EFFECTS OF NICOTINE ON RESPONDING MAINTAINED BY ENVIRONMENTAL STIMULI IN RATS

By

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To Jack, for providing me with alternative sources of reinforcement.

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Past research suggests that nicotine-induced increases in reinforced responding are due to its reinforcer-enhancing effects. It is unclear whether this role is specific to certain kinds of reinforcing consequences (e.g., sensory stimuli, edible reinforcers, drug reinforcers). Furthermore, it is possible that nicotine merely increases behavior that has been trained in the past (i.e., responding reinforced with food consequences). The objectives of Experiments 1 and 2 were to test the generality of the motivating establishing operation (MEO) account of nicotine-induced increases in reinforced responding and to determine whether the history of training (responses that have previously been reinforced with food versus those that have not) would augment the effects.

Experiment 1 used an observing-response procedure to investigate responding maintained by food reinforcers, conditioned reinforcers (i.e., visual stimuli), and responding during extinction. Rats in Experiment 1 received pre-session subcutaneous injections of vehicle (n = 5), 0.3 (n = 6) or 0.56 (n = 6) mg/kg nicotine for 70 sessions. Resistance to extinction was also assessed by removing food for five sessions. Nicotine did not consistently affect food or extinction responding. Both doses of nicotine produced increases in responding maintained by

conditioned reinforcers, but did not increase resistance to extinction. Pre-drug response rates accounted for a small but significant percentage of the variance in the drug effect.

In Experiment 1, contingent houselight presentations alone were shown to slightly increase response rates from operant levels. Experiment 2 further evaluated the putative primary reinforcing functions of turning on and turning off a houselight. One group of rats (n=4) was initially trained to press both levers (one was later designated as the active lever and the other the inactive lever), while a different group of rats (n =4) was only trained to press the lever that was later designated as the active lever. Across two phases, five responses on the active lever resulted in the houselight either turning on (Lights On) or turning off (Lights Off). All subjects made more responses on the active lever, regardless of lever training history and the type of stimulus change, suggesting that both stimuli served as primary reinforcers. Nicotine only increased responding on the active lever, again regardless of lever training history, which further supported the MEO role, and refuted the alternative hypothesis that nicotine generally increases behavior that has been trained.

Although there was a tendency for nicotine to increase low pre-drug response rates in both experiments, nicotine systematically increased responding maintained by conditioned reinforcers in Experiment 1, and only increased responding on an active lever in Experiment 2. The results of both experiments are in accord with the MEO account of nicotine – that it increases responding maintained by moderately reinforcing stimuli, such as the conditioned reinforcers and visual stimuli used in the present studies.

CHAPTER 1
GENERAL INTRODUCTION

Brief History of Tobacco and Cigarette Smoking in the United States

Tobacco use by humans dates back centuries, ranging from religious, recreational and at times even medicinal uses. Columbus and his crew first introduced tobacco to Spain after visiting the Americas in 1492 and seeing a number of indigenous North Americans "drinking the smoke" (Gold, 1995). At the time, many North Americans considered tobacco sacred and in some cases medicinal (Hatch, 1942; Kluger, 1997). Although tobacco was initially used by Europeans for recreational purposes, from the 1600s until the mid 1800s it was considered the "panacea of panaceas" in both Europe and the United States, being prescribed to treat various ailments such as asthma, nasal congestion, thirst, wounds, teeth whitening, and even the bubonic plague (Stewart, 1967). Eventually physicians became skeptical of the substance because of nicotine's apparent "addictive" properties, and by around 1860 tobacco was no longer being prescribed for medicinal purposes (Stewart, 1967). Nevertheless, it was not long after, around 1880, when the first cigarette-rolling machines were invented, which led to the mass production and sales of cigarettes for predominantly recreational purposes (Gold, 1995).

With increasing sales came increasing economic interest in tobacco in the United States. The New Tobacco Company was formed in 1889 and 10 years later RJ Reynolds, the makers of well known Camel cigarettes, was incorporated. In 1902 Philip Morris and Company, makers of Marlboro cigarettes, came to New York (Kluger, 1997), and today Philip Morris claims more than 50% of the U.S. tobacco market (Cooper, 2004). In the U.S alone, over 100,000 hectares of land are devoted to growing tobacco, with most of the farms located in North Carolina (Food and Agricultural Organization, 2003; Gold, 2005).

In 1964, the U.S. Surgeon General's report formally stated that there was a relationship between smoking and cancer and the Federal Cigarette Labeling and Advertising Act of 1965 required that all tobacco products bear a warning label (Centers for Disease Control and Prevention [CDC], 2006). Since 1965, the percentage of current smokers has declined from about 42%, remaining at an estimated 24% of the U.S. adult population since 2003 (CDC, 2006). In addition to cancer, smoking has been associated with a number of other health problems, such as emphysema, coronary heart disease, and stroke, with approximately 440,000 deaths attributed to smoking-related illnesses each year (CDC, 2005). Although about 70% of smokers report a desire to quit (CDC, 2005), approximately 60-90% of those who attempt to quit end up relapsing within one year (Carmody, 1992). Cigarette smoking is currently a primary public health concern in the United States. Despite this long history of tobacco use in the United States, the question remains: what has made tobacco such a successful commodity?

The Culprit: Nicotine?

The answers, of course, are complex. Each year tobacco companies spend over $15 billion dollars on advertising – almost $50 million per day (Federal Trade Commission, 2005). Indeed, advertisements have been shown to influence adolescents' self-reported intentions to smoke cigarettes (Straub, Hills, Thompson, Moscicki, 2003) and smoking initiation (Pierce, Choi, Gilpin, Farkas, Berry, 1998).

In addition to social and cultural influences on smoking, the pharmacological effects of nicotine have been implicated in the success of tobacco products. Of the approximately 4,000 constituents found in tobacco, the primary psychoactive ingredient is nicotine, which was first extracted from tobacco in 1828 (Henningfield & Zeller, 2006). The effects of nicotine on the central nervous system are similar to the effects of other drugs of abuse, such as cocaine, heroin, and amphetamine, in that they all affect the mesolimbic dopamine system (McKim, 1997; Pierce

& Kumaresan, 2006; Wonnacott, Sidhpura, Balfour, 2005). Each drug affects the area in a slightly different way, but they all result in dopamine release, either directly or indirectly. Research suggests that it is particularly important that the drug result in increased dopamine activity in the ventral tegmental area and the nucleus accumbens, which nicotine does both directly by stimulating dopamine neurons and indirectly by initiating glutamate release (Pierce & Kumaresan, 2006). Because these effects on the mesolimbic dompamine system appear to be critical to the reinforcing effects of most other drugs of abuse, the fact that nicotine also has these effects suggests that its presence in tobacco products might be responsible for the high rates of tobacco use (Stolerman & Jarvis, 1995; Stolerman, 1999). Behavioral pharmacologists have been particularly interested in determining whether nicotine is responsible for smoking maintenance and relapse, and have used the self-administration procedure to explore this possibility.

Drug Self-Administration

The discipline of behavioral pharmacology combines the principles of pharmacology with the principles of behavior analysis (Poling & Byrne, 2000; Thompson & Schuster, 1968). Behavior analysis uses a natural science approach to understanding the behavior of organisms, and places an emphasis on environmental variables (Cooper, Heron, Heward, 2007; Skinner, 1953). Operant behavior, in contrast with respondent behavior, is defined as behavior whose future likelihood is affected by its consequences, and it comprises most of the behavior of humans (Cooper, Heron, Heward, 2007; Skinner, 1953). Although there are many facets of both operant and respondent conditioning that are of interest to behavioral pharmacologists, one area that has generated interest is reinforcement. Reinforcement is the process by which a response occurs, a stimulus event follows, and the result is an increase or maintenance in the future probability of the response (Poling & Byrne, 2000; Skinner, 1953; Thompson & Schuster, 1968). Behavioral pharmacologists have extended the concept of reinforcement by conceptualizing

drugs as potential reinforcers and drug seeking and use as operant behavior (Carlton, 1983; McKim, 1997; Poling & Byrne, 2000). For human smokers, these behaviors might include going to the store to buy cigarettes, asking another smoker for a cigarette, inhaling the smoke, etc., with nicotine as the key ingredient thought to be involved in the reinforcing function of the cigarettes.

Drug self-administration procedures were developed by behavioral pharmacologists for use with nonhuman subjects under controlled laboratory conditions (Carlton, 1983; Haney & Spealman, 2008), and are considered analogous to human drug use and drug seeking. Self-administration procedures are often conducted in operant chambers whereby the drug is delivered (usually intravenously through a catheter) after a response is made (e.g., a lever press with rats or non-human primates; Thompson & Schuster, 1964). For example, the lever press that results in a nicotine infusion would be considered functionally equivalent to a smoker lifting a cigarette to one's mouth and inhaling nicotine. Early self-administration studies demonstrated that nonhumans would self-administer drugs such as morphine and cocaine on various schedules of reinforcement (Thompson & Schuster, 1964; Pickens & Thompson, 1968). Thompson and Schuster (1968) demonstrated that the patterns of responding maintained by morphine were similar to the patterns of responding maintained by food, and that morphine deprivation had similar effects as food deprivation on those response patterns. These findings provided empirical support for the notion that drugs could produce effects that were similar to other reinforcing consequences.

One method that has also been used to further investigate the reinforcing function of a drug involves delivering an agonist or antagonist of the drug, either before the session or noncontingent on responding during the session, and determining self-administration of the drug itself is influenced. For example, in one study baboons were given a choice between earning

food and self-administering heroin. Subjects chose to self-administer heroin on approximately half of the trials. When noncontingent morphine, an opioid agonist, was added to the session the number of heroin choices decreased. In this case, morphine could be considered a substitute for heroin, which led subjects to allocate their choices to food instead of heroin. Similar changes in choice allocation were seen when naloxone (an opioid antagonist) was given, suggesting that it blocked the reinforcing effects of heroin (Griffiths, Wurster, Brady, 1981).

Nicotine Self-Administration

It has long been argued that the widespread use of tobacco products can be attributed, in part, to nicotine's primary reinforcing properties (Russell, 1971; Stolerman & Jarvis, 1995). However, unlike most other drugs of abuse, it has been very difficult to establish nicotine self-administration in nonhumans. Eventually, in 1989, Corrigal and Coen (1989) published a study that seemed to convincingly demonstrate nicotine self-administration in laboratory rats. The procedure involved several features that now seem to be important for generating nicotine self-administration. The rat was food-deprived and then trained to press one of two levers. Food was used as the consequence. When lever pressing was established, food was replaced with nicotine for pressing the previously trained lever, and the other lever was designated inactive. Eventually an intermittent (fixed ratio [FR]) schedule was introduced, whereby a fixed number of responses were required for each infusion. Each nicotine infusion was paired with the brief onset of a stimulus light above the active lever, followed by a 60 s time out, during which all visual stimuli, including the houselight, were turned off. Sessions were 1 hr in duration and the entire experiment lasted for a few weeks to one month, but rarely longer. Since the publication of this procedure in 1989, it has been the predominant method used to study nicotine self-administration (e.g., Cohen, Perrualt, Griebel, Soubrié, 2005; Corrigal & Coen, 1989; Caggiula et al., 2001, 2002a,b; Chaudhri et al., 2006a; Donny et al., 2003). Variations of this procedure sometimes

involve more extended access to nicotine (e.g., 23 hr / day), the use of nonhuman primate subjects, and in some cases omitting the food deprivation and lever training protocols (Denoble & Mele, 2006; Goldberg, Spealman, Goldberg, 1981; Harris, Burroughs, Pentel, Lasage, 2008; Valentine, Hokanson, Matta, Sharp, 1997). It should be noted, however, that in all of the procedures just cited, some form of stimulus change always accompanied the nicotine infusions.

In fact, the stimulus change accompanying each nicotine infusion appears to play a critical role in nicotine self-administration with nonhumans. Caggiula and colleagues have conducted a number of experiments demonstrating that when the stimulus change is removed, nicotine self-administration decreases to levels that are almost indistinguishable from vehicle self-administration (Caggiula, et al., 2001; Caggiula, Donny, Chaudhri, Perkins, Evans-Martin, Sved, 2002a; Caggiula et al., 2002b; Chaudhri et al., 2005). Caggiula and colleagues (2002b) conducted a systematic investigation into the features of the stimulus change (e.g., turning on a houselight, turning on a light above the lever, turning off a houselight, or turning on a brief lever light and tone). The authors found that turning off a houselight maintained more responding than the other stimuli, and that adding contingent nicotine increased responding maintained by turning off the houselight to a greater extent than the other stimulus changes investigated. Furthermore, when nicotine was removed, but turning off the houselight continued to be presented contingent on a FR 5 schedule of lever pressing, responding decreased substantially (Caggiula et al., 2001). This finding led the researchers to conclude that nicotine did in fact function as a primary reinforcer, albeit a weak one.

Although it is possible that nicotine serves as a weak primary reinforcer, it is also possible that the mere presence of nicotine has behavioral effects that make it appear to function as a reinforcer (Branch, 2006). One technique that has been employed to distinguish between the

reinforcing effects of a stimulus, as opposed to its eliciting or discriminative effects, is to deliver the stimulus response-independently (Pickens & Thompson, 1968; Sizemore & Lattal, 1977). Donny and colleagues (Donny et al., 2003) did just that by exposing one group of rats to the traditional self-administration paradigm described above and yoking the nicotine infusions earned by this group to a different group of rats who only earned stimulus changes contingent on lever pressing. Interestingly, the group of rats who received yoked nicotine infusions responded almost as much on the stimulus change lever as the group who earned contingent nicotine plus contingent stimulus changes. To rule out adventitious reinforcement in the yoked group, a second study was conducted that involved one continuous infusion of nicotine during each session, along with response contingent stimulus changes. As in the yoked experiment, the mere presence of nicotine resulted in increases in responses maintained by the visual stimulus change. A number of other studies have been conducted to further corroborate the finding that nicotine increases responding maintained by stimulus changes (Chaudhri et al., 2006; Olausson, Jentsch, & Taylor, 2004a, b; Palmatier et al., 2006, 2007; Raiff & Dallery, 2006).

In addition to increasing responses maintained by moderately reinforcing sensory stimuli, nicotine has also been shown to increase responding maintained by more potent primary reinforcers, such as cocaine (Bechtholt & Mark, 2002; McQuown, Belluzi, Leslie, 2007), alcohol (Clark, Lindgren, Brooks, Watson, Little, 2001; Lê, Wang, Harding, Juzytsch, Shaham, 2003; Smith, Horan, Gaskin, Amit, 1999) and sucrose dissolved in water (Jias & Ellison, 1990). Despite these "direct" pharmacological effects of nicotine on responding, many researchers maintain the position that nicotine serves as a primary reinforcer (e.g., Chaudhri et al., 2006; Le Foll, Wertheim, Goldberg, 2007). Thus, there are at least two roles for nicotine: (1) nicotine functions as a primary reinforcer that can maintain responding in the absence of visual stimuli

and can establish neutral stimuli as conditioned reinforcers and (2) nicotine can enhance the reinforcing efficacy of other reinforcers when delivered contingent or noncontingent on a response (Chaudhri et al., 2006). The viability of the first role is beyond the scope of this paper -- instead the hypothesis that nicotine acts as a reinforcer-enhancer will be explored in the section that follows.

Motivating Operation Role for Nicotine

In behavior analysis, the concept of motivating operations is critically important to the concept of reinforcement in general. A motivating operation (MO) is an antecedent event that (1) temporarily alters the efficacy of certain consequences (reinforcer value-altering), and (2) changes the likelihood of responses that have resulted in that consequence in the past (response-altering; Laraway, Snycerski, Michael; Michael, 1982; Michael, 1993; Michael, 2000). MOs can either work by increasing or decreasing the efficacy of certain consequences, and thus increasing or decreasing the future probability of a response, respectively. The former is often referred to as an *establishing operation*, the latter an *abolishing operation* (Michael, 1982). For example, food deprivation is an establishing operation because it temporarily increases the reinforcing value of food, and thus increases the likelihood of responses that have previously resulted in receipt of food. Alternatively, food satiation is an abolishing operation and thus decreases the likelihood of responses which have led to the receipt of food in the past. For the purposes of this discussion, only those antecedent events that increase the future likelihood of a response will be discussed and they will be summarized by the term *motivating establishing operation* (MEO).

The concept of the MEO has been fruitful and practical in applied behavior analysis (Dicesare, McAdam, Toner, Varrell, 2005; Iwata, Dorsey, Slifer, Bauman, Richman, 1994; Iwata, Smith, Michael, 2000; McAdam et al, 2005; McComas, Hoch, Paone, El-Roy, 2000;

Northup, Fusilier, Swanson, Roane, Borrero, 1997). Although the principles of reinforcement, punishment, and stimulus control have been widely applied to behavioral pharmacology research (Branch, 2006; Carlton, 1983; Thompson & Schuster, 1968) the concept of the MEO has been neglected. Only two known studies directly applied the concept of MOs to drug effects (Dicesare, McAdam, Toner, Varrell, 2005; Northup, Fusilier, Swanson, Roane, Borrero, 1997). One study found that the disruptive behavior of an individual with attention deficit hyperactivity disorder (ADHD) was reinforced by therapist attention, but only in the absence, and not the presence, of methylphenidate treatment (Dicesare, McAdam, Toner, Varrell, 2005). This is an example of how the drug served as an abolishing operation (i.e., it decreased the reinforcing efficacy of attention). Another study found that methylphenidate increased the relative reinforcing efficacy of some classroom activities for a child with ADHD, while it decreased the relative reinforcing efficacy of edible items for the same child, suggesting that the drug could function as an establishing operation in some cases and an abolishing operation in others.

Both of the studies just described were conducted by applied behavior analysts and published in the *Journal of Applied Behavior Analysis*. Thus, the application of MOs to the more general behavioral pharmacology community was not made. Indeed, nicotine's reinforcer-enhancing effects are consistent with a MEO account. If nicotine does in fact serve as a MEO, it should increase the value of some reinforcers, and increase the likelihood of responses which have led to the receipt of those reinforcers in the past. Conceptualizing nicotine as a MEO provides a unifying behavioral mechanism of action. Furthermore, investigating the MO role of drugs could be fruitful, both conceptually and empirically, in behavioral pharmacology in general (Poling & Byrne, 2000; Thompson, 2007).

Alternative Accounts

In pursuing the putative MEO role of nicotine, alternative explanations regarding how nicotine might affect behavior must also be considered. The following sections discuss the potential rate-dependent effects of nicotine, and the possibility that nicotine merely increases behavior.

Rate Dependence. One of the most well-known and influential phenomenon in behavioral pharmacology is rate dependence. In 1955, Dews conducted an experiment showing that pentobarbital could have opposite effects on behavior, depending on the schedule of reinforcement maintaining the response (ratio or interval) - the same dose decreased responding on an interval schedule and increased responding on a ratio schedule. This finding was perplexing at the time because it contradicted the notion that some drugs are stimulants and always increase behavior while other drugs are depressants and always decrease behavior. Consequently, behavioral pharmacologists began placing greater emphasis on environmental variables due to their clear interaction with drug effects (Branch, 1984).

