QUANTIFYING NICOTINE'S VALUE ENHANCEMENT EFFECT USING A BEHAVIORAL ECONOMIC APPROACH

By

RACHEL CASSIDY

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To everyone who has been there since the beginning, and everyone who has joined me along the way

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Rachel Cassidy

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Nicotine increases the value of some reinforcing stimuli, and this effect may contribute to nicotine's widespread abuse. We attempted to better quantify this effect using a demand curve analysis. In Experiment 1, four Long- Evans rats were exposed to an observing response procedure. In this procedure, presses to one lever resulted either in food according to a variable ratio 10 schedule (45 mg pellets, VR 10) or extinction; presses to a second, observing lever illuminated stimuli correlated with the schedule in effect on the food/extinction lever (henceforth the "active" lever). The number of responses required on the observing lever increased across sessions (FRs: 1, 3, 5, 8, 10, 15, 30), producing a demand curve for these conditioned stimuli. Nicotine was then administered via osmotic minipumps at a dose of 3 mg/kg/day for 28 days, and the demand curves were re-determined. Nicotine was administered at a dose of 0.3 mg/kg via subcutaneous injection following pump removal and a return to baseline. Then, all demand curves were fit to the Exponential Demand Equation. Comparisons of the α parameter, a putative measure of value, across phases indicated that neither method of nicotine administered altered α. In Experiment 2, six Long-Evans rats were exposed to a similar modified observing procedure; however, the schedule of food

availability on the active lever was changed to a variable interval 15 second (VI15 s) schedule. Nicotine was administered via subcutaneous injection at a dose of 0.3 mg/kg. Under these conditions, nicotine increased the value of the conditioned reinforcers as measured by α. Thus, the extent to which nicotine enhances the value of conditioned reinforcers appears to depend on the schedule of reinforcement on the active lever. Although the generality of nicotine enhancement may be more limited than previously thought, the current analysis has demonstrated - using a robust behavioral economic approach - that nicotine does increase the value of non-drug conditioned reinforcers under certain conditions.

CHAPTER 1
INTRODUCTION

Nicotine is one of the most commonly abused drugs worldwide, leading to many thousands of deaths each year (Hatsukami, Stead, & Gupta, 2008). Most smokers want to stop smoking but find they are unable to do so, or begin smoking again following a quit attempt (Centers for Disease Control and Prevention, 2005). Although nicotine has mild euphoric effects, nicotine itself is a very weak primary reinforcer in both humans and animals (Dar & Frenk, 2009; Matta et al., 2007). Encouragingly, new evidence has emerged that nicotine enhances the value of non-drug reinforcers, in addition to serving as a moderate primary reinforcer. This value-enhancement effect of nicotine may contribute to the maintenance and re-acquisition of smoking behavior, as nicotine may cause other stimuli in the smoker's environment to seem more valuable and pleasant (Chaudhri et al., 2006; Chaudhri et al., 2007, Perkins & Karelitz, 2013). Understanding the value-enhancing effects of nicotine may lead to improved treatment outcomes for smokers.

Evidence for nicotine's value-enhancement effect. Evidence for the enhancement effect first appeared in studies using a nicotine self-administration paradigm, which demonstrated that nicotine self-administration acquisition depended heavily on the non-pharmacological stimuli correlated with nicotine delivery (Caggiula et al., 2001, 2002; Chaudhri et al., 2006). That is, rats responded more for nicotine infusions when those infusions were paired with a visual stimulus than when they were not (Chaudhri et al., 2007). Thus, nicotine self-administration relies on stimuli in the environment in important ways. Environmental stimuli gain value through their pairing

with nicotine, and then the presentation of these stimuli further supports nicotine self-administration (Palmatier et al., 2007).

Nicotine, administered by experimenters, also increased rats' responding for a visual stimulus which had never been paired with any other reinforcer (Donny et al., 2003; Liu, Palmatier, Caggiula, Donny, & Sved, 2007; Palmatier et al, 2009, Raiff & Dallery, 2009; Weaver at al., 2012a). This showed that nicotine directly increased the value of these stimuli, even when they were not paired with nicotine. These findings led to the hypothesis that nicotine enhances responding for primary visual reinforcers – stimuli that have not been paired with any other reinforcer. Logically, nicotine might also affect the value of conditioned reinforcers- stimuli that have been paired with or followed by the presentation of another reinforcer.

