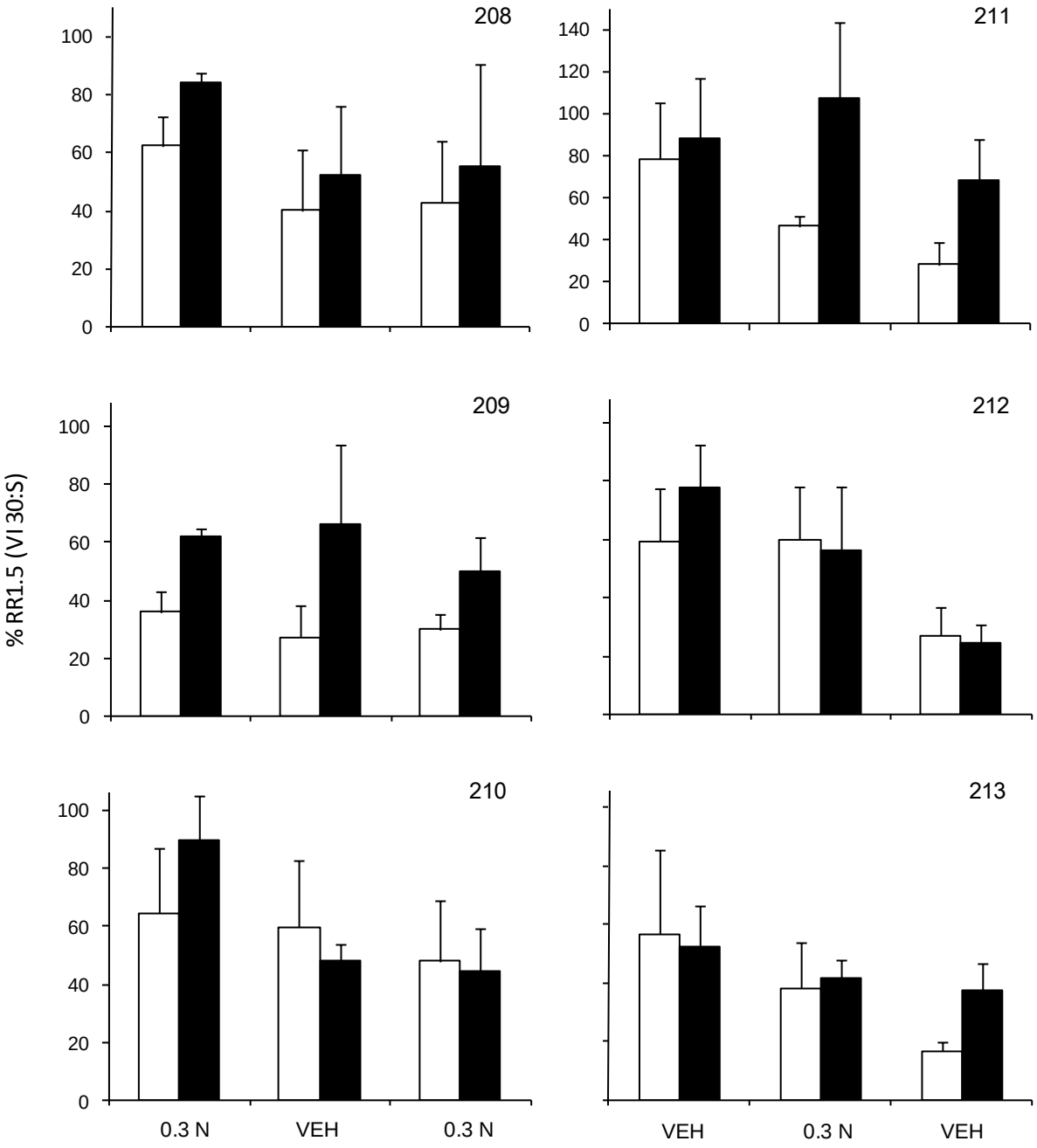

Figure 3-1 .Average responses per minute under extinction when stimuli are present (solid bars) and absent (open bars) expressed as a percentage of responses per minute in the preceding RR 1.5 (VI 30:S), or food, component. Values are displayed as a function of sessions preceded by 0.3 mg/kg nicotine and vehicle administration. Each panel represents data collected from an individual subject. Doses were administered to the subjects in the left column (208, 209, and 210) in a BAB design—chronic nicotine, followed by vehicle, followed by nicotine. Doses were administered to the subjects in the right column (211, 212, and 213) in an ABA design. Each error bar represents one standard deviation from the mean. Note the increase in the maximum value of the y-axis for subject 211.