Since Dews' initial finding, it has been demonstrated repeatedly that baseline, pre-drug, rates of responding are related to the direction of a drug's effect on responding. The most common rate-dependent effects involve increases in low pre-drug response rates and decreases in high pre-drug response rates. Rate-dependent effects have been demonstrated both within subject and across subjects, and for a number of different drugs, but most often with amphetamine (Lucki, 1983; Saulsgiver, McClure, Wynne, 2007; Wenger & Dews, 1976). Rate-dependent effects are typically plotted as a log percentage of pre-drug response rates (i.e., drug/pre-drug x 100) as a function of log pre-drug response rates. Linear regression analyses are then performed on the data, revealing a negative slope if rate-dependent effects exist, such that

low pre-drug rates increase and high pre-drug rates decrease (Branch, 1984; Poling & Byrd, 2000), and a slope of zero if rate-dependent effects do not exist.

Almost all of the studies that have been used to support the reinforcer-enhancing account of nicotine have involved low response rates that increase when nicotine is present (Chaudhri et al., 2006; Olausson, Jentsch, & Taylor, 2004a, b; Palmatier et al., 2006, 2007; Raiff & Dallery, 2006). There are no known studies with laboratory animals that have directly applied rate-dependent analyses described above to the effects of nicotine. However, Perkins (1999) conducted a review of research on nicotine and found a few instances that were consistent with rate-dependent effects (Shaefer & Michael, 1986; Stitzer, Morrison, Domino, 1970; Vale & Balfour, 1989). For instance, in one study intermediate doses of nicotine did not affect the high rates of responding maintained by a FR1 schedule of intracranial brain stimulation (ICSS), but the same doses did increase the lower rates of responding maintained on a FR 15 schedule of ICSS (Shaefer & Michael, 1986). Due to the relative dearth of research aimed at evaluating rate-dependent effects with nicotine, and the pervasiveness of the phenomenon with other drugs, the need for a more systematic investigation is warranted. It is possible that the increases in responding that occur as a function of nicotine administration can be entirely accounted for (although not necessarily explained) by pre-drug rates of responding.

General Motoric Effects. Probably the most outspoken about their disagreement with the conclusion that nicotine serves as a primary reinforcer or a reinforcer-enhancer are Hanan Frenk and Reuven Dar (Frenk & Dar, 2000, 2004; Dar & Frenk, 2002a, b, 2004, 2005). Frenk and Dar have suggested that the nicotine-induced increases seen in laboratory animals can be accounted for by the general locomotor increasing effects of nicotine. Many of the studies used as evidence of nicotine's primary and/or reinforcer-enhancing roles have argued against the

general locomotor activity account by explaining that increases in responding only occur on the active lever, with the inactive lever used as a control for general, undifferentiated increases in responding (e.g., Chaudhri et al., 2006). Recall that in these experiments subjects were initially trained with food to press the active lever only. Frenk and Dar (2004) argued that comparing active to inactive lever presses was not justified because inactive responses were never reinforced. In other words, Frenk and Dar believe that only responses that have been trained should be expected to increase when nicotine is delivered. Furthermore, there are a number of studies that have demonstrated nicotine's general locomotor increasing effects when studied in an open field activity chamber (Dwoskin, Crooks, Teng, Green, Bardo, 1999; Faraday, Elliott, Phillips, Grunberg, 2003; Green, Cain, Thompson, Bardo, 2003; Koehl, Bjijou, Le Moal, Cador, 2000; Kosowski & Liljequist, 2005; Panagis, Nisell, Nomikos, Chergui, Svensson, 1996). Thus, while evaluating the potential MEO effects of nicotine, it will be necessary to consider the possibility that nicotine increases activity in general.

Present Experiments

In the sections that follow, two experiments are described that sought to investigate the MEO account of nicotine-induced increases in responding, while also considering the possible rate-dependent and general activity increasing effects of the drug. The first experiment evaluated the generality of the MEO account by studying the effects of nicotine on responding maintained by sucrose-based food pellets and conditioned reinforcers, as well as investigating the effects of nicotine on responding during periods of extinction. The second experiment further assessed the potential primary reinforcing function of the visual stimuli used in Experiment 1 and the visual stimuli used in nicotine self-administration studies. Furthermore, two groups of rats were given

different lever training histories to determine whether such differences would influence the effects of nicotine.

CHAPTER 2
EXPERIMENT 1
Introduction

The stimuli associated with nicotine infusions have been conceptualized as conditioned reinforcers because of their repeated pairings with nicotine (Caggiula et al., 2001) and have been compared to the stimuli that are associated with nicotine delivered from cigarettes, such as the smell and taste of smoke (Chaudhri et al., 2006). It has become increasingly clear that the stimuli associated with cigarettes may contribute to smoking maintenance and relapse (Dallery, Houtsmuller, Pickworth, & Stitzer, 2003; Dar & Frenk, 2004; Dols, Willems, & van den Hout, 2000; Field & Duka, 2001; Rose, Behm, Westman, & Johnson, 2000; Rose, Tashkin, Ertle, Zinser, & Lafter, 1985; Westman, Behm, & Rose, 1996). Although a number of procedures have been used to study conditioned reinforcement (Kelleher & Gollub, 1962; Williams, 1994), the two procedures most relevant to the current research will be discussed in detail: the "conditioning a new response" and "observing response" procedures.

Conditioning a New Response

The conditioning a new response procedure was recently used to study self-administered and experimenter-delivered effects of nicotine on responding maintained by conditioned reinforcers (Olausson, Jentch, & Taylor, 2004a, b; Chaudhri et al., 2006). This procedure involves pairing a stimulus (e.g., light & tone) with a primary reinforcer (e.g., water or sucrose). After many exposures of the light and tone paired with the primary reinforcer, a new response is trained (e.g., pressing a lever) by having the response produce the light and tone in the absence of the primary reinforcer. If the response is acquired, the stimulus is said to be a conditioned reinforcer because the primary reinforcer was never made contingent on this new response.

When rats were injected with nicotine prior to sessions using the conditioning a new response procedure, they responded more for the conditioned reinforcer than when they were given

vehicle (Olausson et al., 2004a). When a different group of rats were injected with nicotine for 15 consecutive days prior to the conditioning a new response procedure they responded more to produce conditioned reinforcers than rats given vehicle for 15 consecutive days (Olausson et al., 2004b). These results suggest that nicotine potentiates responding acquired by the putative conditioned reinforcer when it is delivered during, or prior to, acquisition of a new response – this finding is consistent with the MEO account of nicotine discussed earlier.

Although the conditioning a new response procedure is highly regarded for studying conditioned reinforcement, it has several limitations compared to other procedures (Fantino, 1977; Williams, 1994). In the experiments described above, it is not clear whether the light and tone were actually conditioned reinforcers. The authors never measured responding for these stimuli prior to pairing them with the primary reinforcer. Some visual stimuli have been shown to serve as weak primary reinforcers, even without being paired with other primary reinforcers (Goodrick, 1970; Robinson, 1959; Segal, 1959; Stewart, 1960; Tapp, Mathewson, Simpson, 1968). Even if the stimuli are conditioned reinforcers, another limitation of the procedure is that only a few sessions can be conducted before responding begins to diminish. This is because during the acquisition of a new response, pairing between the primary and conditioned reinforcer is broken—that is, the conditioned reinforcer is placed on extinction because it is no longer associated with primary reinforcement. One can only observe a few days of responding for conditioned reinforcers before it becomes less likely and eventually ceases (Williams, 1994). If an effect of nicotine on extinction were the only question, this method would be sufficient; however, it restricts the generality of the results because typically nicotine is taken daily over long periods of time in the presence of conditioned reinforcers. Finally, this procedure only assesses effects of nicotine on putative

conditioned reinforcers, while failing to detect potential effects on other reinforcing consequences (Donny et al., 2003).

Observing response

The observing-response procedure can be used to study a number of environmental events, conditioned reinforcement being one of them (Wyckoff, 1952). This procedure has been used to investigate the conditioned reinforcing properties of drug-associated stimuli; specifically, cocaine and remifentanil (Woods & Winger, 2002) and ethanol (Shahan, 2003). The observing-response procedure involves presenting one stimulus (e.g., red light; S+) with periods of food availability and a different stimulus (e.g., blue light; S-) with periods of extinction (i.e., no food availability). Typically there is one response that produces food (i.e., food responses), when it is available and a different response, hereafter the observing response, that briefly turns on the stimulus associated with the schedule in effect. It should be noted that observing responses are not required for food deliveries to occur and making observing responses does not have any effect on the probability of food being delivered.

Over the years there has been controversy regarding why the stimuli in observing response procedures function as reinforcers. Some have argued that it is because of the conditioned reinforcing properties of the stimuli (Case & Fantino, 1981; Williams, 1994), while others have argued that it is because of the information provided by the stimuli (Berlyne, 1957; Hendry, 1969). Proponents of the information hypothesis argued that observing responses occurred because they reduced uncertainty about how to respond in a particular situation. The S+ and S- both provide an equal amount of information regarding how to respond, and thus either stimulus should maintain observing responses similarly. However, an extensive amount of research has shown that observing responses are primarily maintained by the stimulus associated with food (S+) and not

extinction (S-; Case & Fantino, 1981; Dinsmoor, 1983; Dinsmoor, Brown, & Lawrence, 1972), supporting a conditioned reinforcement account.

There are several reasons to prefer the observing response method to other methods of studying conditioned reinforcement. First, it is possible to examine effects of several different kinds of responses during all sessions: (1) responses maintained by food, (2) responses that have never been explicitly reinforced during extinction, and (3) responses maintained by conditioned reinforcers. Table 2-1 illustrates four hypothetical outcomes regarding the effects of nicotine on each response type just listed. As Table 2-1 shows, the observing response procedure allows for the identification of selective increases in responses maintained by primary or conditioned reinforcers (Outcomes #1 or #2), as well as general increases in responding (Outcome #3) as proposed by Frenk and Dar (2004).

One possible limitation of the observing response procedure is if increases were to occur on both the food and observing lever at the same time (Outcome #4). If this were to happen, it would not be clear whether increases were the result of nicotine's independent effects on each type of consequence, or whether increases in observing responses were the indirect result of increases the value of the back-up primary reinforcer, food. In fact, it has been demonstrated that increases and decreases in the magnitude of the back-up reinforcer result in increases and decreases in the rate of observing responses, respectively (Shahan, 2002). The value of the conditioned reinforcer is necessarily associated with the value of the primary reinforcer. If increases in observing responses were indirectly related to increases in the value of the primary reinforcer in this example, one would expect food-maintained responses to increase prior to, or at the same time as, observing responses. Thus, given that all responses are recorded simultaneously, the observing response

procedure provides a method for isolating the effects of nicotine on different environmental consequences.

In a recent experiment conducted in our lab, Raiff and Dallery (2006) used an observing response procedure to investigate the effects of nicotine, and found that intermediate doses of subcutaneous (s.c.) injections of nicotine (i.e., 0.1, 0.3 and 0.56 mg/kg base) increased observing responses during acute and chronic nicotine administration. Furthermore, slight increases in food-maintained responding were found, but only after chronic nicotine administration. This addresses the concern just described in the previous section, suggesting that the increases in observing responses were independent of potential changes in the value of food. The findings from this study were consistent with the hypothesis that nicotine served as a MEO for the conditioned reinforcers, and it suggests that under some conditions it may even serve as a motivating operation for a more potent primary reinforcer— namely, food. However, Raiff and Dallery (2006) relied solely on rate of responding to infer changes in the value of the reinforcer (i.e., rate of observing responses increased under some doses of nicotine). Another method that has been used to infer the relative value of a reinforcer is resistance to extinction (Nevin, 1974).

Resistance to Extinction

The MEO account specifies that responding will increase when the reinforcing stimuli are available or made contingent on some response. Moreover, if nicotine serves as a MEO by increasing the value of reinforcers, then subjects exposed to nicotine should be more resistant to extinction when reinforcing stimuli are withdrawn. Such a prediction follows from behavioral momentum theory, which distinguishes between response-reinforcer relations and stimulus-reinforcer relations (Nevin, 1974). Response-reinforcer relations suggest that the contingencies of reinforcement are responsible for engendering different response rates. For instance, a variable

ratio schedule will produce a higher rate of responding than a fixed ratio schedule of equal value. Stimulus-reinforcer relations, on the other hand, suggest that situations with a higher rate or larger amount of reinforcement will have greater value, which results in greater resistance to extinction (Nevin & Grace, 2000). A number of studies have corroborated this distinction by showing that responses maintained by a richer schedule or greater amount of reinforcement will be more resistant to extinction than responses maintained by a leaner rate or lower amount of reinforcement, regardless of the rate of responding before extinction (Nevin & Grace, 2000; Nevin, 1974). Thus, if nicotine increases the value of primary and conditioned reinforcers, then responding should be more resistant to extinction when nicotine is present compared to when nicotine is absent.

Purpose of Experiment 1

Experiment 1 sought to: (1) replicate the findings reported by Raiff and Dallery (2006) by administering different doses of nicotine (0.3 and 0.56 mg/kg - the doses that consistently produced increases in responding) across groups of rats, (2) investigate whether nicotine-induced changes in responding could be described as rate-dependent, and (3) assess whether the behavior of rats exposed to nicotine are more resistant to extinction than the behavior of rats exposed to vehicle.

Method

Subjects

Subjects were eighteen naive male Long-Evans rats (Harlan; Indianapolis, IN). The rats were approximately 150 days old at the beginning of the experiment. They were individually housed in hanging polycarbonate cages with bedding, in a room that was temperature and humidity controlled. Subjects had free access to water and were maintained at approximately 85% of their 150 day old ad libitum weights, via post-session feeding (Lab Diet Rodent Diet,

Formula 5001; PMI Nutrition International, LLC; Brentwood, MO). The colony room was on a 12:12 hr light dark cycle (lights on from 8am-8 pm).

Apparatus and Materials

Eight Med Associates® extra tall operant chambers (Model ENV 007; 30.48 cm L x 24.13 cm W x 29.21 cm H) were used to conduct experimental sessions. Chambers were contained in large sound attenuating boxes equipped with fans for ventilation. Intelligence panels, sidewalls, grid floors and drop pans were made of stainless steel; back walls, ceilings, and doors were made of clear polycarbonate. Each intelligence panel contained a food receptacle (5 cm x 5 cm x 3 cm) that was equidistant between two levers (requiring approximately 0.31 N force), each of which measured 4.5 cm x 2 cm and were located 22 cm from the chamber ceiling. Seven cm above each lever were three light-emitting diodes (LED; red, yellow, green; 0.8 cm in diameter, 0.7 cm apart from each other). On the wall parallel to the intelligence panel was a house light (28 volt), centered left to right and 1.5 cm from the ceiling. Purified Rodent Tablets (45 mg sucrose food pellets; TestDiet®, Richmand, IN) were located outside of the chamber, but inside of the sound attenuating box in a circular pellet dispenser (Model ENV-203). A white noise generator was in the experimental room to mask extraneous sounds. Experimental events and data collection took place on a computer in the same room, using Med-PC software and hardware (MED Associates). On drug delivery days, nicotine ([-]-Nicotine Hydrogen Tartrate Salt; Sigma, St. Louis, MO), dissolved in a potassium phosphate buffered saline, was used.

Procedure

All sessions were conducted on separate days, seven days per week, at approximately the same time during the light cycle each day. A 10 min blackout period preceded each session, during which lever presses did not have any programmed consequences, but were recorded. The

pre-session blackout period was implemented to allow for nicotine absorption in subjects receiving nicotine during the Drug Administration condition (described in more detail below). Figure 2-1 shows a schematic of the progression of conditions that are described in the sections that follow.

Pre-tests. All pre-test conditions were conducted before subjects had experience earning food for pressing levers. The first pre-test was intended to evaluate the "operant level" of responding in the presence of the stimuli that were to be used later in the observing response procedure. Hereafter, this condition will be referred to as the "Operant Evaluation" condition. After the blackout period, the houselight was illuminated for 10 additional minutes. The houselight was either blinking (0.3 sec on, 0.3 sec off) or continuously illuminated, alternating every 2 min between the two stimulus types. Lever presses during this 10 min period did not have programmed consequences but were recorded. Operant Evaluation tests were conducted for two consecutive sessions.

Next, responding was evaluated when the consequence for pressing the levers consisted of turning on a blinking or continuous houselight. Hereafter, this condition will be referred to as the "Stimulus Evaluation" condition. After the blackout, the session lasted for 10 min during which one lever was designated as the blink lever and the other lever was designated as the continuous lever (counterbalanced across subjects). One response on the blink lever resulted in 10 sec of a blinking houselight (additional responses on either lever during this 10 sec period did not have programmed consequences, but were recorded), whereas one response on the continuous lever resulted in 10 sec of a continuously illuminated houselight. A response only illuminated the appropriate stimulus when there was no stimulus being presented at the time of the response. The lever assignments remained the same for the first two days of Stimulus

Evaluation (e.g., left blink, right continuous), and were switched for the third and final day (e.g., left continuous, right blink) to assess whether side biases had developed.

Lever training. The day after the final pre-test session, research assistants trained lever pressing by giving subjects 45 mg sucrose pellets when successive approximations of lever pressing were made. These initial training sessions ended after 30 min or after 20 responses on each lever. One response resulted in a food pellet, with the exception that after three consecutive responses on the same lever food could only be earned by pressing the other lever. Hand shaping continued for up to three additional sessions, as needed. Once lever pressing was acquired, rats continued to earn food for pressing levers but were required to strictly alternate between the two levers such that the second consecutive response on one lever did not result in food. These alternation sessions lasted for a maximum of 30 min or until 30 responses had been made on each lever, on seven separate days. The houselight was continuously illuminated during all lever training sessions.

Discrimination training. After rats were trained to press both levers, the Discrimination Training condition began. During the last minute of the blackout period, all three LEDs above each lever were illuminated to signal the beginning of the session. The LEDs turned off after 1 min and the houselight was simultaneously illuminated, either blinking or continuous (component type was randomly determined at the beginning of each session). Components alternated between a continuously illuminated houselight (S+) which signaled periods when food was available for pressing the left, food-extinction, lever (i.e., food components) and a blinking houselight (S-) which signaled periods when food was not available for pressing the food-extinction lever (i.e., extinction components). Initially, the first response on the food-extinction lever after an average of 15 sec (i.e., variable-interval 15 sec [VI 15]) resulted in a food delivery.

After seven sessions, this value was increased to a VI 20 sec schedule of food delivery. VI distributions were composed of 15 values based on the Fleshler-Hoffman distribution (Fleshler & Hoffman, 1962). Components lasted an average of 60 sec (rectangular distribution ranging from 10 to 110 sec); however, if the extinction component was scheduled to change to a food component, it would not change until 5 sec elapsed without a response on either lever (i.e., differential reinforcement of other behavior [DRO] 5 sec). The DRO procedure was implemented to prevent adventitious pairings between responding during extinction components and subsequent transitions to food components. Aside from the DRO contingency, responses on the right, observing, lever did not have any additional programmed consequences during Discrimination Training.