New techniques were used to investigate whether nicotine enhanced the value of conditioned reinforcers, in addition to enhancing the value of primary reinforcing visual stimuli. Using the conditioning-a-new-response procedure, Olausson, Jentsch, & Taylor (2004) conditioned an auditory and visual stimulus as a CS that predicted the availability of water in mildly water-deprived rats. Then, they arranged a new situation in which the CS and presentation of the empty water dipper was made contingent on a new response (lever pressing). Nicotine enhanced responding on this new lever relative to a lever that had no programmed consequences. The same conditioning-a-new-response procedure has been used to show that nicotinic receptors are necessary for animals to respond for sucrose-paired CSs when these stimuli are made contingent on a novel response, and nicotine has also been shown to increase responding for a sucrose-

paired CS during extinction (Grimm, Ratliff, North, Barnes, & Collins, 2012; Löf, Olausson, Stomberg, Taylor, & Söderpalm, 2010).

Nicotine thus appears to enhance responding for CSs when their presentation is made contingent on a novel response. These CSs can be considered conditioned reinforcing stimuli due to their previous paring with other reinforcers. The results from the conditioning-a-new-response procedure, however, are somewhat difficult to interpret. Nicotine also increases responding for visual stimuli alone, even when these stimuli have never been paired with any other reinforcer, as discussed previously (Raiff & Dallery, 2009). When nicotine enhances responding for visual stimuli in the conditioning-a-new-response procedure, is it due to the primary or conditioned reinforcing effects of the visual stimuli? Furthermore, when using the conditioning-a-new-response procedure, the visual stimuli are never again paired with primary reinforcement. Thus, the visual stimuli – and, therefore, the lever press that produces them – undergo extinction as conditioned reinforcers across trials of the procedure, causing response rates to change over time (Williams, 1994). In light of these considerations, other researchers have used a more robust paradigm for studying conditioned reinforcement: the observing response procedure.

The observing response procedure as a method to study conditioned reinforcement. The observing response procedure was developed by Wyckoff (1952) and is one of the most useful procedures yet developed to study conditioned reinforcement (Williams, 1994). In this procedure, two levers are concurrently available. One lever produces primary reinforcement according to a mixed schedule, one component of which is typically extinction (henceforth, the “active” lever). The other

lever produces only stimuli correlated with the schedule in place on the active lever (henceforth, the “observing” lever). Thus, the animal can “observe” what schedule is in effect on the active lever by responding on the observing lever. Responding on the observing lever is maintained solely by conditioned reinforcement: only schedule-correlated stimuli are produced by pressing on the observing lever. Changes in responding for primary reinforcement on the active lever, responding under extinction on the active lever and responding maintained by conditioned reinforcement on the observing lever can all be examined as a function of drug administration. Decades of research using the observing response procedure have led to the development of a solid empirical basis from which to interpret the effects of drugs on responding in this procedure (Fantino, 1977; Gaynor & Shull, 2002; Shahan, 2002).

The observing response procedure affords several advantages over the conditioning-a-new-response procedure for studying nicotine’s value-enhancement effect. The conditioned reinforcers are continually re-paired with the availability of the primary reinforcer in the observing response procedure; thus, responding for them is more stable and does not degrade over time due to extinction. This affords a stable baseline from which to observe the effects of drugs such as nicotine on responding for conditioned reinforcers. Furthermore, nicotine’s effects on responding for both primary and conditioned reinforcers can be examined because both primary reinforcers (food) and conditioned reinforcers are concurrently available. This is an important facet of the procedure given nicotine’s proposed effects on both primary and conditioned reinforcement.

Using the observing-response procedure, previous research has found that nicotine enhances responding for food-paired conditioned reinforcers. Raiff & Dallery (2006) found that acute nicotine selectively increased responding on the observing lever, while chronic nicotine administration increased responding for both conditioned reinforcers and for food. Raiff & Dallery (2008) replicated and extended these results with a larger group of rats (N = 18); however, they found that chronic nicotine did not increase responding for food, but did selectively increase responding on the observing lever. Similarly, Jones, Raiff, & Dallery (2010) again found that nicotine selectively increased responding on the observing lever, and their data suggested that this effect of nicotine was mediated by centrally, rather than peripherally, located nicotinic receptors.

Interpretive problems with measures of "value" and behavioral economics. These data show than nicotine enhances the value of conditioned reinforcers. The evidence for this lies in an increase in response rate on the observing lever in the presence of nicotine. This begs the question, however, of whether an increase in *rate* is equivalent to an increase in *value.* The concept of value, in and of itself, deserves attention as a theoretical construct. The term "value" is often invoked as an explanatory variable without a firm conceptual framework in which to place it. This makes is difficult to determine whether a change in "value" has occurred, as "value" does not seem to have the status of a behavioral mechanism on its own. Placing this term in a lager theoretical framework that encompasses other recognized behavioral mechanisms of drug action will allow a more rigorous and fruitful empirical use of the term (Bickel, Marsch & Carroll, 2000).