CHAPTER 4
GENERAL DISCUSSION

Results of the current study did not reveal an effect of nicotine on responding under extinction in the presence versus the absence of food-paired stimuli. This finding is contrary to the results of Files et al. (1989) who found that pre-session methylphenidate administration resulted in an increase in rates of key-pecking in pigeons responding under extinction in the presence of food-paired stimuli relative to responding in the absence of these stimuli. Based on the results of Files et al., it could be argued that methylphenidate enhanced the value of conditioned reinforcers. That nicotine may have the same effect is a plausible assumption given its classification as a stimulant as well as previous research demonstrating the effects of nicotine on responding maintained by nonpharmacological stimuli (cf. Chaudhri et al., 2006b). Nevertheless, results of the current study suggest that the effects of nicotine on responding under extinction in the presence versus the absence of food-paired stimuli are not the same as the effects of methylphenidate on responding under these circumstances.

However, not only were different drugs used in the study conducted by Files et al. (1989) and in the current study, so were different species. Thus, any number of variables related to these factors could account for the discrepant findings. One potential explanation for why results of the current study were dissimilar to those of Files et al. may even be related to the different dependent variables in the two studies. The current study measured rate of lever-pressing; whereas, Files et al. measured rate of key-pecking. Schwartz (1977) suggested that some key-pecks may be classified as respondent behavior. Perhaps methylphenidate enhanced responding elicited by the stimulus complex presented under extinction in the study conducted by Files et al.; thus, demonstrating an effect of the drug on respondent behavior.

The findings of the current study may contradict the findings of Files et al. (1989) because the behavior of interest emitted by pigeons and rats in the two studies are simply under the control of different variables, despite the relatively similar experimental context. Further, methylphenidate and nicotine may simply have different effects on the behavior under investigation. Curiously though, findings from the current study also appear to contradict those of other research on the effects of nicotine on lever-pressing maintained by nonpharmacological stimuli in rats. If nicotine enhances the reinforcing efficacy of nonpharmacological primary or conditioned reinforcers, it might be expected that rates of responding in the food-paired stimulus extinction components would have been elevated above rates in the standard extinction components in Experiments 1 and 2. It is unclear exactly why this did not happen.

It is possible that the doses of nicotine used in the current study had a different effect on responding than doses used in previous research. Much of the previous research on the effects of nicotine on responding maintained by nonpharmacological stimuli involved within-session intravenous administration of relatively low doses of nicotine (e.g., 0.03 mg/kg nicotine; Donny et al., 2003) due to the fact that infusions were administered repeatedly within sessions. The doses used in the current study were higher because they were administered only once prior to the beginning of the session. However, the range of doses used in Experiment 1 (0.03, 0.1, 0.3, 0.56 mg/kg nicotine) and in Experiment 2 (0.3 mg/kg nicotine) were similar to those used in other studies in which pre-session nicotine administration was found to increase responding maintained by nonpharmacological primary or conditioned reinforcers. For example, using an observing response procedure, Raiff and Dallery (2006) found that pre-session subcutaneous injection of 0.3 mg/kg nicotine increased responding maintained by conditioned reinforcers.

Additionally, Palmatier et al. (2007b) found that pre-session administration of 0.4 mg/kg nicotine increased responding maintained by visual stimuli.

In addition to dose, several of the experimental procedures used in the current study were quite different from those used in most previous studies which support the "reinforcement-enhancing effect" hypothesis. As mentioned above, the composition of the nonpharmacological stimulus complex used in the current study was somewhat dissimilar to the stimuli used in previous studies. If nicotine enhances the value of moderately reinforcing primary reinforcers, the reinforcing value of the visual stimuli used in the current study may not have been high enough to reveal the effect of nicotine on responding. In previous studies that have demonstrated the effect of nicotine on responding maintained by nonpharmacological stimuli, the stimulus complex included the termination of a houselight. The offset of the houselight in previous research ranged from 5 sec (Palmatier et al., 2007b) to 1 min (Donny et al., 2003). In the current study, meeting the appropriate schedule requirement resulted in the termination of the houselight for only 2 sec in Experiment 1 and did not result in the termination of the houselight in Experiment 2. It seems unlikely that 2 sec termination of a houselight is significantly less reinforcing than 5 sec; however, this is a question that should be empirically addressed.

It is much more likely that another procedural variation of the current study might account for the lack of effect of nicotine on responding maintained by visual stimuli. To our knowledge, none of the studies that have investigated the effects of nicotine on responding maintained by nonpharmacological stimuli delivered food within sessions. It is possible that the within-session availability of sucrose masked the effects of nicotine on responding maintained by the stimulus complex. Rates of responding under extinction may have reached a ceiling due to the availability of food at the beginning of each session.