Discrimination Training lasted a minimum of 65 days and until all but two subjects displayed a discrimination index (DI) of 0.75 or higher. Discrimination index was calculated by taking the rate of responding on the food-extinction lever in the presence of the S+, divided by the sum of the rate of responding on the food-extinction lever in the presence of the S+ and S-. Values could range from zero to unity, with higher values indicating greater stimulus control. Two subjects (R223 and R224) did not reach the 0.75 DI criterion. The DRO requirement was then increased from 5 to 10 seconds for these two subjects. This effectively increased DI (0.53 to 0.73 for R223; 0.59 to 0.66 for R224). Because of this improvement, all subjects were moved to the next condition.

Observing response procedure. The DRO contingency was discontinued when the observing response procedure began. During the last minute of the blackout period, all three LEDs above each lever were illuminated to signal the beginning of the session. At the end of one minute, the LEDs turned off making the chamber dark. At the beginning of the session, the

computer randomly determined whether a VI 20 sec food or extinction component would be in effect; however, the stimulus corresponding to the selected component was only shown contingent on a response to the right, observing lever. Initially, only one response (i.e., FR 1) on the observing lever was required to illuminate the schedule correlated stimulus for 10 sec. If a component was scheduled to end during the 10 sec stimulus presentation, the component continued until the stimulus turned off. Immediately after the stimulus turned off the schedule changed. For example, if after 5 sec of S+ stimulus presentation the food component was scheduled to switch to extinction, the S+ and food schedule would remain in effect for the final 5 sec of the stimulus presentation and the component would immediately change to extinction when the stimulus turned off. For the first five sessions of the observing response procedure, the first five observing responses resulted in the S+ stimulus being presented. If the extinction component was in effect when one of the first five responses occurred, the component switched to VI 20 sec food (Shahan, 2002). Otherwise, components alternated every 60 sec on average as described for Discrimination Training.

After 11 sessions under the conditions described above, the VI 20 sec food schedule was increased to a VI 30 sec food schedule. Ten sessions later the observing response requirement was increased from FR1 to VI 5 sec. Thus, the terminal parameters of the observing response procedure consisted of a VI 30 sec food schedule alternating with extinction approximately every 60 sec, and stimuli were presented for 10 sec on a VI 5 sec schedule. Unless otherwise noted, all sessions from this point forward were arranged according to these terminal parameters and were 30 min in duration.

Subjects experienced the terminal parameters for 26 sessions, after which they were stratified into three groups of six based first on observing response rate, second on DI, and third,

when possible, on food-extinction response rates in the presence of the S+ and S-. The three groups differed with respect to the dose of nicotine administered during all subsequent conditions: Vehicle (0 mg/kg nicotine), 0.3 mg/kg Nicotine (base), or 0.56 mg/kg Nicotine (base).

Drug administration. For 70 sessions, subjects received daily pre-session subcutaneous injections of the dose they were assigned. The 70 session Drug Administration condition was divided into four sections for the purposes of clarity and data analysis: Acute administration (sessions 1-5), Chronic administration (sessions 31-35), Resistance to Extinction (sessions 36-40), and Extended Chronic administration (sessions 66-70). Everything operated as normal during the Resistance to Extinction sessions, except that food was no longer delivered during food components. After five sessions food was reintroduced.

Data Analyses. One subject in the Vehicle group never acquired the observing response, defined as an increase in observing responses relative to the Stimulus Evaluation pretest condition. Thus, this subject was eliminated from all analyses, leaving the Vehicle group with n = 5.

To investigate responding during the pretest conditions, a repeated-measures ANOVA was conducted on the left and right levers during the Operant and Stimulus Evaluation conditions. Because of repeated measurement, all results were adjusted for sphericity using Huynh-Feldt correction (Huynh & Feldt, 1976). An additional ANOVA was conducted on mean right lever response rates during the Operant Evaluation, Stimulus Evaluation, the last five sessions of Discrimination training, and the first five sessions of the Observing Response Procedure. Tukey's HSD post-hoc analyses were performed when significant main effects were found.

ANOVAs were also performed to determine whether there were significant differences across the three drug administration groups (Vehicle, 0.3 Nicotine, 0.56 Nicotine) just prior to the Drug Administration condition in mean DI, observing response rates, and food-extinction response rates in the presence of the S+ and S-.

To determine whether there were differences across groups during the Acute, Chronic, Resistance to Extinction, and Extended Chronic sections of the Drug Administration condition, ANOVAs were conducted, with Huhyn-Feldt corrections and Tukey's HSD post-hoc analyses were performed when significant main effects were found.

Finally, to evaluate the presence of rate-dependent effects, linear regression analyses were performed on the log percentage of pre-drug response rates graphed as a function of the log pre-drug response rates during the Acute, Chronic, and Extended Chronic sections of the Drug Administration condition. All response types (i.e., observing, responses maintained by food, and responses during extinction) were included in the same graph to generate a suitable amount of variability in pre-drug response rates to assess rate dependence.

All results were deemed statistically significant at $p < 0.05$.

Results

Because subjects had not yet been divided into groups during the pretest conditions, these conditions were evaluated with all subjects considered as one group. Response rates (resp/min) were low on both the right and left levers during the two days of Operant Evaluation (mean $\pm$ SEM right lever = 0.25 ± 0.04 resp/min; left lever 0.15 ± 0.03 resp/min). Response rates increased on both levers during the Stimulus Evaluation pretest (mean $\pm$ SEM right lever = 0.85 $\pm$ 0.12 resp/min; left lever = 0.67 $\pm$ 0.10 resp/min). There was a significant difference across conditions ($F(1,83) = 28.48$), but there was no significant difference in response rates between the two levers and there was no lever x condition interaction.

Because there was no difference in responding between the right and left levers, Figure 2-2 shows only responding on the right lever, which later became the observing lever. The first two panels of Figure 2-2, labeled "Operant Evaluation" and "Stimulus Evaluation," respectively, show the mean and standard error of the mean (±SEM) for all subjects during the pretests. The third panel of Figure 2-2 shows responding during the last five days of Discrimination Training. The only consequence for pressing the lever during this condition was the DRO contingency that prevented transition from the extinction to the food component. Response rates during the last five days of the Discrimination Training condition averaged 0.78 resp/min (±SEM = 0.08), and were not significantly different from response rates during the Stimulus Evaluation pretest. Finally, the fourth panel of Figure 2-2 shows the rates of responding during the first five days of the Observing Response condition. Response rates increased during this condition to an average of about 4.02 resp/min (±SEM = 0.23). There was a significant difference across conditions ($F(3,251) = 114.1$) and post-hoc analyses revealed that responses during the first five days of the Observing Response condition were significantly higher than the three previous conditions, which were not significantly different from each other.

Mean DI, observing response rate, and food-extinction response rates in the presence of the S+ and S- were computed based on the last five sessions of the Observing Response condition, just prior to the Drug Administration condition, for each subject in a group. These sessions were used to determine group assignment and the means and SEMs for each group are shown in Table 2-2. There were no significant differences between groups on any of the measures.

Figure 2-3 shows mean (±SEM) food-extinction response rates during S+ components (top graph) and S- components (middle graph), as well as observing response rates (bottom

graph). Table 2-3 displays the means (±SEM) of the response rates displayed in Figure 2-3. Figures 2-4, 2-5, and 2-6 show response rates for individual subjects on the Food-Extinction lever in the presence of the S+, S- and Observing lever, respectively, with a different subject in each individual graph and groups organized in columns (from left to right: Vehicle, 0.3 Nicotine, 0.56 Nicotine). All of the graphs in Figures 2-3 through 2-6 are organized the same, with the first panel of each graph showing the last five sessions of the pre-drug condition, the second panel showing the acute sessions, the third panel showing the chronic sessions, and the fourth panel showing the extended chronic sessions.

The top graph in Figure 2-3 shows that food-extinction response rates in the presence of the S+ were high for all groups during the pre-drug condition, and there were no significant differences across groups. Response rates in the presence of the S+ remained high throughout the three Drug Administration sections shown in Figure 2-3, and there were no significant differences in response rates across groups during any of the sections.

The middle graph in Figure 2-3 illustrates that food-extinction response rates during S- presentations were lower during the pre-drug condition than food-extinction response rates during S+ presentations, but again there were no significant differences across drug administration groups. During the Acute Drug Administration section there was a significant difference across groups ($F(2,81) = 4.472$) and post-hoc analyses revealed that the 0.3 Nicotine group responded significantly more than the Vehicle and 0.56 Nicotine groups (Table 2-3). There were also significant differences in response rates across groups during the Chronic Drug Administration section ($F(2,81) = 3.35$). However, unlike during the Acute section, during the Chronic section post-hoc analyses revealed a marginally significant ($p=0.05$) increase in the 0.56 Nicotine group. Finally, there were significant differences in response rates across groups during

the Extended Chronic Drug Administration section ($F(2,81) = 3.69$). Post-hoc analyses revealed that the Vehicle group responded significantly more than the 0.3 Nicotine group, but not more than the 0.56 Nicotine group. There were no significant differences between the 0.3 and 0.56 Nicotine groups.

The bottom graph in Figure 2-3 shows that observing response rates during the pre-drug condition were similar across groups (also see Table 2-3). Acute nicotine administration resulted in a significant difference across groups ($F(2,81) = 7.25$), and post-hoc analyses revealed that response rates for the 0.3 Nicotine group were significantly higher than response rates for both the Vehicle and 0.56 Nicotine groups. Similarly, there were significant differences across group during the Chronic Drug Administration section ($F(2,81) = 6.58$). During Chronic, however, post-hoc analyses revealed a significant increase in response rates for both the 0.3 and the 0.56 Nicotine groups, relative to the Vehicle group. This significant increase in response rates continued ($F(2,81) = 13.62$) for both groups after extended exposure to nicotine. It is worth noting that there was a decreasing trend in observing responses across the last five sessions of the Chronic section for the 0.3 Nicotine group; however, after Resistance to Extinction observing responses increased and remained stable at this higher rate. The mean effects shown in Figure 2-3 are consistent with the majority of the individual subject effects shown in Figures 2-4 through 2-6 for each response type.

The Chronic Drug Administration section immediately preceded the five days of Resistance to Extinction. Because response rates were different across groups for each of the three responses during the Chronic section, it was necessary to control for these differences to evaluate resistance to extinction (Nevin, 1974). Figure 2-7 shows that, as expected, all three response types decreased across the five days of Resistance to Extinction. There were no

significant differences in the proportions of food-extinction responding in the presence of the S+ (top graph) or in the proportions of observing responses (bottom graph) across the five extinction sessions. There were also no significant differences in the food-extinction proportions of responding in the presence of the S- (middle graph) during the first four days of extinction. On day five, there was a significant difference across groups ($F(2,14) = 9.982$) and post-hoc analyses revealed that subjects in the Vehicle group had significantly higher proportions of responding than subjects in the 0.3 and 0.56 Nicotine groups (mean $\pm$ SEM Vehicle = 0.38 $\pm$ 0.04; 0.3 Nicotine = 0.18 $\pm$ 0.05; 0.56 Nicotine = 0.13 $\pm$ 0.03).

To examine rate-dependent effects, scatter plots were created for each group of subjects. Pre-drug response rates were calculated by averaging response rates during the last five sessions of the Observing Response procedure that immediately preceded the Drug Administration condition. Log percentage of pre-drug rates were calculated and graphed as a function of log pre-drug rates. Three separate plots were created for each condition across the three groups, with all of the response types (i.e., observing, food-extinction S+ and S-) included in each plot, as shown in Figure 2-8. Lines were fitted to the data by least-squares regression and the fitted parameter values for the slope and *y*-intercept, as well as the r^2 value, for each line is shown in Table 2-4. There were seven instances, out of nine, in which the fitted slopes were significantly different from zero: a positive slope for the Vehicle group during the Chronic section, and negative slopes for the 0.3 and 0.56 Nicotine groups during all three sections.

Discussion

Experiment 1 supports the MEO account by showing that nicotine increased responding maintained by conditioned reinforcers (i.e., visual stimuli that had been associated with food availability). Extended, repeated exposure to nicotine more than doubled the number of

responses per 30 min session from approximately 125 responses, seen with the Vehicle group, to over 250 responses, seen with the two nicotine groups (see Table 2-3). The increases in the present study were reliable and robust, and sustained changes in responding over the course of the experiment were specific to responses maintained by conditioned reinforcers. That is, nicotine did not reliably increase responding maintained by food reinforcers at any point, and any increases in responding during extinction (e.g., 0.3 Nicotine during Acute and 0.56 Nicotine during Chronic) were not sustained.

To investigate further the MEO account of nicotine, resistance to extinction was compared across groups of rats given nicotine or vehicle. If nicotine increased the reinforcing value of the conditioned reinforcers, then this should have resulted in a context with a richer amount of reinforcement relative to the vehicle control group. According to behavioral momentum, responses occurring in the context of a richer amount of reinforcement should be more resistant to extinction (Nevin, 1974; Nevin & Grace, 2000). Instead, nicotine did not affect resistance to extinction on any of the response types studied. Several possibilities might account for this lack of effect. One possibility is that nicotine did not serve as a MEO in the present study, and that the increases in observing responses were due to a different mechanism. One alternative mechanism that has been discussed is that nicotine generally increases lever pressing because of its effects on activity (Frenk & Dar, 2004). However, responding during extinction served as a control for detecting general increases in motor capacity, and nicotine did not increase responding during extinction.

On the other hand, a lack of effect of nicotine on resistance to extinction may have been due to limitations in the behavioral momentum account of resistance to extinction. The current study was designed to compare resistance to extinction across subjects, whereas behavioral

momentum theory has been almost entirely developed by comparing resistance to extinction within subjects and within sessions. The typical paradigm for studying behavioral momentum is to use a multiple schedule comprised of a rich and lean schedule, with greater resistance to extinction in the rich relative to the lean schedule (for a review see Nevin & Grace, 2000). In fact, one study was unable to demonstrate greater resistance to extinction in a rich relative to a lean schedule when resistance was compared across conditions or sessions with simple schedules of reinforcement, rather than within the same session (Cohen, Riley, Weigle, 1993).

Furthermore, it has not yet been demonstrated that higher rates of conditioned reinforcement will necessarily result in greater resistance to extinction, as it occurs with higher rates of primary reinforcement. Shahan and Podelsnik (2005) used a complex multiple observing response procedure, whereby a rich component resulted in a higher rate of conditioned reinforcement, contingent on observing responses, relative to a lean component. Observing response rates were higher in the rich component, but subjects did not demonstrate greater resistance to extinction in the rich component relative to the lean component. The authors explained that two levels of conditioning would need to take place for resistance to occur with conditioned reinforcers: (1) pairings between the primary reinforcers and the stimuli that are being established as conditioned reinforcers and (2) pairings between the higher rate or amount of conditioned reinforcers and the context in which they occur. The same can be said of the current study in that the visual stimuli were being paired with food during S+ presentations, and subjects in the two nicotine groups presumably experienced an experimental context with a larger amount of reinforcement than subjects in the Vehicle group. At this time it is not clear whether the behavioral momentum theory of resistance to extinction applies to such second-order levels of conditioning because of a general lack of research designed to study such phenomena.

The present study also had the advantage of generating a range of response rates, making it possible to evaluate whether nicotine produced rate-dependent effects (Table 2-4 and Figure 2-8). Of the nine regression analyses, six resulted in negative slopes that were significantly different from zero (increases in low pre-drug rates and decreases in high pre-drug rates). It is important to note that there was never more than 21% of the variance accounted for by the linear equations, as indicated by the r^2 values shown in Table 2-4. Nevertheless, the data do suggest a tendency for rate-dependent effects of nicotine.

Finally, pretests were conducted to determine whether the illumination of a continuous and blinking houselight would function as a primary reinforcer, similar to what other researchers have demonstrated (Barry & Symmes, 1963; Goodrick, 1970; Kiernan, 1965; Marx, Henderson, Roberts, 1955; Roberts, Marx, Collier, 1958; Robinson, 1959; Segal, 1959; Tapp, Mathewson, Simpson, 1968; Stewart, 1960), and whether the stimuli would later come to function as conditioned reinforcers. There was, indeed, an increase in lever pressing during the Stimulus Evaluation condition, relative to the Operant Evaluation condition, suggesting a weak primary reinforcing function of the stimuli. During Discrimination Training the stimuli were associated with a multiple schedule of food and extinction – conditions which have been shown to establish stimuli as conditioned reinforcers (Dinsmoor, 1983). During the first five days of the Observing Response condition, responses that turned on a houselight increased to more than four times the response rates seen during the Stimulus Evaluation condition. In fact, observing response rates continued to increase with extended exposure to the procedure (compare Figures 2-2 and 2-3). The increases were not simply due to the presence of food during the sessions, which may have caused some arousal (Killeen, Hanson, Osborne 1978), because there were no significant

increases during Discrimination Training. This finding suggests that the stimuli were established as conditioned reinforcers.

Table 2-1. Hypothetical effects of nicotine on responding maintained by each of the response types investigated with the observing response procedure

	Outcome			
Response	#1	#2	#3	#4
Food-extinction (S+)	↑	--	↑	↑
Food-extinction (S-)	--	--	↑	--
Observing	--	↑	↑	↑

Table 2-2. Mean ± SEM DI, Observing response rate, food-extinction response rates in the presence of the S+ and S- from the five sessions prior to the Drug Administration condition

Group	D.I.	Observing	Food-extinction (S+)	Food-extinction (S-)
Vehicle	0.73 ± 0.02	5.63 ± 0.53	37.62 ± 1.01	14.68 ± 1.65
0.3 Nicotine	0.73 ± 0.02	6.21 ± 0.97	37.34 ± 3.34	15.97 ± 2.34
0.56 Nicotine	0.74 ± 0.02	5.62 ± 0.76	47.31 ± 5.54	16.09 ± 1.47

Table 2-3. Mean ± SEM response rates just prior to and during the Drug Administration condition for food-extinction response rates in the presence of the S+ and S-, and for observing responses

	Pre-Drug	Acute	Chronic	Extended Chronic
		Food-Extinction (S+)		
Vehicle	37.62 ± 1.01	41.27 ± 1.32	46.59 ± 2.92	46.54 ± 2.31
0.3 Nicotine	37.34 ± 3.34	45.24 ± 3.54	38.88 ± 2.56	42.84 ± 2.11
0.56 Nicotine	47.31 ± 5.54	34.45 ± 4.14	38.83 ± 2.27	42.13 ± 2.50
		Food-Extinction (S-)		
Vehicle	14.68 ± 1.65	15.20 ± 1.82 [a]	12.07 ± 1.90 [c]	15.53 ± 1.55 [e]
0.3 Nicotine	15.97 ± 2.34	22.78 ± 2.48 [a b]	11.74 ± 0.99 [d]	11.33 ± 0.94 [e]
0.56 Nicotine	16.09 ± 1.47	15.87 ± 1.45 [b]	15.97 ± 1.05 [c d]	14.54 ± 0.98
		Observing Responses		
Vehicle	5.63 ± 0.53	5.52 ± 0.48 [a]	4.65 ± 0.52 [c d]	4.25 ± 0.38 [e f]
0.3 Nicotine	6.21 ± 0.97	9.69 ± 1.05 [a b]	7.32 ± 0.89 [c]	7.99 ± 0.69 [e]
0.56 Nicotine	5.62 ± 0.76	5.84 ± 0.86 [b]	8.19 ± 0.56 [d]	9.02 ± 0.77 [f]

Note: Within each response type, values in each column indicated by the same superscripted letter (e.g., [a]) were significantly different from each other with $p < 0.05$.