A promising theoretical framework is emerging in the field of behavioral economics. Behavioral economics tackles the concept of value by equating value with reinforcing efficacy. In behavioral economics, the primary relationship of interest is between the cost of a good and consumption. When plotted in graphical space, this relation describes a demand curve. The demand curve can be used as a parametric measure of reinforcing efficacy. In other words, the extent to which a commodity, such as food, can act effectively to maintain responding over a range of schedule values can be used as an index of reinforcing efficacy (Hursh, 1980, 1984). The slope of the demand curve is termed the degree of elasticity of the function.

The concept of elasticity forms one of the keystones of behavioral economic theory. The elasticity of a good can be thought of as synonymous with reinforcer efficacy and value. Recently, Hursh & Silberberg (2008) developed a new equation in an attempt to quantify reinforcer value (i.e., elasticity) using a single parameter. The model proposed by Hursh & Silberberg is the Exponential Demand Equation:

$$\log Q = \log Q_0 + k(e^{-\alpha \cdot Q_0 \cdot C} + 1) \quad (1\text{-}1)$$

Equation 1-1 includes three parameters: Q_0, k, and α. The variables Q and C represent reinforcer consumption and price, respectively. K is a constant (usually between the values of 1 and 4) that is set according to the observed range of the dependent variable in logarithmic units, and the parameters Q_0 and α are free to accommodate the data. Q_0 is the estimate of the level of consumption in units of the reinforcer at the lowest price possible (i.e., an estimate of demand level at theoretical price 0). The rate constant parameter α of Equation 1-1 measures the rate of change in elasticity across the function.

Hursh & Silberberg (2008) propose that the single parameter α is a measure of "essential value", because it should remain constant across manipulations that alter the size of or delay to the same reinforcer. That is, the essential value of food pellets should remain constant regardless of whether the demand function is determined using a one-pellet, two-pellet, or four-pellet reinforcer, even if the demand function shifts up or down in absolute terms. Similarly, the essential value of a self-administered drug should remain constant across demand functions determined using different doses of the drug. In other words, while a larger or smaller amount of the same reinforcer could shift the demand function up or down, the slope of the function should remain invariant. This slope is what the α parameter captures[1].

In contrast, essential value may change as a function of a change in reinforcer efficacy. Manipulations characterized as changing the relevant motivating operations may alter the slope of the demand function, and thus may change the essential value of that reinforcer. For example, administering a drug to an animal prior to determining a demand function for food may alter the reinforcing efficacy of food. Recent research has found that cocaine, when it was available for self-administration by rats concurrently with food availability, decreased the essential value of food in rats compared to the essential value of food available alone (Christensen, Silberberg, Hursh, Hunstberry, & Riley, 2008).

Using the α parameter to assess reinforcer value may afford several advantages over using rate as a measure of value. An increased rate of responding for a given reinforcer following some change may be quantitatively similar across different value

[1] Note essential value is inversely related to the absolute value of the α parameter- a very *small* α parameter would indicate a fairly slow rate of decline, and therefore a *high* essential value.

manipulations. That is, we may see twice as much responding for food whether we have doubled the magnitude of the food reinforcer or have administered a drug. In contrast, as noted above, α should not change across manipulations that only alter the quantitative properties of a reinforcer, but should change across manipulations that can be considered motivating operations (Hursh & Silberberg, 2008). Furthermore, response rate increases are generally compared in the presence and absence of a drug at one parametric value at a time (e.g., in our previous data we have observing the effects of various doses of nicotine on rate of responding at one observing lever schedule). Changes in α as a function of drug administration provide more information, as α is an indicator of the overall slope of the entire demand function. Thus, α may be both more specific and more informative with respect to drug-induced changes in responding.

Previous research on nicotine's effects using demand curve analysis. Cassidy & Dallery (2012) used Equation 1-1 to determine the effects of nicotine on the essential value of food. Rats responded for food during 23-hour, closed economy sessions. The FR schedule in place in the food lever increased across days according to the following fixed sequence: FR 1, 5, 10, 20, 40, 80, 160, 320, 640, 1280. Then, the rats were exposed to chronic nicotine via osmotic minipumps at a dose of 3 mg/kg/day. The data from the baseline and nicotine phase were fitted separately to Equation 1-1 and α parameter values were compared across phases. Cassidy & Dallery found that nicotine did not appreciably alter demand for food as measured by this equation.