Response rates are generally higher for food than for visual stimuli. By introducing food at the beginning of each session, we may have maintained responding at such a high level—even during extinction after food was no longer available—that the effects of nicotine on responding maintained by much less reinforcing visual stimuli were masked. In a study conducted by Palmatier et al. (2007b), responding maintained by the termination of a houselight on an FR 5 schedule was much higher when nicotine was delivered prior to each session than when vehicle was administered prior to each session. However, even when response rates were highest, they were still less than 2 responses per minute. In the current study, rates of responding under extinction for some subjects were as high as 10 responses per minute during those sessions in which nicotine was administered prior to session.

Perhaps the effects of nicotine on responding maintained by food-paired stimuli were simply not revealed due to one of the procedural differences between the current study and previous research. The lack of effect detected in the current study, however, does suggest that the generality of previous findings may be somewhat limited. The "reinforcement-enhancing effect" appears to be reliable, but not particularly robust.

Interestingly, some evidence suggests that the reinforcement-enhancing effect is not unique to nicotine. Other drugs of abuse may also enhance the value of nonpharmacological stimuli. For example, some researchers have shown that noncontingent cocaine administration increases responding maintained by contingent visual stimuli (cf. Chaudhri et al., 2006b). Future research should continue to investigate this effect among other drugs. Like nicotine, other drugs of abuse may maintain self-administration due, in part, to the ability of the drugs to enhance the value of environmental stimuli. Unlike nicotine, however, there is considerable evidence that other drugs of abuse act as potent primary reinforcers (e.g., Mierzejewski et al., 2003).

Although the reinforcement-enhancing effect may play some role in the self-administration of nicotine and other drugs of abuse, it seems unlikely that it is the dominant behavioral process responsible for maintaining smoking. Even when contingent nicotine is paired with nonpharmacological stimuli, rates of responding are relatively low compared to rates maintained by other non-nicotine drugs. For example, Mierzejewski et al. (2003) demonstrated that rats would emit approximately 300 responses in a two-hour session when nose-pokes were maintained by intravenous administration of 0.3 mg/kg cocaine on a FR 5 schedule of reinforcement. Using a similar procedure, Shoaib, Schindler, and Goldberg (1997) showed that rats would only emit approximately 15 responses per two-hour session when nose-pokes were maintained by intravenous administration of 0.06 mg/kg nicotine on a FR 5. (In both studies, drug infusions were followed by a "signaled" time-out period.)

The fact that nicotine appears to serve as a relatively weak primary reinforcer in the lab seems to contradict the assumption that it maintains a significant amount of smoking among humans outside the lab. One way for researchers to better understand this apparent contradiction is to investigate behavior maintained by other chemical compounds that are found in cigarettes in addition to nicotine. It is possible that smoking is reinforced by the delivery of several compounds in combination with nicotine (e.g., monoamine oxidase inhibitors; Villegier, Lotfipour, Belluzzi, & Leslie, 2007).

Although, for some, smoking appears to be one of the most difficult behaviors from which to abstain; unlike other drugs of abuse, nicotine alone appears to serve as only a weak primary reinforcer. As noted by Caggiula, et al. (2001), abuse and relapse behavior associated with smoking are at least as prevalent with cigarette smoking as they are with other addictive drugs, despite the fact that the reinforcing properties of nicotine are much weaker. In addition to

other chemicals, other behavioral processes likely play a role in the acquisition, maintenance, and relapse of cigarette smoking. The development of more efficacious treatment alternatives relies on a better understanding of these processes.

Investigating animal models of nicotine self-administration may prove to be the most useful strategy for identifying the behavioral processes that maintain smoking in humans. Future research should continue to examine the effects of nicotine on responding maintained by nonpharmacological stimuli using such models. However, future researchers who examine the effects of nicotine on responding maintained by nonpharmacological stimuli should continue to investigate the effects of the drug when it is administered prior to experimental sessions or continuously throughout each session in order to avoid potential pitfalls associated with within-session nicotine administration.

Thus far, nicotine has been demonstrated to increase responding maintained by visual stimuli (Palmatier et al., 2007b), cocaine (Bechtolt and Mark, 2002), alcohol (Smith, Horan, Gaskin, & Amit, 1999), and liquid sucrose (Jias & Ellison, 1990); however, it does not increase responding maintained by sucrose pellets as evidenced by the current study and by Raiff and Dallery (2008). If indeed the effects of nicotine serve as an MEO, the drug likely enhances the value of some stimuli to the exclusion of others (e.g., water deprivation enhances the value of water but not necessarily food). Identifying which stimuli nicotine establishes as reinforcers is an important direction for future research which could shed considerable light on why organisms self-administer nicotine.

Finally, another particularly important direction for future research has been indicated by the current study. The results of Experiments 1 suggest that nicotine may affect the ability of time or other variables to control responding. It is possible that nicotine interferes with the

discriminative control timing has over behavior. This is an area of research that has received little attention and could provide significant insight into the effects of nicotine on behavior.

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BIOGRAPHICAL SKETCH

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