Table 2-4. Fitted parameter values and corresponding r^2 for each linear regression applied to the rate-dependent graphs shown in Figure 2-8.

Phase	Group	Slope	*y*-intercept	r^2
Acute	Vehicle	0.16	102	0.01
	0.3 Nicotine*	-2.30	211	0.15
	0.56 Nicotine*	-2.00	176	0.06
Chronic	Vehicle*	1.27	71	0.12
	0.3 Nicotine*	-0.8	125	0.08
	0.56 Nicotine*	-3.2	252	0.16
Extended Chronic	Vehicle	0.53	99	0.01
	0.3 Nicotine*	-1.8	169	0.21
	0.56 Nicotine*	-3.7	282	0.13

Note: Asterisks denote slopes that were significantly different from zero.
Vehicle: Chronic - F (1,73) = 9.9;
0.3 Nicotine: Acute - F (1,88) = 16.67; Extended Chronic - F (1,88) = 24.02
0.56 Nicotine: Acute - F (1,84) = 11.74; Chronic - F (1,88) = 164.53; Extended Chronic - F (1,88) = 82.4

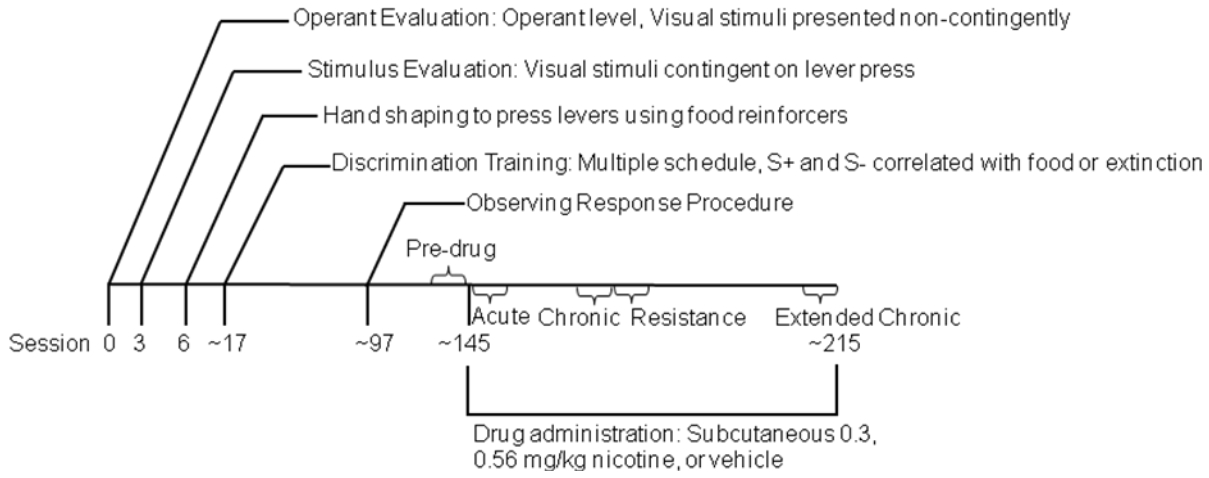

Figure 2-1. Experiment 1 schematic. Shows the progression of conditions throughout the experiment. Vertical lines indicate the beginning of a condition and the number below the line is the approximate session number. Bracketed areas indicate different sections within the observing response procedure that were subjected to statistical analyses.

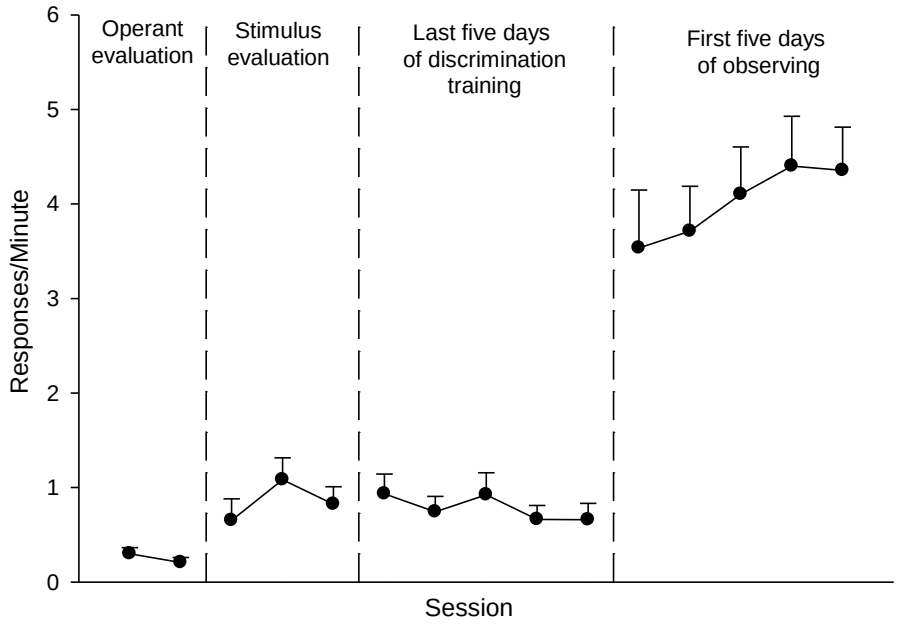

Figure 2-2. Pretests. Mean ± SEM resp/min for all subjects are shown. The first two panels show resp/min on the right (future observing) lever during the Operant and Stimulus Evaluation pretests. The third and fourth panels show resp/min on the right lever during the last five sessions of Discrimination Training and the first 5 days of the Observing Response procedure, respectively. The third and fourth panels represent 10 consecutive sessions.

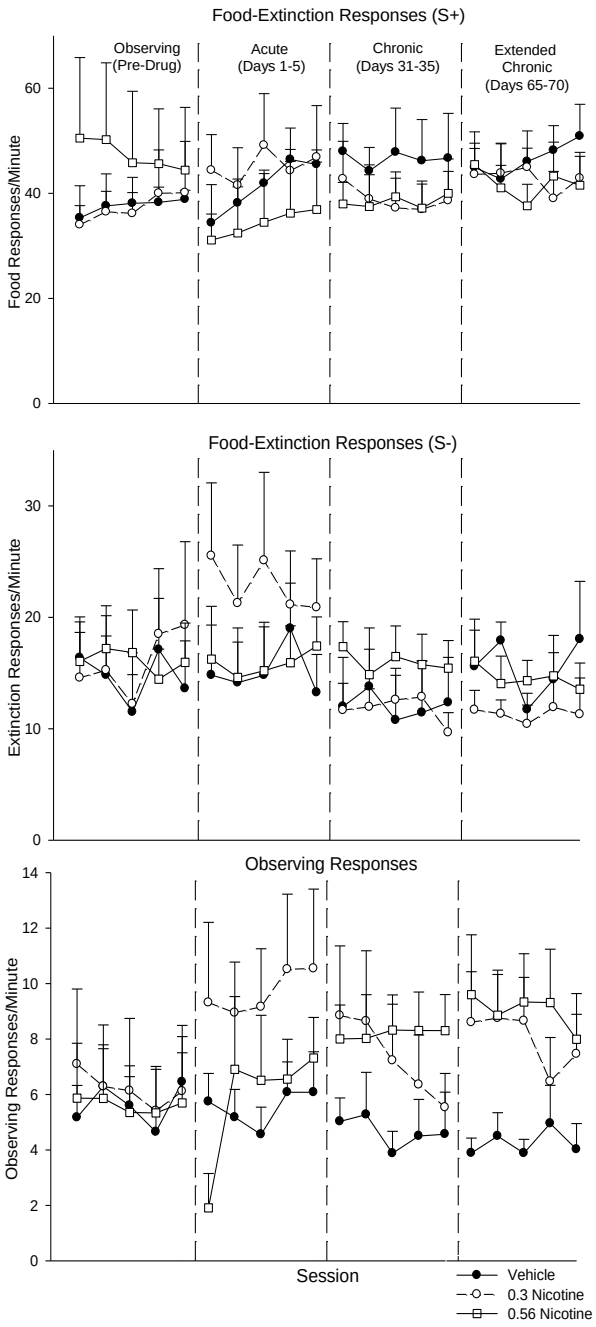

Figure 2-3. Mean (±SEM) Food-Extinction S+, S- and Observing Responses for the Vehicle group (filled circles), the 0.3 Nicotine group (open circles), and the 0.56 Nicotine group (open squares). The first panel of each graph shows the last five sessions of the Observing Response condition, immediately preceding the Drug Administration condition. The next three panels represent five sessions from three of the sections of the Drug Administration condition: Acute, Chronic, Extended Chronic. The top graph (a) shows resp/min on the food-extinction lever in the presence of the S+ (i.e., food-maintained responses). The middle graph (b) shows resp/min on the food-extinction lever in the presence of the S- (i.e., responses during extinction) and the bottom graph (c) shows resp/min on the observing response lever. Note different y-axes for each of the three response types.

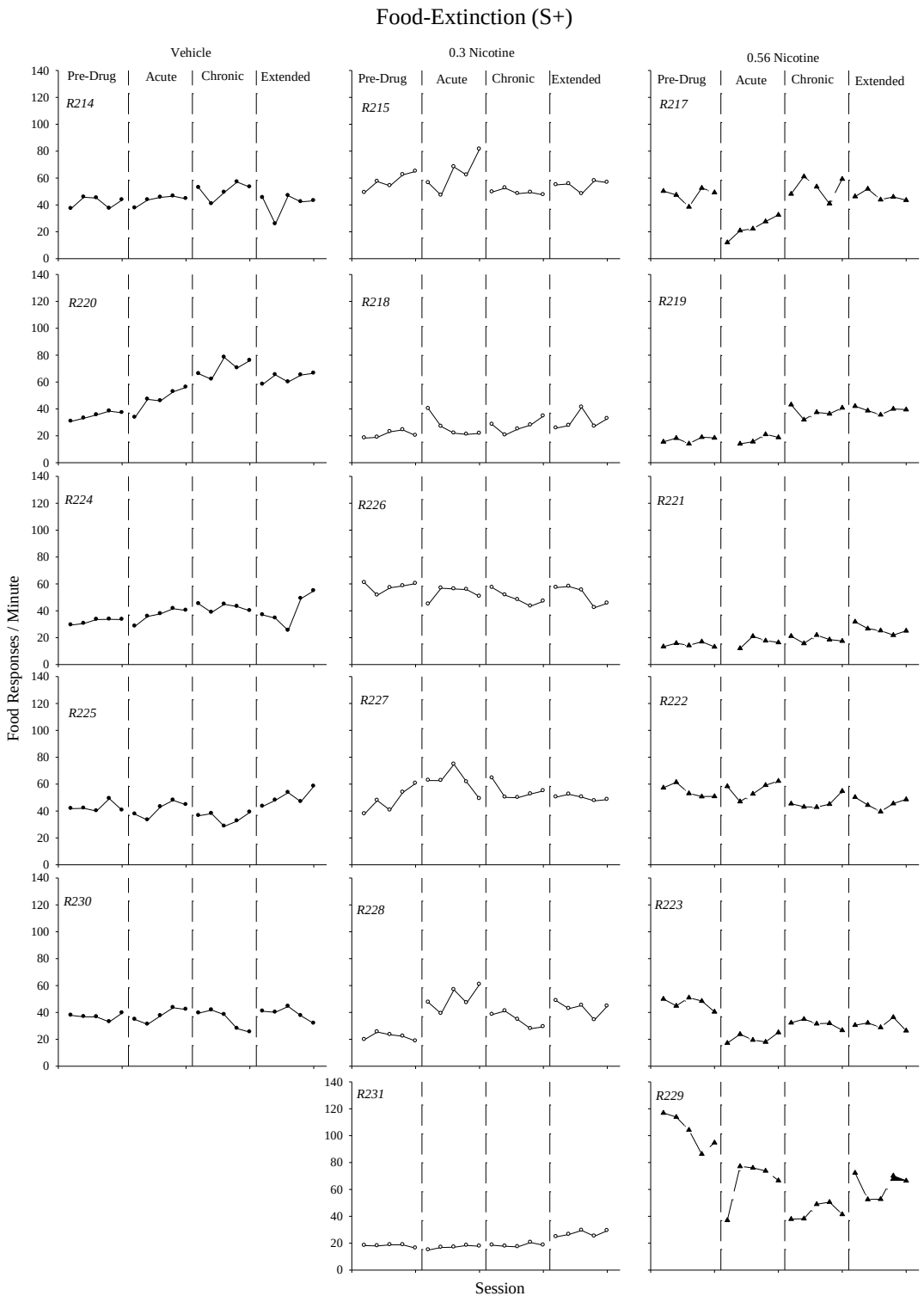

Figure 2-4. Individual subject data showing Food-Extinction responses on the S+ for the last five sessions of the Pre-Drug, Acute, Chronic, and Extended Chronic sections. Each graph is a different subject, with drug administration group organized in columns, from left to right, showing the Vehicle (filled circles), 0.3 Nicotine (open circles), and 0.56 Nicotine groups (filled triangles), respectively.

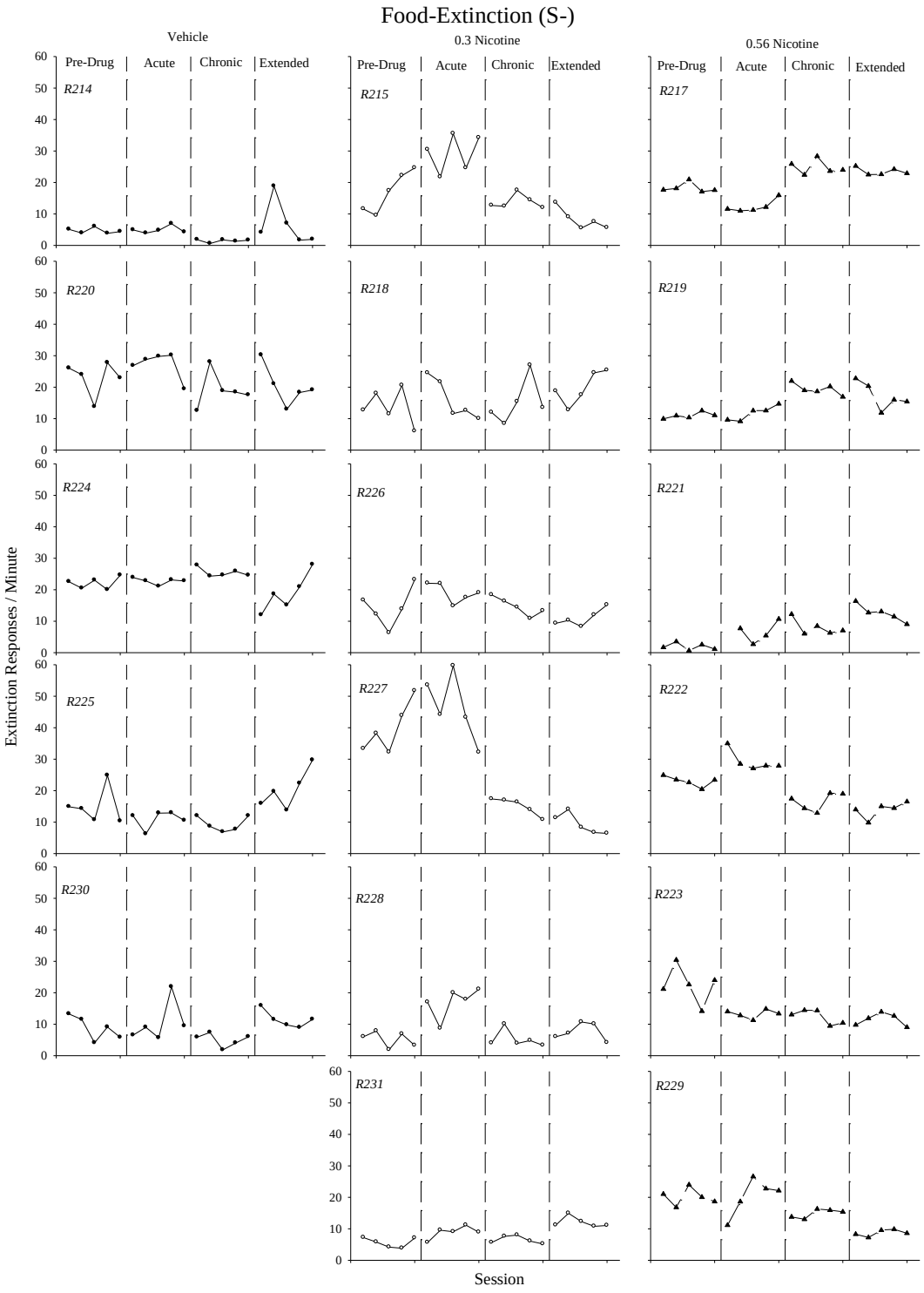

Figure 2-5. Individual subject data showing Food-Extinction responses on the S- for the last five sessions of the Pre-Drug, Acute, Chronic, and Extended Chronic sections. Each graph is a different subject, with drug administration group organized in columns, from left to right, showing the Vehicle (filled circles), 0.3 Nicotine (open circles), and 0.56 Nicotine groups (filled triangles), respectively.