Equation 1-1 has also been used to determine the effects of nicotine on primary reinforcing visual stimuli. Barrett & Bevins (2012) exposed rats to FR schedules of visual stimulus presentations. Completion of the FR requirement resulted in a 5 s cue

light presentation and a 1-min period of darkness (i.e., houselight off). Following this, the animals received subcutaneous injections of nicotine and the demand curves were re-determined. The authors were able to generate a demand curve for these stimuli, and they subsequently fit Equation 1-1 to the data. The data showed that nicotine increased the essential value of these primary visual stimuli. Thus, in this case, the data from a behavioral economic preparation corresponded with the data generated using other methods (e.g., Caggiula et al., 2009; Donny et al., 2003).

Will nicotine increase the essential value of conditioned reinforcers, in addition to primary reinforcing visual stimuli? In order to answer this question, the essential value of conditioned reinforcers alone must be determined. To determine the essential value, a demand curve for conditioned reinforcers must be generated. This requires a systematic increase in the FR requirement necessary to produce conditioned reinforcers. Thus, to produce a demand curve for conditioned reinforcers, in the present experiments we used a modified observing response procedure. Observing stimuli were presented after completion of a fixed ratio schedule, which varied across sessions - as in a typical demand curve for primary reinforcers - and the number of stimulus presentations earned at each FR value formed the primary dependent variable.

The modified observing response procedure requires an FR schedule on the observing lever. Ideally, changes in the FR value on the observing lever should lead to changes in the number of stimulus presentations earned. There is evidence to suggest that observing responding is sensitive to changes in the FR value on the observing lever, just as responding for a primary reinforcer is sensitive to changes in the FR requirement. Kelleher (1958) demonstrated that chimpanzees would work to produce

food schedule-correlated stimuli at FR values from FR 1 up to FR 60. Similarly, Woods & Winger (2002) replicated this finding along a similar parametric function in rhesus monkeys when the observing lever produced stimuli correlated with the availability of cocaine or remifentanil injections. Using pigeons as subjects, Kelleher, Riddle, & Cook (1962) found that highest the FR value that did not result in ratio strain on the observing key varied across individuals pigeons, from FR 20 to FR 60; thus, the demand function for observing stimulus production may be quite constrained and idiosyncratic. To our knowledge, however, a parametric evaluation of the extent to which rats' observing behavior can be maintained across increasing observing schedule requirements has not been conducted.

The present series of experiments sought to determine quantitatively whether and to what extent nicotine alters the essential value of conditioned reinforcers using behavioral economic methods. If nicotine reliably alters the value of these conditioned reinforcers as measured by α, then this would be the first parametric, quantitative evidence of nicotine's reinforcer-enhancing effect. Given that several lines of evidence support to the idea that nicotine enhances the value of conditioned reinforcers as interpreted by response rate data, convergent evidence from an economic framework would further support the hypothesis that nicotine enhances the value of reinforcers.

CHAPTER 2
EXPERIMENT 1

Experiment 1a

There were several purposes of Experiment 1a. We sought to determine the feasibility of using a modified observing procedure to generate a demand curve for conditioned reinforcers. To that end, we modified a typical observing-response procedure such that the FR requirement on the observing lever systematically increased across sessions. Producing a demand curve using this method had not yet been attempted, and it was unknown how elastic demand might be for conditioned reinforcers. Thus, to ensure that the conditioned reinforcers would be valuable, we implemented a relatively rich schedule of reinforcement on the active lever (variable ratio 10). In other words, in the presence of the S+, a relatively large number of reinforcers could be earned. Earning a larger number of reinforcers in the presence of the S+ tends to increase the value of conditioned reinforcers (Kelleher & Gollub, 1962), and more valuable goods tend to be less elastic (Hursh, 1984).

Nicotine has been shown to enhance responding in an observing response procedure (Jones, Raiff & Dallery, 2010; Raiff & Dallery, 2006; Raiff & Dallery, 2008). However, The modified observing procedure used in the present experiment differed from previous experiments using an observing response procedure in three ways: (a), the schedule of stimulus presentations on the observing lever was an increasing FR (in previous experiments using the observing response procedure to show nicotine enhancement, stimuli were presented according to a VI schedule); (b) the schedule of food presentation on the active lever was a VR (previously, a VI); and (c), nicotine was administered via osmotic minipump as opposed to via subcutaneous injection. Thus,

although we expected to see enhancement using the modified observing procedure, these procedural differences may contribute to the enhancement effect. Although the first modification is inherently necessary to create a demand curve, the remaining two factors are open to experimental manipulation to determine the extent to which they impact nicotine enhancement.

Experiment 1a Materials and Methods

Subjects

Four male Long-Evans rats, obtained from Harlan Laboratories, maintained at 85% of their free-feeding weight served as subjects. The subjects were individually housed in a windowless colony room and had unrestricted access to water in their home cages. The colony room had a 12:12 hour light/dark cycle, and subjects received any extra-session feeding in their home cages.

Apparatus

Four MED-PC aluminum and Plexiglas modular rodent operant chambers with steel grid floors, measuring approximately 11”W x10”D x11”H and encased in light- and sound-attenuating outer cases and equipped with two standard levers, were used as experimental chambers. Each lever had an array of three LED lights above it, and the levers were situated approximately 1” from the bottom of the chamber. Each chamber also had a houselight that was used in the current experiments as a discriminative stimulus rather than for general illumination. Each chamber contained a pellet dispenser that dispensed 45-mg 50% sucrose pellets.

Discrimination Training

During discrimination training, components of fixed ratio (FR) 1 reinforcer availability alternated with components of extinction according to a VI 60s schedule of component

duration during each session. The schedule then increased gradually until a variable ratio 10 (VR 10) final schedule of food availability was reached. One stimulus was paired with food components (either a solid or blinking house light, which was counterbalanced across rats) and the other stimulus was paired with extinction components, hereafter referred to as the S+ and S- respectively. Either the right or left lever was designated the active (food-reinforced) lever, while the other lever had no programmed consequences at this stage. When discrimination training was in effect, the S+ or S-, depending on the current schedule, was always illuminated. Sessions lasted 60 minutes, and continued until the following stability criteria were met: discrimination indices (that is, presses in S+/Total presses) were over 0.75 on average for seven consecutive sessions; rate of responding in S+ for each session was within 20% of the seven-day average, and rates of responding in S+ for the first and last day of the last seven sessions were within 10% of the seven-day average. Following discrimination training, the animals began the observing response procedure.

Observing Response Procedure

At this time, the S+ and S- were only presented after a right (or left, as stated above) lever press, the observing response. One observing response illuminated the S+ or S-, depending on the current schedule, for fifteen seconds (Shahan, 2002). If no observing response was made, or the stimuli that were produced went dark after fifteen seconds, the chamber was dark; however, VR 10 and extinction components remained in effect. Thus, producing the S+ and S- had no effect on the VR-extinction schedule. If the schedule was programmed to change-for instance from VR to extinction-during the fifteen seconds of stimulus illumination, the current schedule remained in effect until the stimulus terminated. Observing responses during stimulus presentation had no effect.

The terminal schedule parameters were: a VR 10 food schedule which alternated extinction approximately every 60 s (VI 60s component duration), and conditioned reinforcing stimuli presented for 15 s beginning on an FR 1 schedule. Each session lasted for 1hr.

Baseline

Following establishment of FR 1 observing lever responding, the schedule in place on the observing lever increased across days according to the following sequence: FR 1, FR 3, FR 5, FR 8, FR 10, FR 15, FR 30. Each FR was in place for one session. The curves were re-determined a minimum of three times until the last two consecutive curves were similar enough that an extra sum-of-squares F-Test determined that the curves were similar enough to warrant a shared α parameter.

Nicotine Administration

The subjects were surgically implanted with subcutaneous osmotic minipumps (Alzet® model 2ML4, mean flow rate 2.54 µl/hr, mean fill volume 2125 µl). The subjects were anesthetized via gaseous isoflurane. Then, an area on their dorsal side was shaved and a 3cm incision was made, cleansed with betadine, and gently enlarged so that the pumps could be inserted underneath the skin. The incisions were then closed using Roboz® Surgical Instruments (Gaithersburg, MD, USA) 2cm surgical staples, and the subjects were treated with an injectable analgesic following implantation. The pumps were filled with a solution of nicotine tartrate salt (Sigma Chemical Co., St. Louis, Missouri, USA) dissolved in saline solution such that nicotine would be delivered at the behaviorally active dose of 3 mg/kg/day for 28 days (Matta et al., 2007). Following a minimum two-day recuperative procedure, the subjects then experienced two full sequences of FR values on the observing lever.