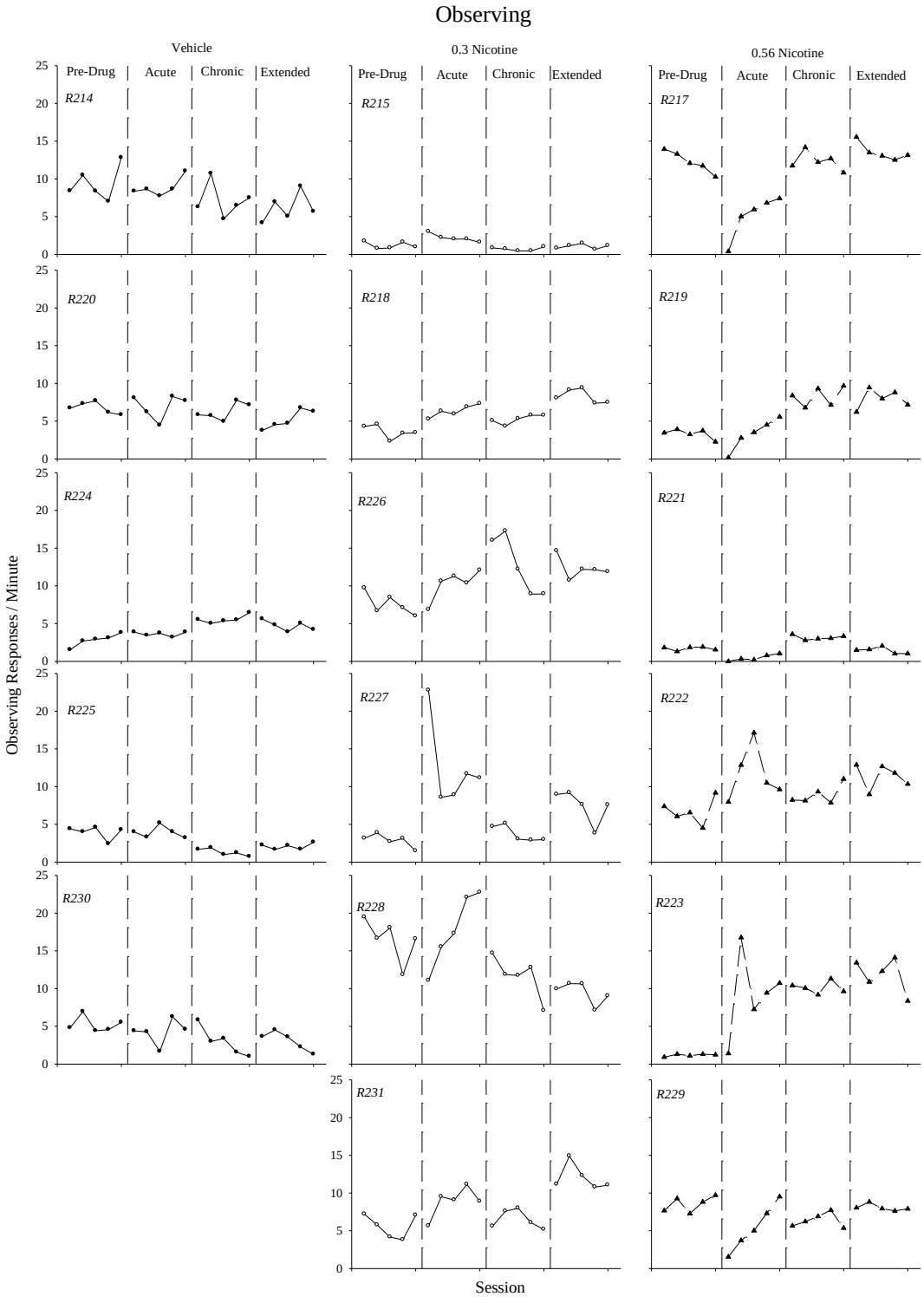

Figure 2-6. Individual subject data showing Observing responses for the last five sessions of the Pre-Drug, Acute, Chronic, and Extended Chronic sections. Each graph is a different subject, with drug administration group organized in columns, from left to right, showing the Vehicle (filled circles), 0.3 Nicotine (open circles), and 0.56 Nicotine groups (filled triangles), respectively.

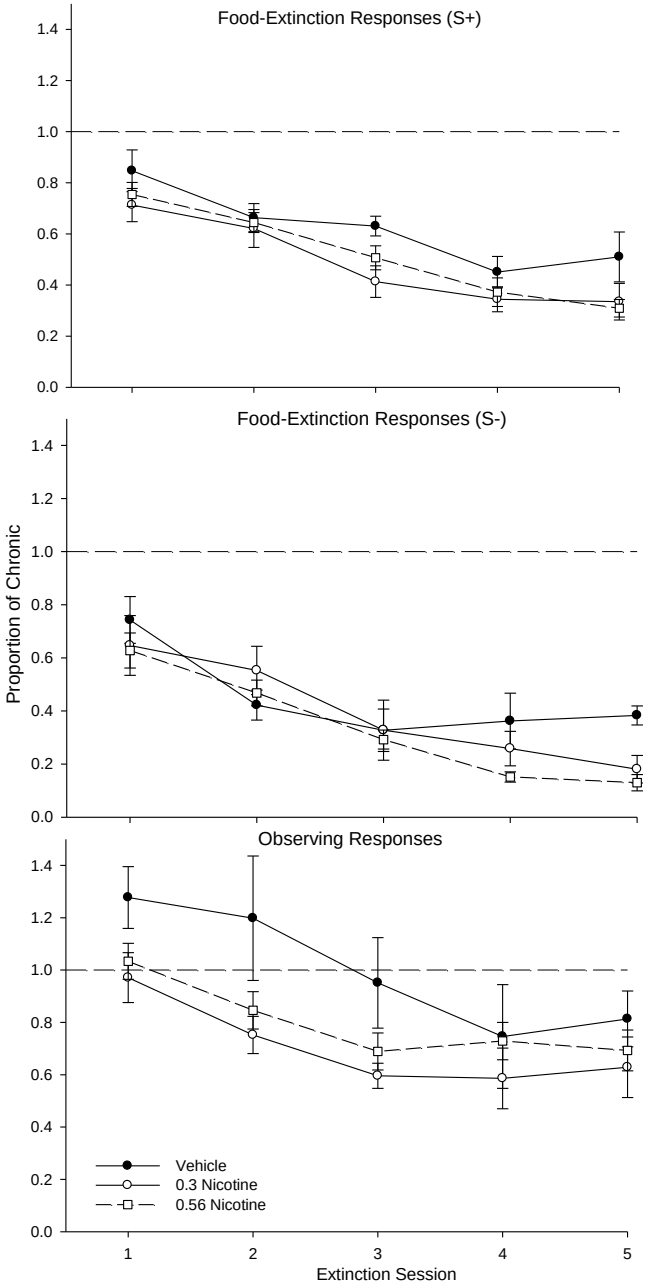

Figure 2-7. Resistance to Extinction. Mean ± SEM proportion of Chronic resp/min for subjects in the Vehicle group (filled circles), the 0.3 Nicotine group (open circles), and the 0.56 Nicotine group (open squares). The top graph (a) shows proportion of Chronic resp/min on the food-extinction lever in the presence of the S+ (i.e., food-maintained responses). The middle graph (b) shows proportion of Chronic resp/min on the food-extinction lever in the presence of the S- (i.e., responses during extinction) and the bottom graph (c) shows proportion of Chronic resp/min on the observing response lever. The dotted line at 1.0 indicates no change from Chronic, with values above and below the line indicating increases and decreases, respectively.

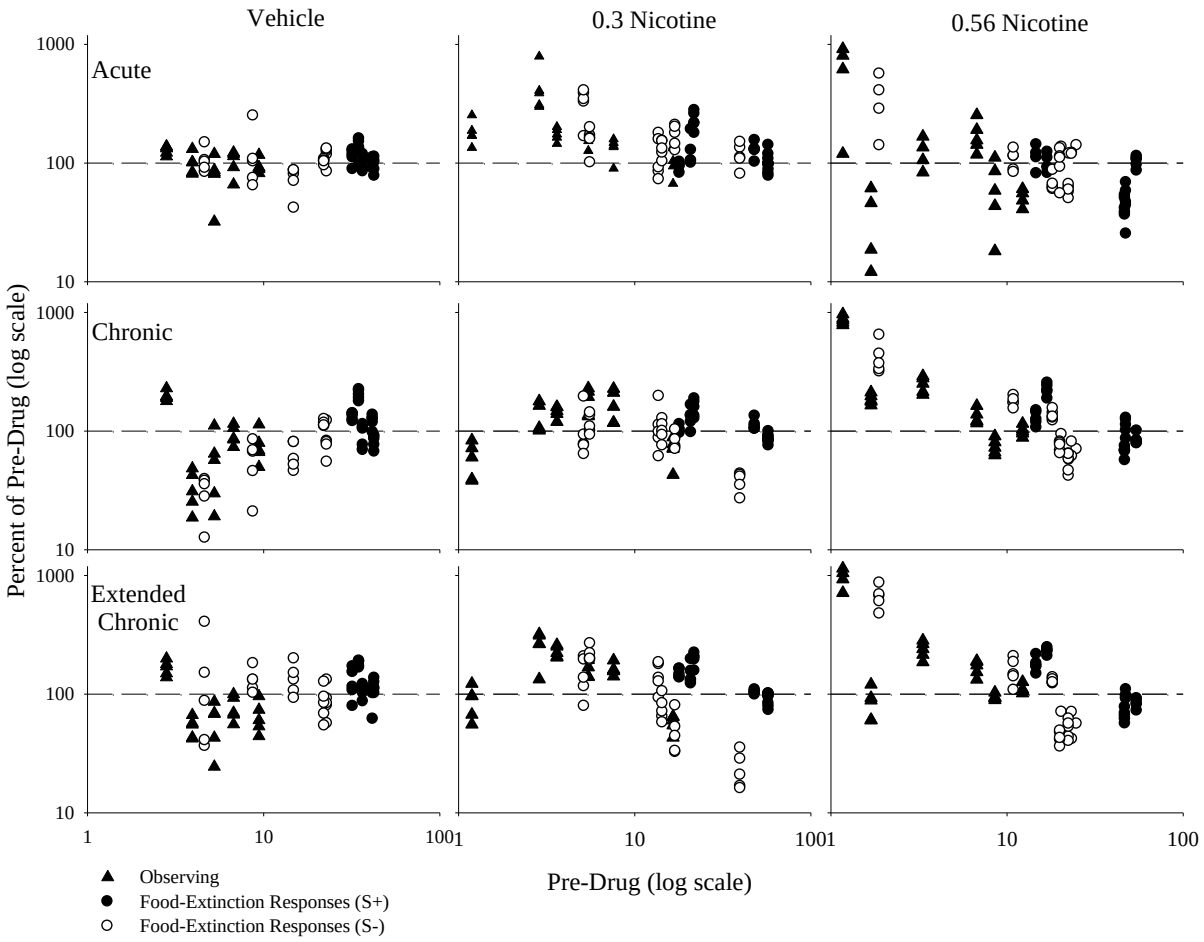

Figure 2-8. Rate-dependent scatterplots. Rate-dependent scatter plots for the Vehicle (left column), 0.3 Nicotine (middle column), and 0.56 Nicotine (right column) Groups. Shown are the log percentage of pre-drug response rates plotted as a function of log pre-drug response rates for the Acute (top row), Chronic (middle row), and Extended Chronic (bottom row) sections. All three response types are shown together on each plot – observing (filled triangles), food-extinction S+ (filled circles), and food-extinction S- (open circles). Equations, with the fitted parameter values and r^2 can be found in Table 2-4

CHAPTER 3
Experiment 2
Introduction

The results of the Stimulus Evaluation condition of Experiment1 showed that rates of responding increased slightly, relative to the operant level, when the visual stimuli were made contingent on a response. This finding suggested that the stimuli may have initially functioned as weak or moderate primary reinforcers. It is important to note, however, that the Operant and Stimulus Evaluation sessions were brief (10 min) and were only conducted over a five day period to avoid over-exposure – and perhaps conditioned inhibition – to the stimuli that would later be used as conditioned reinforcers (Lubow & Moore, 1959). It is possible that the increases seen during the Stimulus Evaluation condition were due to general increases in lever pressing that would have occurred over time, regardless of the consequences arranged. Thus, although the data suggested that the stimuli did serve a primary reinforcing function, this conclusion was only tentative.

Other researchers have suggested that under some conditions visual stimuli can function as weak or moderate primary reinforcers (Barry & Symmes, 1963; Goodrick, 1970; Kiernan, 1965; Kish, 1966; Marx, Henderson, Roberts, 1955; Roberts, Marx, Collier, 1958; Robinson, 1959; Segal, 1959; Tapp, Mathewson, Simpson, 1968; Stewart, 1960). A recent study compared groups of rats to determine the effects of pre-session injections of nicotine on responding maintained by two visual stimuli that generated different levels of responding: (a) turning off the houselight in an operant chamber for 5 sec, which resulted in approximately 35 responses during a 60 min session, and (b) turning on a stimulus light in an operant chamber for 5 sec, which resulted in approximately 10 responses during a 60 min session (Palmatier et al., 2007). Nicotine administration increased responding in the group of rats whose behavior was maintained by

turning off the houselight, to about 100 responses per session, but there were no significant increases in responding in the other group of rats whose behavior was maintained by turning on the stimulus light. All rats in the study were initially trained to press the active lever using food as a consequence for pressing, in the same way that active lever responses are typically trained in nicotine self-administration studies (Caggiula et al., 2001; Chaudri et al., 2006; Donny et al., 2003). As discussed earlier, Frenk and Dar (2004) posited that lever training history may contribute to the nicotine-induced increases seen only on the active lever. Thus, a more systematic investigation of lever training history is warranted.

Purpose of Experiment 2

Experiment 2 sought to: (1) explore the putative primary reinforcing function of the visual stimuli used in Experiment 1 (i.e., turning on a houselight), as well as the visual stimuli used in a number of nicotine self-administration studies (i.e., turning off a houselight; Caggiula et al., 2002; Palmatier et al, 2007), (2) determine whether different histories of lever training would influence the apparent primary reinforcing effects of the visual stimuli, (3) assess whether nicotine would have different effects on responding, as a function of lever training history and the type of visual stimulus (turning on versus turning off the houselight), and (4) further investigate the rate-dependent effects of nicotine. The lever training protocol and general procedural design were based on the procedures used by Caggiula and colleagues (e.g., Caggiula et al., 2002b) to investigate nicotine self-administration. Such procedures consisted of food-depriving subjects and then exposing them to two sessions of lever training with food reinforcers, then gradually increasing the FR schedule of contingent stimulus presentations (five sessions of FR1, five sessions of FR2, ending with a terminal FR5 schedule).

Methods

Subjects

Eight experimentally naïve male Long-Evans rats (Harlan; Indianapolis, IN), maintained at 85% (326-408 g) of their 150 day old ad libitum weights, served as subjects. Subjects were housed in individual home cages with bedding, and received free access to water and post-session supplemental rodent chow (Lab Diet Rodent Diet; Formula 5001). The colony room was on a 12:12 hour light dark cycle (light from 8am-8pm).

Apparatus and Materials

Sessions were conducted in 8 Med Associates® extra tall operant chambers. The operant chambers were identical to those used during Experiment 1 described earlier. Med-PC software and hardware were used to program experimental events on a computer located in the experimental room. The computer also collected and stored data after each session. On drug delivery days, nicotine ([-]-Nicotine Hydrogen Tartrate Salt; Sigma, St. Louis, MO), dissolved in potassium phosphate buffered saline, was used.

Procedure

Subjects were randomly assigned to one of two groups, differing only with respect to their lever training history. One group of subjects (n = 4) was trained to press both the right and left lever, hereafter the "Two-Lever" group. The second group of subjects (n = 4) was trained to press the right lever only, hereafter the "One-Lever" group. During lever training the only lights that were illuminated in the chamber were the red LEDs located above each lever. Lever training took place on two separate days.

Two-Lever Training. Day one of training consisted of research assistants delivering food for approximations of pressing either the right or left lever, until one response was made on

each lever. From that point forward, one food pellet was delivered for each lever press, with the restriction that the same lever could not be pressed more than three consecutive times. The fourth, and all subsequent, responses on the same lever did not have any programmed consequences, until at least one response on the alternate lever was made. The first day of training lasted 30 min or until subjects earned 20 pellets for pressing each lever (i.e., 40 total pellets). The second day of training was identical to the first, except that there were no time limits and sessions ended after 37 pellets had been earned for pressing each lever (74 total).

One-Lever Training. As with the Two-Lever group, the first day of training began with research assistants delivering food for approximations of lever pressing, but for pressing the right lever only. This continued until one response was made on the right lever, after which only responses to the right lever were followed by food pellet delivery. Responses on the left lever never had programmed consequences. The first training day ended after 30 min or after 40 pellets had been earned for pressing the right lever. The second training day was identical to the first, except that there was no time limit and sessions ended after 74 pellets had been earned for pressing the right lever.

Lights On and Lights Off. After lever training, subjects in both the One-Lever and the Two-Lever groups experienced all of the same procedures. Sessions were conducted at approximately the same time during the light cycle, seven days per week. To begin, all 6 LEDs were illuminated five seconds after the subject was placed into the operant chamber. A single response on either lever, or 60 sec without any response, turned off the LEDs and began the 60 min session. The active lever was designated as the right lever. At the beginning of the session the operant chamber was dark during the Lights On phase, whereas the operant chamber was lit by the houselight during the Lights Off phase. If no response was made on the active lever,

subjects remained in a dark or lit operant chamber, depending on the phase. Initially only one response on the active lever (i.e., fixed ratio [FR] 1) produced 10 sec of the houselight turned on (Lights On) or off (Lights Off). Additional active lever responses during the stimulus presentation did not have any programmed consequences, nor did responses on the inactive lever, but all responses were recorded. After five sessions of FR1 stimulus presentation, the response requirement was increased to FR2 for an additional five sessions, after which the response requirement was increased to a final value of FR5. A minimum of 10 sessions at FR5 were required before stability was evaluated. The total number of responses per 60 min session were deemed stable by visual inspection if there were no increasing or decreasing trends (i.e., five consecutive sessions with all responses moving in the same direction) and as long as the highest or lowest number of responses did not occur during one of the last three sessions. Conditions changed upon meeting the stability criteria or after a maximum of 30 sessions, whichever occurred first.

Exposure to the Lights On and Lights Off phases was counterbalanced across subjects within a group, such that two subjects in each group were exposed to the Lights On phase first. The first phase for all subjects, regardless of whether it was Lights On or Lights Off, was an ABAB design (with the exception of two subjects, R251 from the Two-Lever group and R257 from the One-Lever group, for whom it was an ABABA and ABAC design, respectively). The A conditions were baseline with a FR5 schedule of stimulus presentation and without drug administration. The B conditions consisted of daily subcutaneous (s.c.) administration of 0.3 mg/kg nicotine (base). For subject R257 the C condition consisted of daily s.c. administration of 0.56 mg/kg nicotine (base).

Between phases subjects remained in their home cages for 7 days, but continued to be weighed daily and maintained at 85% of their ad libitum weights. At the beginning of phase 2, stimuli were again initially available on a FR1 schedule and the FR requirement increased to 5, as described earlier. Because subject R257 was not responding, lever training was repeated for this subject over a two day period in the same way that it was described earlier. All of the other subjects pressed the levers reliably and thus did not need additional lever training. The second phase for all subjects consisted of an ABABAC design. For all but subject R257, the A and B conditions were the same as those just described for phase 1 and the C conditions consisted of daily s.c. administration of potassium phosphate vehicle. The only difference for subject R257 was that the B conditions consisted of daily s.c. administrations of 0.1 mg/kg nicotine instead of 0.3 mg/kg.

Data Analysis. Two, 2 x 2 x 6 repeated-measure ANOVAs were conducted with lever training group (One-Lever versus Two-Lever), lever (active versus inactive) and condition (three baseline, two nicotine, one vehicle) compared for each phase (Lights On and Lights Off). An additional ANOVA was conducted to compare phase (Lights On versus Lights Off), lever, and condition, regardless of group assignment. All results were adjusted for sphericity using Huynh-Feldt corrections (Huynh & Feldt, 1976). To evaluate the presence of rate-dependent effects, linear regression analyses were performed on the log percentage of pre-drug responses graphed as a function of the log pre-drug responses during the Lights On and Lights Off phases. Active and inactive responses were included on the same graph and three linear regression analyses were performed for each phase: (1) both active and inactive responses grouped together, (2) active responses only, and (3) inactive responses only. All analyses were deemed statistically significant at $p < 0.05$.