Experiment 1a Results & Discussion

Figure 2-1 shows the absolute number of stimulus presentations (conditioned reinforcers) earned at each observing FR value under both baseline and nicotine conditions. This demand curve for conditioned reinforcers can be compared with demand curves for other reinforcers. A relatively inelastic good would generate a demand curve with a fairly flat initial arm, followed by a point of inflection at which consumption begins to decline. In contrast, these demand curves are steeply declining across both conditions, which indicate relative elasticity. Judging from these simple demand curves, nicotine does not appear to greatly change the slope or elasticity of the demand curves. Nicotine also generally decreased or failed to change the absolute number of stimulus presentations earned (absolute consumption), which would be indicated by a shift up or down in the demand curve. It is important to keep in mind, however, that a change in absolute consumption may or may not correspond with a change in the essential value of a good.

Next, Equation 1-1 was fitted via least-squares regression (GraphPad Prism version 5.0 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com) to the relation between FR value and number stimulus presentations earned. The fitted curves, across both baseline and nicotine phases, are shown for each subject in Figure 2-2. The essential value of the conditioned reinforcers both prior to and during nicotine exposure is indicated by the fitted α parameters listed in Table 2-1. The F-test data shown in Table 2-1 indicates whether an extra sum-of-squares F test found that the α parameter was shared. In other words, although a model that incorporated two separate alpha parameters for each data set would fit the data better, such a model would also be more complex. The F-test weighs the better fit of the

more complex model against a simpler model in which the α parameter is shared (Motulsky & Christopoulos, 2003). The computed F-ratio compares the difference in the sum-of-squares across the two models with the difference in parameters, with the higher number of parameters in the more complex model "counting against" the more complex model. The results shown in Table 2-1 state whether the F-Test suggested the simpler model be accepted, in which case the α is stated as "shared", or rejected and thus "not shared". Table 2-1 also indicates the variance accounted for by Equation 1-1. The high percentage of variance accounted for by Equation 1-1 indicates that a behavioral economic approach is feasible and appropriate for describing data obtained from this procedure.

Rates of responding on the observing lever, as a function of FR value on that lever, are shown in Figure 2-3. These data are averaged across all four animals; no animal showed a pattern inconsistent with the group-level data. In previous experiments using the observing response procedure to test whether nicotine enhances responding on the observing lever, increased rates of responding on the observing lever were observed in the presence of nicotine (Raiff & Dallery, 2008; Jones, Raiff & Dallery, 2010). As is evident from Figure 2-3, nicotine did not increase responding on the observing lever. A lack of effect of nicotine on this measure, which is in contrast to previous data using this procedure, could be due to several experimental factors: the FR schedule of stimulus presentations on the observing lever (as opposed to a VI schedule), the VR schedule of food presentation on the active lever (as opposed to a VI), or the method of nicotine administration (minipumps as opposed to injection). The latter two factors were manipulated in Experiments 1b and 2, respectively, to determine

if either route of nicotine administration or active lever schedule impacted either essential value or rate of responding on the observing lever.

Increasing the FR schedule on the observing lever could have influenced responding on the food/extinction lever. Figure 2-4 addresses this question. It shows total responding on the active lever, collapsed across both VR and extinction components, and averaged across animals. Besides a slight dip in responding when the FR is very low, neither responding during baseline or in the presence of nicotine appears to be differentially affected by the FR schedule in place on the observing lever. As in the case of observing response rates, nicotine decreased responding for food. This is consistent with other experiments using a minipumps method of nicotine administration; however, it is important to note that while nicotine may decrease rates of responding for food, nicotine does not decrease the essential value of food (Cassidy & Dallery, 2012).

It is safe to say that nicotine did not enhance the value of conditioned reinforcers using this preparation, given that nicotine decreased or failed to alter essential value and decreased rates of responding on the observing lever. The conclusion that nicotine did not increase the essential value of these stimuli is demonstrated by Figure 2-5, which shows the data from all subjects fit to Equation 1-1 across both baseline and nicotine conditions. In fact, at the group level, nicotine appears to slightly decrease the value of these stimuli. Why did nicotine fail to enhance the value of these stimuli, despite previous data showing that nicotine enhances responding on the observing lever?