Results

At the completion of the experiment a computer malfunction was discovered for subject R251 during all but the first two conditions of phase 1 (Lights Off), making the data uninterpretable. Thus, only the first two conditions are shown and applied to the data analyses for this subject during Lights Off.

Table 3-1 displays the mean (±SEM) proportion of responses allocated to the active lever during the two days of shaping and during each subsequent experimental condition. During shaping for the Two-Lever group, both levers were technically active; however, the data are expressed as a proportion of the lever that became active in subsequent conditions. Two subjects in the Two-Lever group (R252 & R253) responded about equally on both levers during shaping, while the other two subjects showed a slight preference for the lever that became inactive during subsequent conditions (R251 & R255). All of the subjects in the One-Lever (R254, R256, R257, R258) group allocated more responses to the active lever than on the inactive lever during shaping. During all of the remaining conditions, every subject, regardless of group assignment, allocated most of their responses to the active lever (almost always 90% or more).

Figure 3-1 shows the last five sessions per condition for each subject during the Lights On phase. As indicated in Table 3-1, a greater number of responses were allocated to the active lever than to the inactive lever for every subject and every condition (mean ± SEM: Active lever = 81.3 ± 4.5, Inactive lever: 4.4 ± 0.3) with the exception of subject R257 during the second nicotine condition (recall that this subject received a 0.56 mg/kg dose of nicotine during this condition) - this difference was statistically significant ($F(1,188) = 425.6$). There was a significant effect of condition ($F(5, 188) = 23.8$), as well as a significant lever x condition interaction ($F(5,188) = 23.6$), with nicotine reliably increasing responses on the active lever

(mean ± SEM = 126.7 ± 14.0), relative to baseline (mean ± SEM = 51. 7 ± 6.9) and vehicle conditions (mean ± SEM = 65.2 ± 11.0), but not reliably increasing responses on the inactive lever. There were no significant lever x group or lever x group x condition interactions.

Likewise, Figure 3-2 shows the last five sessions per condition during the Lights Off phase. As during the Lights On phase, a greater number of responses were allocated to the active lever than to the inactive lever for every subject and every condition (mean ± SEM: Active lever = 135.1 ± 8.6, Inactive lever: 4.8 ± 0.4), with the exception of the first baseline condition for subject R255 ($F(1,188) = 375.0$). Again, there was a significant effect of condition ($F(5, 188) = 33.2$) and a significant lever x condition interaction ($F(5, 188) = 34.2$), with nicotine reliably increasing active (mean ± SEM = 228.3 ± 26.6), but not inactive, responses relative to baseline (mean ± SEM = 74.5 ± 11.6) and vehicle (mean ± SEM = 117.7 ± 18.7) conditions. As before, there were no lever x group or lever x group x condition interactions. Furthermore, there was a significant lever x phase interaction ($F(1, 378) = 52.9$), whereby a greater number of responses occurred on the active lever during the Lights Off phase (mean ± SEM = 135.1 ± 8.7) than during the Lights On phase (mean ± SEM = 81.3 ± 4.5).

Figures 3-3 and 3-4 are cumulative response records for one representative rat from each group (R252 and R258) during the Lights On and Lights Off phases, respectively. Each row for a subject shows the final session from a condition. Deflections in the record represent the beginning of the 10 sec stimulus presentation, and the pen resets at the end of the 10 sec. Responses that occurred after the deflection took place during the stimulus presentation. In both phases, the slopes became steeper during nicotine conditions, relative to baseline and vehicle conditions. Additionally, pauses between responses appeared to be less frequent and shorter in duration during nicotine conditions. It is also important to note that during all conditions, it was

rare for a response to occur during the stimulus presentation. Table 3-2 shows the proportion of stimulus presentations during which at least one response occurred (active or inactive). For most subjects under most conditions, less than 40% of the stimulus presentations contained a response. One subject, R251, was more likely than all the other subjects to respond during a stimulus presentation.

The cumulative response records also revealed two distinct patterns of responding during nicotine administration conditions, which warranted further investigation. One pattern was an increase in response rates during the first 5-10 min of the session that diminished during the remainder of the session, as seen for both subjects during the Lights On phase (Figure 3-3). The other pattern was a constant high rate of responding throughout the entire session, as seen during both nicotine conditions for R258 and the second nicotine condition for R252 during Lights Off (Figure 3-4). All other subjects, except R257, showed one or both of these patterns during nicotine administration conditions. Time course analyses were conducted on all of the last five sessions of each condition for both the Lights On and the Lights Off phases to further investigate these patterns. Because there were no differences between lever training groups, all subjects were evaluated as one group. Furthermore, because post-hoc analyses and visual inspection of the data did not reveal a significant difference across subsequent exposures to a particular condition (e.g., the first versus the second exposure to baseline), such conditions were collapsed into one. Shown in Figure 3-5 are the mean ($\pm$ SEM) number of responses during each 2 min bin of the 60 min session. Figure 3-5 shows that there is a peak in responding on both the active and inactive lever during the first 10 min of the session, regardless of phase. The peak in responding during this early portion of the session increased substantially during the nicotine conditions, but only on the active lever.

During the Lights On phase, nicotine-induced increases in responding occurred throughout the entire session. Although responding remained elevated, relative to baseline levels, there were no differences in responding between nicotine and vehicle during the last 10 min of the session because of increases in responding during the vehicle condition. During the Lights Off phase, the nicotine-induced increases became stable after approximately 10 min and remained well above baseline levels for the remainder of the session. Again, responding increased during the vehicle condition during the last 20 min of the session, such that by the end of the session levels were just slightly less than those seen during the last 20 min of the nicotine conditions. Although there was a similar peak in responding occurred during the first 5-10 min of the session on the inactive lever, the total number of responses was very low (note the difference in scales). There was a general tendency for responding to be higher during the nicotine conditions; however, these increases were not reliably present during the session and were small in magnitude.

Finally, to examine rate-dependent effects scatter plots were created for each phase. Pre-drug responses were calculated by averaging responses during the last five sessions of the baseline conditions that immediately preceded the nicotine conditions. Log percentage of pre-drug response rates were calculated and graphed as a function of log pre-drug response rates for both the active and inactive lever, with both responses shown on the same graph. Lines were fitted to the data three separate times for each phase, using least-squares regression, and the fitted parameter values (slope and *y*-intercept) for each line are shown in Table 3-3, as well as the percentage of variance accounted for by the line (r^2). The first line for each phase was fitted to both active and inactive responses together, which did not result in slopes that were significantly different from zero for either phase. The second line was fitted to the active lever only, and for

both phases the slope was negative and significantly different from zero. Finally, the third line was fitted to the inactive lever only, and again the negative slopes were significantly different from zero during both phases.

Discussion

Experiment 2 showed that visual stimuli, turning on and turning off a houselight, functioned as primary reinforcers for rats. Regardless of whether subjects were initially trained to press one or both levers, all subjects eventually showed a strong preference for the active lever. It is important to note that during lever training, subjects who were trained to press both levers allocated their responses equally across the two levers, until food was removed and stimulus changes were presented contingent on active lever responses only (Table 3-1, subjects R251, R252, R253, and R255). Thus, visual stimulus change as a consequence in its own right engendered preference for the active lever for a group of rats who were trained to press both levers equally often. This finding suggests that the visual stimuli used in the present study functioned as primary reinforcers.

An alternative account regarding the responses occurring in Experiment 2 is that visual stimulus change elicited responses, rather than reinforced responses. There are at least two lines of evidence that make the elicitation account implausible. First, if the stimuli elicited lever pressing then they should have been just as likely to elicit inactive responses as they were to elicit active responses, especially for the Two-Lever training group. Second, this account becomes even less likely when examining Table 3-2 and the cumulative records of Figures 3-3 and 3-4, which all show that when the stimuli were present, responding was not likely to occur. The mean proportion of stimuli that contained a response averaged around 0.32 – in other words, during almost 70% of stimulus presentations no response was made. Furthermore, even with the

reliable, pronounced increases in responding during nicotine conditions, there were no consistent changes (increases or decreases) in the proportion of stimuli that contained a response.

The present study also had the advantage of generating a range of response rates across the active and inactive levers, making it possible to evaluate whether nicotine produced rate-dependent effects (Table 3-3 and Figure 3-6). When active and inactive responses were evaluated with a single regression analysis, the slopes were not statistically significant during either phase. However, when active and inactive response rates were analyzed separately, the negative slopes (increases in low pre-drug rates and decreases in high pre-drug rates) were significantly different in all four cases. It is important to point out that on the inactive lever, regardless of the phase, there were increases at the low pre-drug rates and decreases at the high pre-drug rates. Alternatively, on the active lever there were only a few instances of responses decreasing, all of which were during the Lights Off phase with subject R257 (recall that this subject did not show nicotine-induced increases in responding at any time during this phase). Otherwise, active lever response rates only increased – but to a greater extent, proportionally, with lower pre-drug rates than with higher pre-drug rates. Similar to Experiment 1, Table 3-3 shows that the percentage of variance accounted for by the linear regressions were small, in this case never exceeding 12%. Nevertheless, as with Experiment 1, the data do suggest a tendency for rate-dependent effects of nicotine.

The results from Experiment 2 provide additional support for the MEO account of nicotine by showing that responding maintained by primary reinforcing visual stimulus changes increased when nicotine was delivered. Similar increases were not noted on the inactive lever, even for subjects who were initially trained to press the inactive lever with food as a consequence (Two-Lever group). Nicotine increased responding maintained by both types of

stimulus change (Lights On and Lights Off). The absolute increases in responding in the Lights Off phase of the current study were comparable with the increases noted by other researchers (Donny et al., 2003; Palmatier et al., 2007). However, the increases seen in the current study during the Lights On phase are contrary to the findings by Palmatier et al (2007), who only saw increases in responding maintained by turning off the houselights. The current study involved turning on the houselight, from a dark chamber, whereas Palmatier et al. had subjects turning on a stimulus light located above the lever. Furthermore, the current study maintained a greater number of responses per session during the Lights On phase than were seen in the lights on group in the Palmatier et al study. Indeed, stimulus intensity has been found to affect the primary reinforcing function of visual stimulus reinforcers on FR 5 schedules of reinforcement (Stewart, 1960), with lights of stronger intensity maintaining a greater number of responses. Furthermore, in the current study not only were sessions conducted during the light cycle but subjects were also fed during the light cycle. Palmatier et al. conducted sessions and fed subjects during the dark cycle. Rearing conditions (light or dark) have been shown to influence the reinforcing effects of turning on and off houselights (Roberts, Marx, Collier, 1958).

It is important to note, however, that the effects of nicotine were not identical across the two stimulus types, as indicated by the time-course analyses in Figure 3-5. Although nicotine produced a peak in responding in the second 2 min block for both the Lights On and the Lights Off phase, the nicotine-induced increases in responding diminished to a greater extent throughout the remainder of the Lights On session relative to the Lights Off session. Palmatier at al. (2007) did not begin experimental sessions until 5 min after the nicotine injection was administered, whereas in Experiment 2 sessions began immediately after nicotine administration. Although not statistically significant, there were slight increases in responding in the group of

rats who turned on the stimulus lights in the Palmatier et al. study. This procedural difference may also account for some of the differences between the current study and that of Palmatier et al. (2007); however, in Experiment 2 there were still significant increases in responding to turn on the lights when nicotine was delivered, even when the first five minutes were omitted from the analyses.

At least two hypotheses have been offered regarding why turning on and turning off visual stimuli might function as primary reinforcers: (1) curiosity, exploration, or novelty and (2) stimulus change (Kish, 1966). If the visual stimuli used in Experiment 2 maintained responding because of curiosity, exploration, or novelty, then with extended exposure responding maintained by such stimuli should have decreased. Instead responding was sustained over dozens of sessions, and in some cases even increased over time. Thus, a stimulus change hypothesis is more consistent with the results of Experiment 2, especially because responding during the lights on and lights off phases were comparable.

Ultimate explanations regarding *why* a particular consequence serves as a reinforcer are not typically addressed by behavior analysts; however, speculations regarding why visual stimulus change might function as a reinforcer can be made. It is possible that stimulus change in general corresponds with an increase in access to reinforcement. In the past, rats for which stimulus change functioned as a reinforcer may have been more likely to survive. In other words, the reinforcing effects of visual stimulus change may be due to phylogeny – behavior that occurs because of the natural selection history of the species (Skinner, 1969).

Table 3-1. Proportion of responses on the active lever

		Lights On					
Subject	Shaping	Baseline 1	Nicotine 1	Baseline 2	Nicotine 2	Baseline 3	Vehicle
R251	--	0.93 ± 0.02	0.93 ± 0.01	0.93 ± 0.02	0.94 ± 0.01	0.96 ± 0.01	0.98 ± 0.01
R252	0.46 ± 0.02	0.93 ± 0.02	0.88 ± 0.02	0.93 ± 0.02	0.90 ± 0.01	--	--
R253	0.47 ± 0.11	0.91 ± 0.03	0.98 ± 0.01	0.97 ± 0.03	0.98 ± 0.01	--	--
R254	--	0.93 ± 0.01	0.97 ± 0.01	0.95 ± 0.01	0.98 ± 0.01	0.97 ± 0.01	0.93 ± 0.01
R255	--	1.00 ± 0.00	0.98 ± 0.01	0.94 ± 0.04	0.95 ± 0.01	1.00 ± 0.00	0.97 ± 0.02
R256	0.60 ± 0.01	0.94 ± 0.02	0.93 ± 0.01	0.96 ± 0.02	0.95 ± 0.02	--	--
R257	0.82 ± 0.13	0.77 ± 0.05	0.96 ± 0.04	0.85 ± 0.01	0.70 ± 0.12	--	--
R258	--	0.92 ± 0.02	0.96 ± 0.01	0.90 ± 0.03	0.97 ± 0.01	0.96 ± 0.01	0.94 ± 0.02
		Lights Off					
R251	0.38 ± 0.11	0.92 ± 0.02	0.88 ± 0.01	--	--	--	--
R252	--	0.83 ± 0.04	0.90 ± 0.02	0.97 ± 0.01	0.98 ± 0.01	0.97 ± 0.01	0.97 ± 0.01
R253	--	0.91 ± 0.01	0.99 ± 0.01	1.00 ± 0.01	0.99 ± 0.01	0.98 ± 0.01	0.99 ± 0.01
R254	0.72 ± 0.12	0.77 ± 0.04	0.92 ± 0.01	0.91 ± 0.02	0.99 ± 0.01	--	--
R255	0.40 ± 0.02	0.64 + 0.11	0.96 ± 0.01	0.98 ± 0.01	0.99 ± 0.01	--	--
R256	--	0.96 ± 0.01	0.98 ± 0.01	0.97 ± 0.01	0.98 ± 0.01	0.97 ± 0.01	0.99 ± 0.01
R257	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.99 ± 0.01	0.99 ± 0.01
R258	0.87 ± 0.05	0.81 ± 0.05	0.95 ± 0.01	0.96 ± 0.01	0.97 ± 0.02	--	--

Table 3-2. Proportion of stimulus presentations during which a response was made

Lights On						
Subject	Baseline 1	Nicotine 1	Baseline 2	Nicotine 2	Baseline 3	Vehicle
R251	0.52 ± 0.07	0.45 ± 0.06	0.58 ± 0.08	0.63 ± 0.02	0.66 ± 0.07	0.65 ± 0.03
R252	0.13 ± 0.02	0.37 ± 0.04	0.31 ± 0.06	0.34 ± 0.05	--	--
R253	0.15 ± 0.07	0.10 ± 0.02	0.20 ± 0.04	0.18 ± 0.05	--	--
R254	0.23 ± 0.08	0.28 ± 0.05	0.28 ± 0.04	0.30 ± 0.02	0.22 ± 0.02	0.32 ± 0.07
R255	0.13 ± 0.10	0.20 ± 0.02	0.44 ± 0.20	0.28 ± 0.02	0.34 ± 0.20	0.30 ± 0.20
R256	0.41 ± 0.10	0.38 ± 0.03	0.37 ± 0.07	0.47 ± 0.09	--	--
R257	0.00 ± 0.00	0.00 ± 0.00	No stimuli	No stimuli	--	--
R258	0.34 ± 0.10	0.37 ± 0.03	0.36 ± 0.04	0.34 ± 0.04	0.21 ± 0.06	0.30 ± 0.08
Lights Off						
R251	0.45 ± .05	0.55 ± 0.06	--	--	--	--
R252	0.06 ± 0.06	0.20 ± 0.04	0.38 ± 0.07	0.27 ± 0.03	0.27 ± 0.03	0.29 ± 0.04
R253	0.30 ± 0.09	0.38 ± 0.06	0.25 ± 0.02	0.29 ± 0.03	0.28 ± 0.03	0.27 ± 0.04
R254	0.28 ± 0.10	0.50 ± 0.06	0.39 ± 0.02	0.33 ± 0.03	--	--
R255	No stimuli	0.46 ± 0.02	0.46 ± 0.01	0.40 ± 0.02	--	--
R256	0.20 ± 0.04	0.28 ± 0.02	0.23 ± 0.06	0.41 ± 0.01	0.30 ± 0.04	0.39 ± 0.05
R257	0.08 ± 0.07	0.14 ± 0.10	0.13 ± 0.10	0.34 ± 0.07	0.57 ± 0.20	0.18 ± 0.10
R258	0.42 ± 0.10	0.58 ± 0.04	0.35 ± 0.05	0.34 ± 0.02	--	--

Table 3-3. Fitted parameter values and corresponding r^2 for each linear regression applied to the rate-dependent graphs shown in Figure 3-6.