Experiment 1b

Several procedural variables may account for the failure of nicotine to enhance either essential value or responding on the observing lever in the previous experiment. As noted previously, the present preparation differed from previous experimental preparations using the observing procedure to demonstrate nicotine enhancement. One of these is the route of nicotine administration. Most studies demonstrating the nicotine enhancement effect, whether using primary reinforcing visual stimuli or conditioned reinforcers, have administered nicotine via injection (Glenn Guy & Fletcher, 2013, Weaver et al., 2012b) -though minipump-administered nicotine also enhances primary reinforcing visual stimuli (Weaver et al., 2012a). In particular, all previous studies using the observing response procedure to study nicotine enhancement have administered nicotine via injection. Therefore, we sought to examine the effects of nicotine on responding for in this modified observing response procedure when nicotine was administered via subcutaneous injection.

Experiment 1a Materials and Methods

Subjects

Three male Long-Evans rats, housed as described in Experiment 1a, maintained at 85% of their free-feeding weight served as subjects. All the subjects also previously served as subjects in Experiment 1a; however, one subject, 550, was euthanized following a necrotic skin complication at the site of the minipump insertion.

Apparatus

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

Procedure

The same observing response procedure described in Experiment 1a was used for Experiment 1b. All subjects were returned to baseline conditions following pump removal. Once at least two curves had been completed, and two consecutive curves were similar enough to share an α parameter according to an F-test, nicotine administration was begun.

Nicotine Administration

Nicotine (nicotine hydrogen tartrate salt; Sigma, St. Louis, MO) was dissolved in potassium phosphate and administered via subcutaneous injection at a dose of 0.3 mg/kg. Nicotine was administered for two consecutive curve determinations, for a total of 14 days of administration.

Experiment 1b Results & Discussion

Figure 2-6 shows the demand curves generated by this procedure, both following the return to baseline after Experiment 1a and when nicotine was administered via subcutaneous injection. As in the previous experiment, the curves drop off sharply after the lowest FR values. For two subjects, 547 and 548, nicotine increased the number of stimulus presentations that were earned at the lowest FR values, while for the remaining subject, nicotine slightly decreased the number of stimulus presentations earned. In contrast, in the previous experiment when nicotine was administered via osmotic minipump, nicotine did not significantly increase the number of stimulus presentations earned for any animal.

Figure 2-7 depicts the consumption data for each subject fit to Equation 1-1, both under baseline conditions and when nicotine was present. For subject 547, nicotine appeared to increase the essential value of the conditioned reinforcers. Table 2-2 lists

the α values associated with each replication of the FR sequence under both baseline conditions, the percent of variance accounted for by the model, as well as the F-test result. As indicated, the F-test revealed that the α values across baseline and nicotine conditions differ significantly for this subject. However, for subjects 548 and 552, the α values are shared. This is interesting in the case of 548, for whom injected nicotine increased the absolute number of stimulus presentations earned at some FR values (see Fig. 2-6); however, this increase did not translate to a change in essential value.

A difference between the present results and those of the previous experiment can be seen in Figure 2-8. Figure 2-8 shows rate of responding on the observing lever, averaged across subjects, at each FR value under both baseline and nicotine conditions. As is evident, nicotine increased rates of responding on the observing lever. All animals showed rate increases as a function of nicotine under at least some FR values; however, the magnitude and extent of the increase varied across animals. An increase in rate of responding on the observing lever is consistent with previous findings showing this effect of injected nicotine using the observing response procedure (Jones, Raiff & Dallery, 2010; Raiff & Dallery, 2006; Raiff & Dallery, 2008). In contrast, in the previous experiment (Fig. 2-4), nicotine slightly decreased rates of responding on the observing lever. Figure 2-9 shows the total rate of active lever responses, averaged across animals, as a function of FR value under both baseline and nicotine conditions. Nicotine appeared to slightly increase responding on this lever; however, this increase was not significant.

Figure 2-10 shows the global fit of all of the subjects' data to Equation 1-1 across both conditions. A change in essential value at this level would be indicated by different

slopes of the fitted lines. However, the closeness of the lines and the substantial overlap of the data points indicate that at this level, nicotine did not alter the essential value of the conditioned reinforcers. This visual analysis was confirmed by an extra-sum-of-squares F-test that indicated that the null hypothesis that the α parameter was similar enough across both conditions to be shared by both data sets was not rejected.

Comparing Figures 2-8 and 2-10 demonstrates the power of a behavioral economic approach for characterizing nicotine's enhancement effect. Figure 2-8, which shows rates of responding on the observing lever, shows an increase in responding when nicotine is present. This selective rate-increasing effect could be interpreted as enhancement. However, a behavioral economic analysis (Fig. 2-10) indicates that the change in response rate does not correspond to a change in *elasticity*, which would indicate a change in the form of the function relating responding to FR value. Thus, using a behavioral economic analysis, these two effects of nicotine can be dissociated.