Phase	Lever	Slope	*y*-intercept	r^2
Lights On	Both	-68	374	0.006
	Active*	-252	576	0.08
	Inactive*	-4020	527	0.11
Lights Off	Both	-97	559	0.007
	Active*	-486	1223	0.12
	Inactive*	-1494	374	0.08

Note: Asterisks denote slopes that were significantly different from zero.
Lights On: Active - F (1,78) = 6.42; Inactive - F (1,73) = 9.02
Lights Off: Active - F (1,73) = 10.34; Inactive - F (1,63) = 5.76

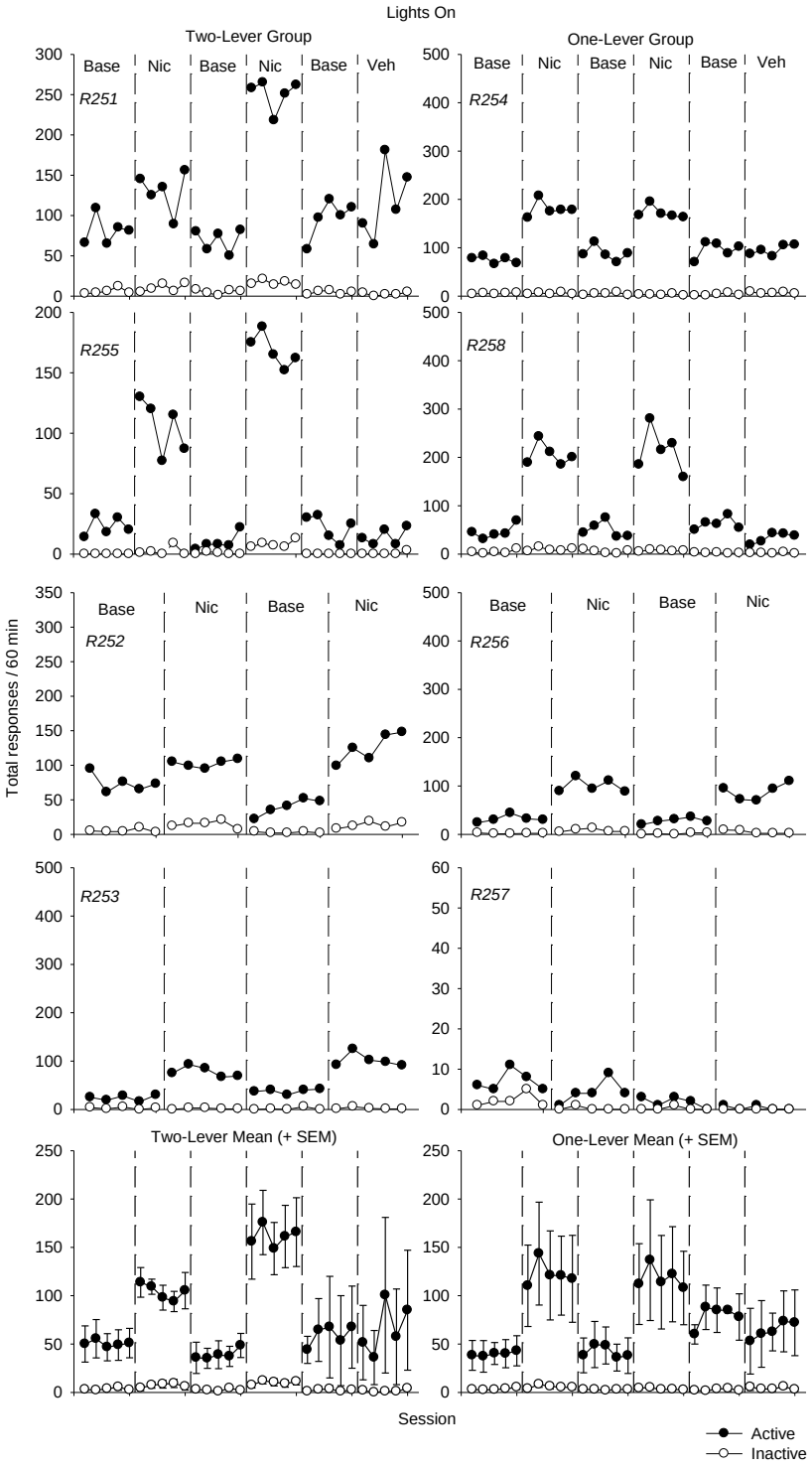

Figure 3-1.Total Responses during Lights On. Shown are total responses per 60 min for the last five sessions of each condition. The left column shows data from subjects in the Two-Lever training group and the right column shows those from the One-Lever training group. The bottom row shows the mean (±SEM) for each group. Filled circles represent responding on the active lever and open circles represent responding on the inactive lever. Note the different y-axes for each subject. Base = baseline, Nic = Nicotine, Veh = Vehicle.

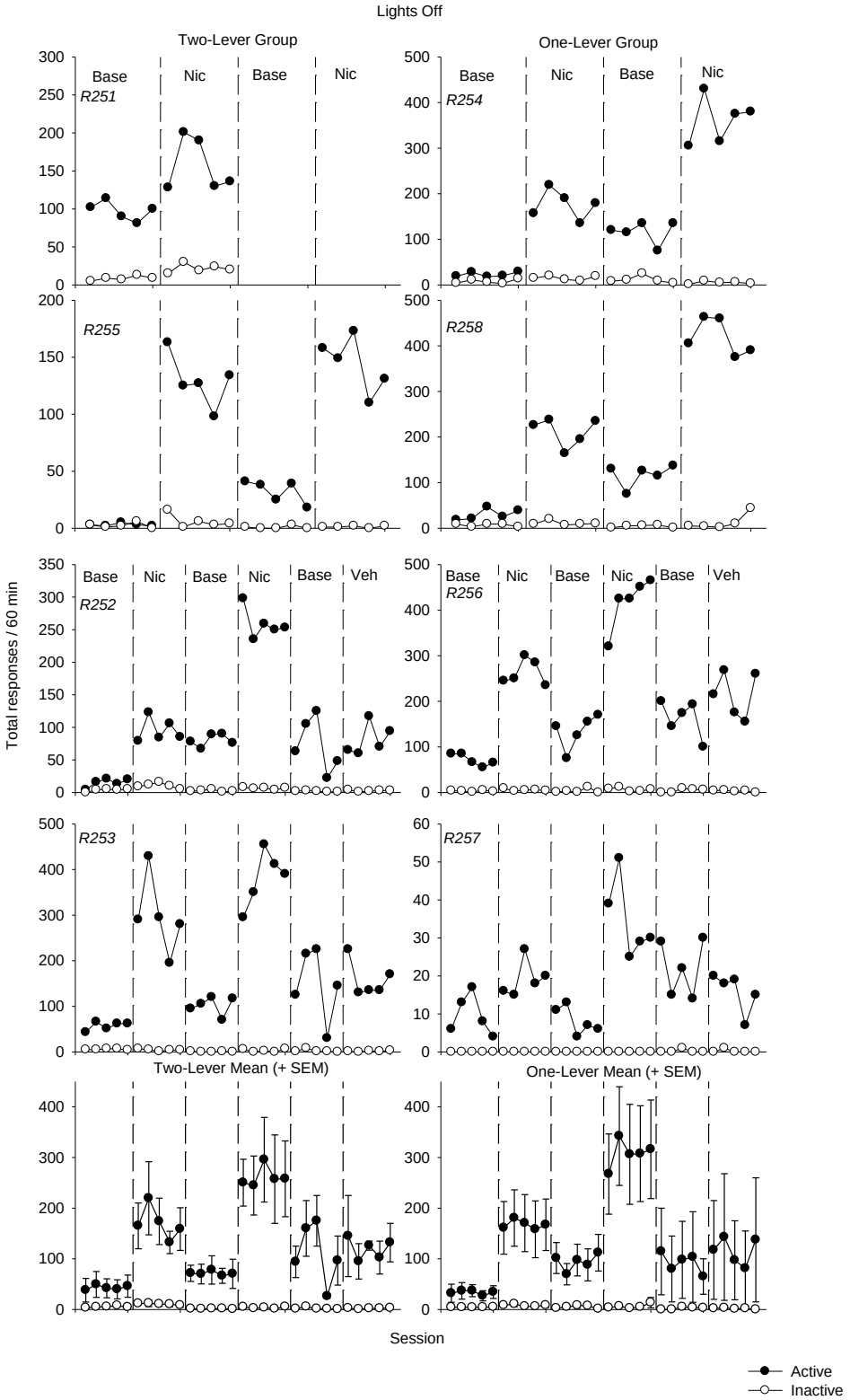

Figure 3-2. Total Responses during Lights Off. Shown are total responses per 60 min for the last five sessions of each condition. The left column shows data from subjects in the Two-Lever training group and the right column shows those from the One-Lever training group. The bottom row shows the mean (±SEM) for each group. Filled circles represent responding on the active lever and open circles represent responding on the inactive lever. Note the different y-axes for each subject. Base = baseline, Nic = Nicotine, Veh = Vehicle.

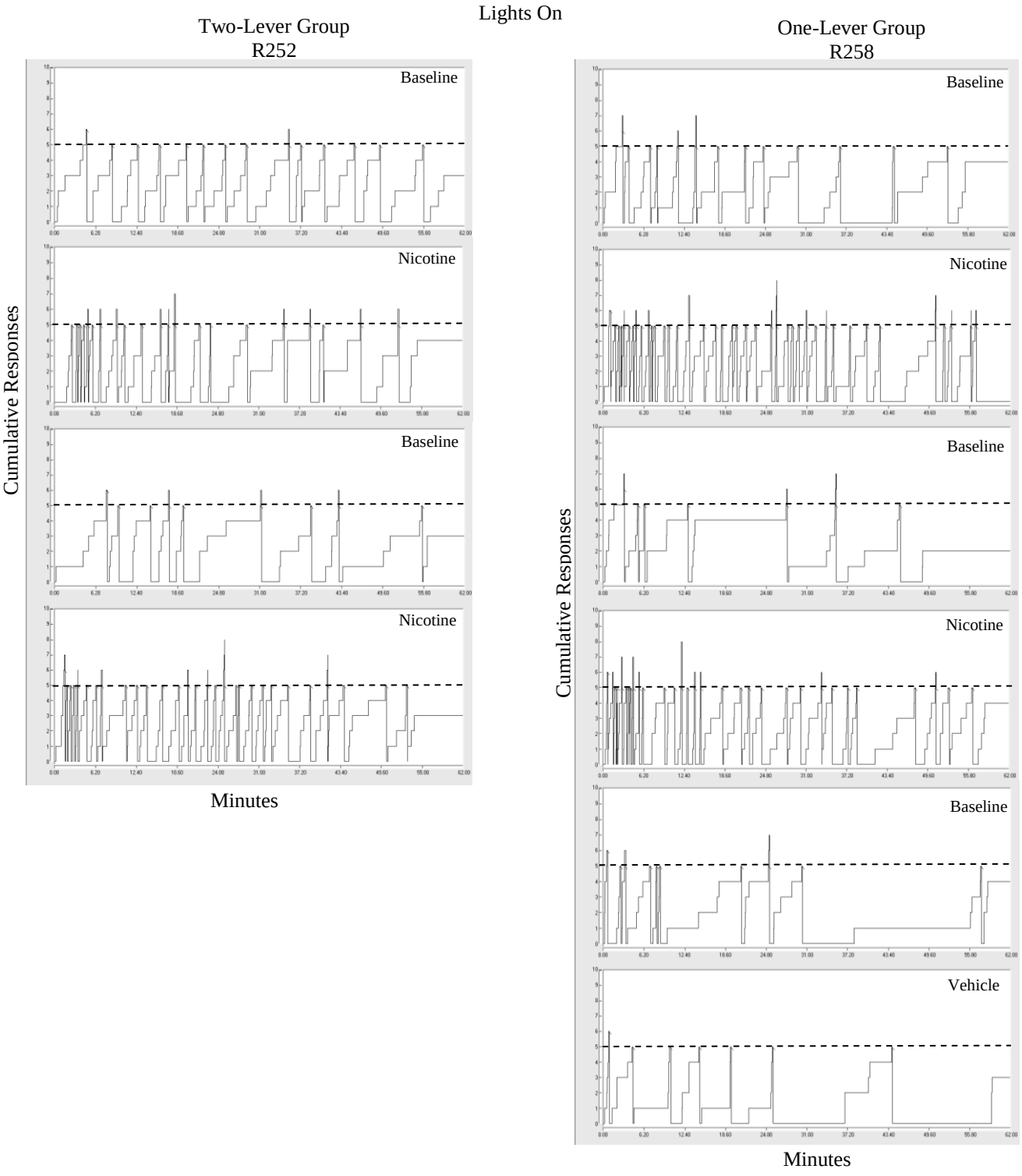

Figure 3-3. Cumulative Response Records during Lights On. Shown is the last session of each condition for two representative subjects from each group (R252 & R258). Deflections in the record indicate stimulus presentations -- the pen was reset back to zero at the end of each 10 sec stimulus. Responses after the deflection and above the

horizontal dotted line, but before the pen reset, occurred during the stimulus presentation.

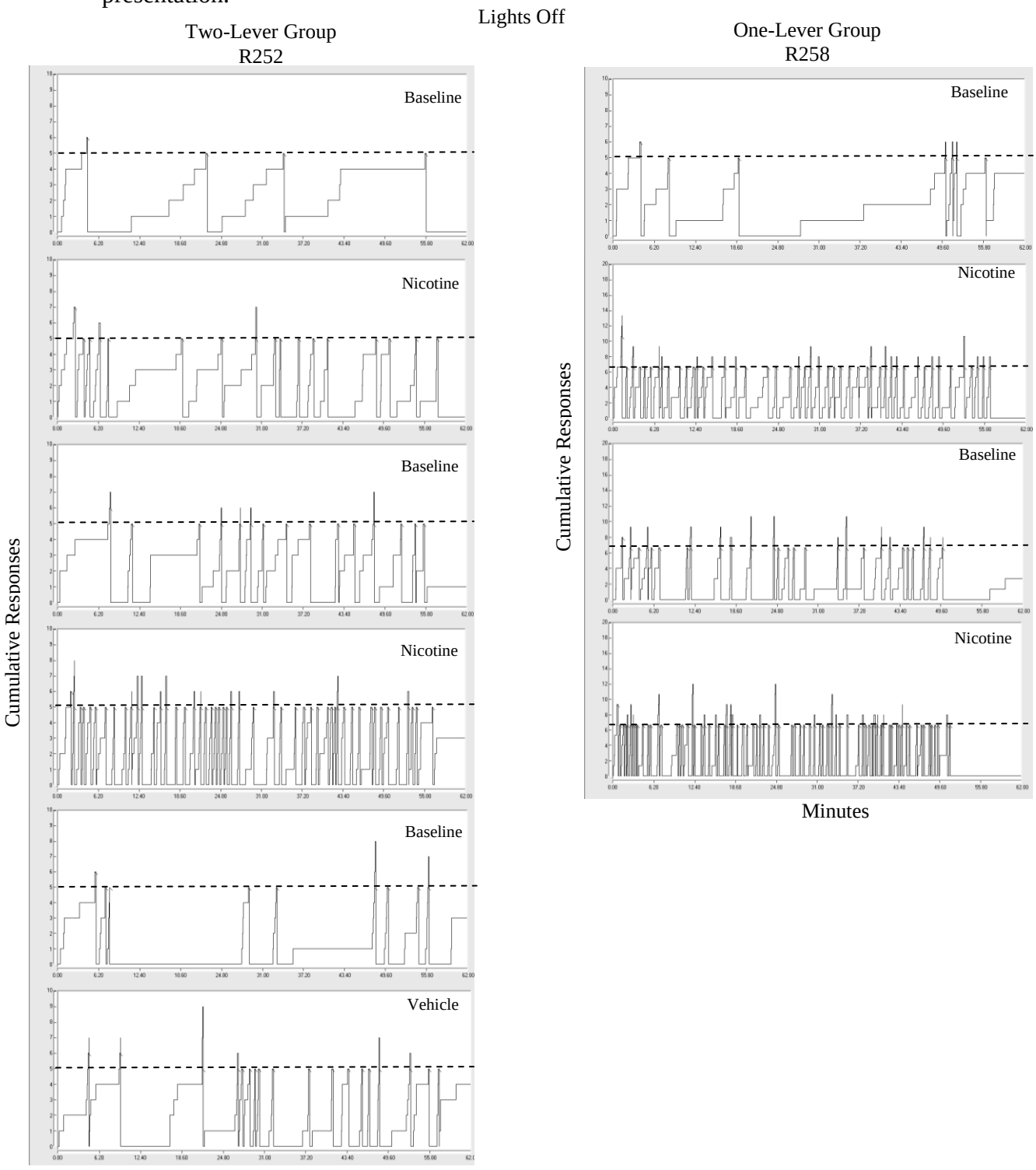

Figure 3-4. Cumulative Response Records during Lights Off. Shown is the last session of each condition of the Lights Off phase for two representative subjects from each group (R252 & R258). Deflections in the record indicate stimulus presentations -- the pen was reset back to zero at

the end of each 10 sec stimulus. Responses after the deflection and above the horizontal dotted line, but before the pen reset, occurred during the stimulus presentation. Note the higher y-axis for the bottom three records of subject R258.

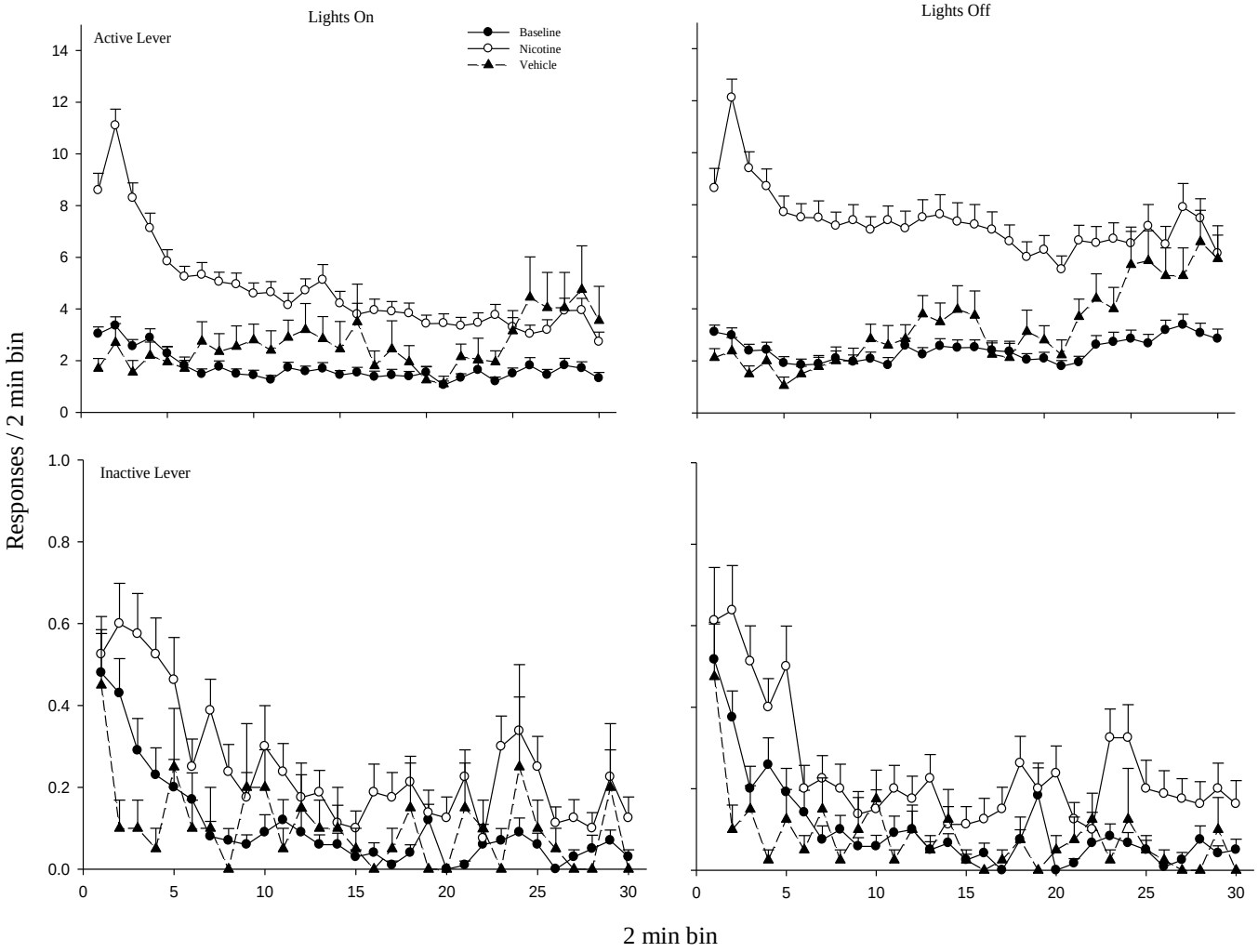

Figure 3-5. Within-SessionTime Course Analyses. Mean ± SEM number of responses per 2 min bin during the 60 min session. The left column shows active (top row) and inactive (bottom row) responding during the Lights On phase, while the right column shows responding during the Lights Off phase. Each data path within a panel corresponds with a different condition: first baseline (filled circles), first nicotine (open circles), second baseline (filled triangles), second nicotine (open triangles), third baseline (gray stars), vehicle (open stars). Note the different y-axes for active and inactive responses.

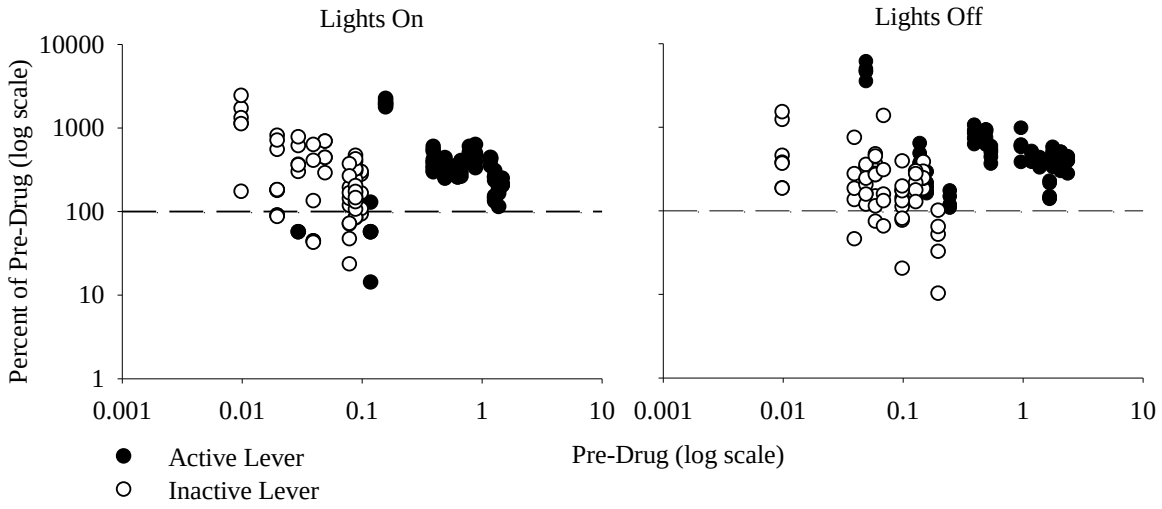

Figure 3-6. Rate-dependent scatterplots. Rate-dependent scatter plots for the Lights On (left column) and Lights Off (right column) phases of the experiment. Shown are the log percentages of pre-drug response rates plotted as a function of log pre-drug response rates. Response rates on both the active (filled circles) and inactive (open circles) levers are shown together on each plot.

CHAPTER 4
General Discussion
Mechanisms of Action

Behavioral Mechanisms

Nicotine as a motivating establishing operation. Thus far, the behavioral mechanism of action implicated by researchers investigating the effects of nicotine on reinforced responding is that it serves as a motivating establishing operation (MEO). In other words, it serves to enhance the reinforcing value of certain environmental consequences (Chaudhri et al. 2006; Olausson, Jentsch, Taylor, 2004a, b; Palmatier et al, 2007, Xiu et al., 2007; Raiff & Dallery, 2006). With an observing response procedure, Experiment 1 used a group design to show that nicotine increased responding maintained by conditioned reinforcers, but did not cause a general increase in behavior. Experiment 2 demonstrated that turning on and turning off a houselight functioned as moderately effective primary reinforcers for rats and that nicotine selectively increased responding maintained by such consequences. The results of Experiments 1 and 2 are consistent with a MEO account of nicotine-induced increases in responding.

It is interesting that the MEO effects of nicotine were relatively specific to responding maintained by the conditioned reinforcing visual stimuli in Experiment 1. One might also have expected food-maintained responding in Experiment 1 to increase (i.e., food-extinction responses in the presence of the S+), but no such increases were noted. Although it is possible that the lack of effect was simply due to a ceiling effect, there are a few other possibilities that should be considered. First, it may be the case that nicotine selectively increased moderately reinforcing stimuli, as others have suggested (Palmatier et al., 2007). However, there have been other demonstrations of nicotine increasing responding maintained by more potent reinforcers, such as liquid sucrose (Jias & Ellison, 1990), cocaine (Bechtholt & Mark, 2002; McQuown, Belluzi, Leslie, 2007), and alcohol (Clark, Lindgren, Brooks, Watson, Little, 2001; Lê, Wang, Harding,

Juzytsch, Shaham, 2003; Smith, Horan, Gaskin, Amit, 1999). In a previous study conducted in our lab, responding maintained by food was increased after chronic nicotine administration (Raiff & Dallery, 2006). There were a number of procedural differences between the current study and the other studies in which nicotine increased responding maintained by more potent primary reinforcers, and thus it is possible that there are specific conditions under which nicotine will serve as a MEO for such consequences. It is also possible that the effects of nicotine on the more potent reinforcers listed above were due to a different behavioral or biological mechanism of action. At this time, however, the MEO role for nicotine provides the most cohesive account with respect to the current data and those listed above.

One potential disadvantage of adopting the motivating operation account is that it could be used as a hypothetical construct. The term motivating operation is currently used as a summary term, or an intervening variable. In other words, it refers to a group of environmental variables that is related to behavior, but is completely anchored in observable events (MacCorquodale & Meehl, 1948; Mazur, 2005). For instance, motivating operations could refer to deprivation procedures, satiation procedures, or introduction of some environmental event, like nicotine. All of these manipulations correspond with a concomitant change in behavior (either becoming more or less likely) and are all considered motivating operations. The changes in behavior do not depend in any way on the term motivating operation, but instead on the environmental manipulations which the term summarizes. Even if the term were abandoned, the phenomena would continue to exist.

The concern is if the term motivating operation drifts from an intervening variable to a hypothetical construct. A hypothetical construct is an actual entity that is thought to exist independent of the observations that led to its identification. These entities are used to explain

the very phenomena that led to their presumed existence (MacCorquodale & Meehl, 1948). In fact, the term motivation has been used to refer to something an individual has or something within an individual (Patall, Cooper, Robinson, 2008). Skinner (1953, pg 31) warned that, "… such terms as 'hunger,' 'habit,' and 'intelligence' convert essentially the properties of a process or relation into what appear to be things." Using motivating operations as hypothetical constructs would be dangerous because they could lead to circular explanations, thereby preventing a more detailed investigation into the environmental determinants of behavior (Skinner, 1953).

As long as the term remains an intervening variable, it carries with it a number of advantages. At the most basic level, adopting the term MEO in behavioral pharmacology would make the discipline more conceptually systematic with behavior analysis, from which it has already adopted a number of concepts and procedures (Baer, Wolf, Risley, 1968; Thompson & Schuster, 1968). MEOs have been critically important to behavior analysts' understanding of reinforcement, and thus the concept could bear great benefits for behavioral pharmacologists as well. Without the concept of motivating operations, the dynamic nature of a stimulus' ability to function as a reinforcer would be perplexing.

Furthermore, adopting the concept of motivating operations could tie together a number of seemingly disparate areas in behavioral pharmacology. Because drugs have been conceptualized as reinforcers, various treatment manipulations could be conceptualized in terms of motivating operations. For instance, as described in the General Introduction, nicotine is the primary constituent in tobacco thought to be responsible for smoking maintenance - the assumption being that nicotine serves as a primary reinforcer. Nicotine replacement therapies (NRT), such as the patch or gum, are widely available and are marketed as reducing smoking-

abstinence-induced cravings (Shiffman, Ferguson, Gwaltney, Balabanis, Shadel, 2006;Teneggi, Tiffany, Squassante, Milleri, Ziviani, Bye, 2002). Thus, NRT products could be conceptualized as motivating abolishing operations in that they decrease the reinforcing aspects of using tobacco products. Pharmacological agents used to treat other drugs of abuse are also thought to function in a similar manner, such as methadone maintenance for opioid dependence (Donny, Brasser, Bigelow, Stitzer, Walsh, 2005). In addition to drug abuse treatment, other research areas in behavioral pharmacology that might be linked by, or benefit from, the notion of motivating operations are self-administration (Haney & Spealman, 2008; Woolverton, Wang, Vasterling, Carroll, Tallarida, 2008), priming (de Wit, 1996; James-Walke, Williams, Taylor, & McMillan, 2007), reinstatement (Bongiovonni & See, 2008; Liu, Caggiula, Nobuta, Poland, Pechnick, 2006), sensitization to the reinforcing effects of drugs (Liu, Roberts, Morgan, 2005; Ward, Läck, Morgan, Roberts, 2006) and drug interactions (Tanda & Goldberg, 2000; Ward, Läck, Morgan, Roberts, 2006).

Specifically related to nicotine, the MEO account has more immediate and obvious benefits in that it can account for extant data on the reinforcer-enhancing effects of nicotine and it may lead to novel experiments. For instance, the definition of a MEO specifies that it leads to an increase in the probability of all responses which have led to the reinforcer in the past. However, the appropriate discriminative stimuli must also be present if the response is to occur, regardless of whether the motivating operation is in place (Michael, 1982). One experiment might consist of training a few different responses that all have the same outcome, but that are trained in the context of a multiple schedule, and thus the different responses occur in the presence of different discriminative stimuli (e.g., lever press, nose poke, chain pull). If nicotine increases the motivating operation for the consequence in question, then only the response

appropriate to each discriminative stimulus should increase, whereas the other responses should remain unchanged. Furthermore, the different response topographies could generate different rates of responding, even within the same organism. These differences in rate of responding would not be expected to affect the outcomes if nicotine does in fact serve as a MEO. Such a procedure might be able to address the rate-dependent tendencies of nicotine that were found in Experiments 1 and 2.

Other future directions, mentioned earlier, include determining the conditions under which nicotine serves as a MEO for different consequences. Consider the example of food deprivation as a MEO given in the General Introduction. Food deprivation will not increase the value of all reinforcers; it is specific to food consequences. It may be that nicotine is a MEO for some reinforcers but not others, as the results from Experiment 1 suggested. Most of the research demonstrating the MEO role of nicotine has used visual stimulus reinforcers; therefore, it will be necessary to determine whether responding maintained by reinforcers in other sensory modalities (e.g., auditory, olfactory) are also increased by nicotine administration. Furthermore, it is not clear how nicotine might influence responding maintained or suppressed by different behavioral processes, such as negative reinforcement or punishment. Exploring the scope of nicotine as a MEO is an important task if the concept is to have predictive utility.

Other behavioral accounts. Before accepting the MEO account for nicotine-induced increases in responding, it is necessary to rule out other behavioral accounts. Two such accounts were addressed in Experiments 1 and 2: (1) general increases in behavior and (2) rate-dependence. To investigate whether nicotine caused general increases in behavior, Experiment 1 showed that responding did not reliably increase during an extinction component, while

Experiment 2 showed that nicotine only increased responding on an active lever, even in subjects who were initially trained to press both the active and inactive levers.

The rate-dependent analyses from Experiments 1 and 2 indicated that there was a tendency for nicotine to increase low pre-drug response rates and to decrease high pre-drug response rates. Although there were significant negative slopes, the percentage of variance accounted for was always low, never exceeding 21%, which suggests that the relationship between pre-drug and drug response rates is not very well described by a linear function. Thus, the present studies provided weak evidence that nicotine has rate-dependent effects.

Even if the rate-dependent effects were more robust, such a finding would only indicate a relationship between two dependent variables (i.e., pre-drug response rates and drug response rates), but would not specify a behavioral or biological mechanism of action, such as changes in stimulus control, motoric capabilities, or motivating operations (Branch, 1984; Odum, Lieving, Schaal, 2002). Thus, a rate-dependent relationship does not rule out the possibility that changes in responding were a function of nicotine serving as a MEO. More work will be necessary to test whether nicotine merely increases low rates of responding, or whether such increases are specific to parameters of the reinforcing stimuli (Lamb & Ginsburg, 2008). A recent study showed that nicotine also increased the number of completed ratios on a progressive ratio schedule of visual stimulus presentation (Chaudhri et al., 2007), suggesting that nicotine does more than merely increase response rates. However, future studies should be aimed at teasing apart the importance of response rates on the effects of nicotine administration.

Neurobiological Mechanisms

In addition to the behavioral mechanisms of action just described, researchers have investigated corresponding neurobiological mechanisms that might be relevant to the results seen

in Experiments 1 and 2. Although research in this area is extensive, only a brief overview of the findings that seem particularly relevant to the current studies will be addressed.

Similar to other drugs of abuse, nicotine administration results in the release of dopamine (DA) in the mesolimbic system, which is comprised of the ventral tegmental area (VTA) and the nucleus accumbens (NAc), among other structures (Wonnacott, Sidhpura, Balfour, 2005). The NAc can be further divided into two distinct sections – the core and the shell. Recently, the core and shell have been found to contribute in different ways to drug self-administration. Ito, Robbins and Everitt (2004) compared the effects of NAc core and shell lesions on cocaine self-administration, using a standard self-administration procedure and a second-order schedule of self-administration. Second-order schedules are sometimes used to study conditioned reinforcement. The standard procedure consisted of a FR1 schedule of cocaine infusions paired with a 20 s blackout and illumination of a stimulus light. The second-order schedule consisted of a FR 10 schedule of stimulus light illumination, such that every 10^{th} stimulus was paired with a cocaine infusion and 20 s blackout (FR10 [FR10:S]). There were no differences in cocaine self-administration in core- and shell-lesioned rats when the standard procedure was used. However, when the second-order schedule was employed, fewer core-lesioned rats met the self-administration criterion and those who did meet the criterion made significantly fewer responses than rats in the shell-lesioned and control groups. Furthermore, core-lesioned and control subjects showed a significant increase in response rates after the first cocaine infusion in the second-order schedule, whereas shell-lesioned subjects did not. The authors concluded that, "The core seems to mediate control by conditioned reinforcers, whereas the shell seems to mediate the potentiation of that control by cocaine, perhaps reflecting stimulant or motivational effects of the drug." In other words, although not distinguished in their paper, the authors suggested that the

NAc shell may be related to general increases in behavior induced by cocaine or to the MEO effects of cocaine on sensory reinforcers. Although they attributed conditioned reinforcing properties to the visual stimuli used in their study, it is not clear whether the stimuli were actually primary reinforcers, as the results from the present Experiment 2 might suggest. Nevertheless, their findings are directly related to the current experiments in that increased DA activity in the NAc core and shell may differentially influence sensory and/or conditioned reinforcers.

The implications of nicotine-induced DA release in the NAc have also been addressed by a number of researchers, and Balfour (2004) recently proposed a theory that directly relates to the MEO mechanism of nicotine outlined above. Balfour was particularly interested in addressing how nicotine could maintain tobacco use, even if nicotine itself did not function as a primary reinforcer. He suggested that nicotine-induced DA release in the NAc core makes it possible for nicotine-associated environmental stimuli to become conditioned reinforcers. Furthermore, Balfour suggested that nicotine-induced DA release in the NAc shell further potentiates, or serves as a MEO, for those associated stimuli. Thus, Balfour suggested that the NAc core and shell each contribute to nicotine self-administration, or tobacco use, by establishing and increasing the reinforcing properties of tobacco-related stimuli. It might be useful to use the procedures described in Experiments 1 and 2 to further explore this possible neurobiological mechanism of action.

Concluding Remarks

Given the weak primary reinforcing effects of nicotine, as evidenced by the difficulties in establishing nicotine self-administration with nonhumans, the popularity and success of smoking and tobacco use in humans is surprising. Thus, we return to the original question: what has made tobacco such a successful commodity? The current findings support a MEO role for nicotine,

which may account for the prevalence of smoking and the difficulty smokers have in quitting. If nicotine enhances the reinforcing value of other environmental consequences, then quitting would not only result in a loss of cigarette reinforcers, but also a loss in the value of alternative reinforcers that were enhanced by nicotine.

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BIOGRAPHICAL SKETCH

My first experiences with behavior analysis and radical behaviorism were with Dr. Gregory Madden at the University of Wisconsin-Eau Claire. While I was in Eau Claire I took several behavior analysis courses (e.g., Learning, Applied Behavior Analysis, Advanced Experimental Analysis of Behavior) and I had the chance to work as a teaching assistant for an introductory course in behavior analysis. Dr. Madden and I collaborated on two areas of research: (1) studying potential differences in human responding on a delay discounting task when the consequences were real versus hypothetical, and (2) investigating whether human behavior was better described by the matching law when responses were maintained by concurrent schedules of negative reinforcement versus concurrent schedules of positive reinforcement. The former project resulted in two publications and the latter project served as my undergraduate thesis. Both projects were presented at the annual conferences for the Association for Behavior Analysis and the Midwestern Association for Behavior Analysis, providing me with opportunities to talk to and get feedback from important figures in the field.

As an undergraduate I was introduced to the subdiscipline of behavioral pharmacology, which was particularly important to me because I was always interested in drug use and abuse. Specifically, Dr. Madden talked about a behavioral treatment for drug abuse known as "contingency management." When I began looking for graduate programs I found that Dr. Jesse Dallery, in the Behavior Analysis program at University of Florida, was conducting research on contingency management with smokers, in addition to studying issues that were consistent with the topics I studied as an undergraduate (e.g., matching law, delay discounting). Not only were Dr. Dallery's research interests a perfect match with mine, but the Behavior Analysis program at University of Florida also consisted of several other faculty members with broad interests.

While a student at the University of Florida, I have had extensive professional, research, and academic development experiences. I first authored three manuscripts and co-authored a number of others. I wrote two grants submitted to the National Institue of Health (an R03 and NRSA). I was co-investigator on the R03 grant which supported the animal research discussed in this manuscript. In addition to writing, I served as a Graduate Instructor for two semesters, where I was able to design a course in Applied Behavior Analysis. I conducted numerous research experiments with Dr. Dallery, ranging from the basic non-human animal studies described in my dissertation, as well as human laboratory and outpatient research with smokers. In addition to the research I conducted with Dr. Dallery, I also had the opportunity to collaborate on a couple of research projects with Dr. Timothy Hackenberg, studying token loss as a form of response cost punishment with pigeons.

Collectively, my undergraduate and graduate school experiences solidified my enthusiasm about pursuing a career that allows me to teach the principles and theoretical foundations of behavior analysis and behavioral pharmacology. I am interested in working in an academic setting that includes a balance between teaching and research.