Taken together, Experiments 1a and 1b are informative. First, they demonstrate the feasibility of using a modified observing response procedure to generate demand curves for conditioned reinforcers. Furthermore, the results indicate that Equation 1-1 can account for the data generated by this procedure fairly well. Neither experiment, which differed only in terms of method of nicotine administration, showed that nicotine increased the essential value of the conditioned reinforcers. However, Experiment 1b demonstrated that injected nicotine led to an increase in rate of responding on the observing lever while nicotine administered via osmotic minipumps did not.

Table 2-1. The fitted α parameters and percent variance accounted for by Equation 1-1 for each replication of the demand curve, under both baseline and nicotine conditions, for all subjects. Also shown are the results of an extra-sum-of-squares F-Test (see text for details).

Subject	547	548	550	552
Baseline α	0.0004861	0.0001392	0.0002212	0.0003638
Values	0.0004848	0.0001392	0.0002651	0.0003935
Baseline R^2	0.86	0.92	0.90	0.88
	0.86	0.92	0.85	0.88
Nicotine α	0.00009398	0.00002373	0.0003656	0.0006763
Values	0.0006589	0.0002028	0.0002485	0.0005119
Nicotine R^2	0.73	0.83	0.94	0.96
	0.88	0.94	0.96	0.96
F-test result	α shared	α not shared	α not shared	α shared

Table 2-2. The fitted α parameters and percent variance accounted for by Equation 1-1 for each replication of the demand curve, under both baseline and nicotine conditions, for all subjects. Also shown are the results of an extra-sum-of-squares F-Test (see text for details).

Subject	547	548	552
Baseline α	0.0003441	0.0001742	0.000409
Values	0.0003791	1.75E-04	0.0004553
Baseline R^2	0.931	0.8981	0.8888
	0.7986	0.8701	0.9219
Nicotine α	0.0001582	0.0002032	0.0001455
Values	0.0001666	0.0001907	0.00007864
Nicotine R^2	0.91	0.85	0.73
	0.96	0.96	0.90
F-test result	α not shared	α shared	α shared

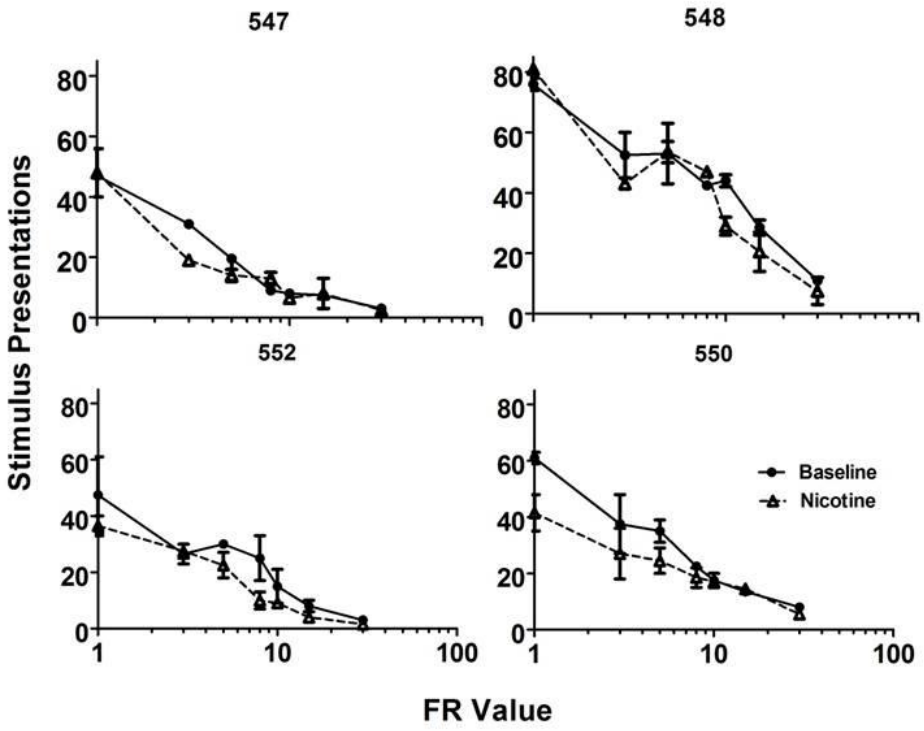

Figure 2-1. The absolute number of stimulus presentations earned for each subject, averaged across replications within subject at each schedule value, across baseline and nicotine conditions. Error bars represent standard error of the mean.

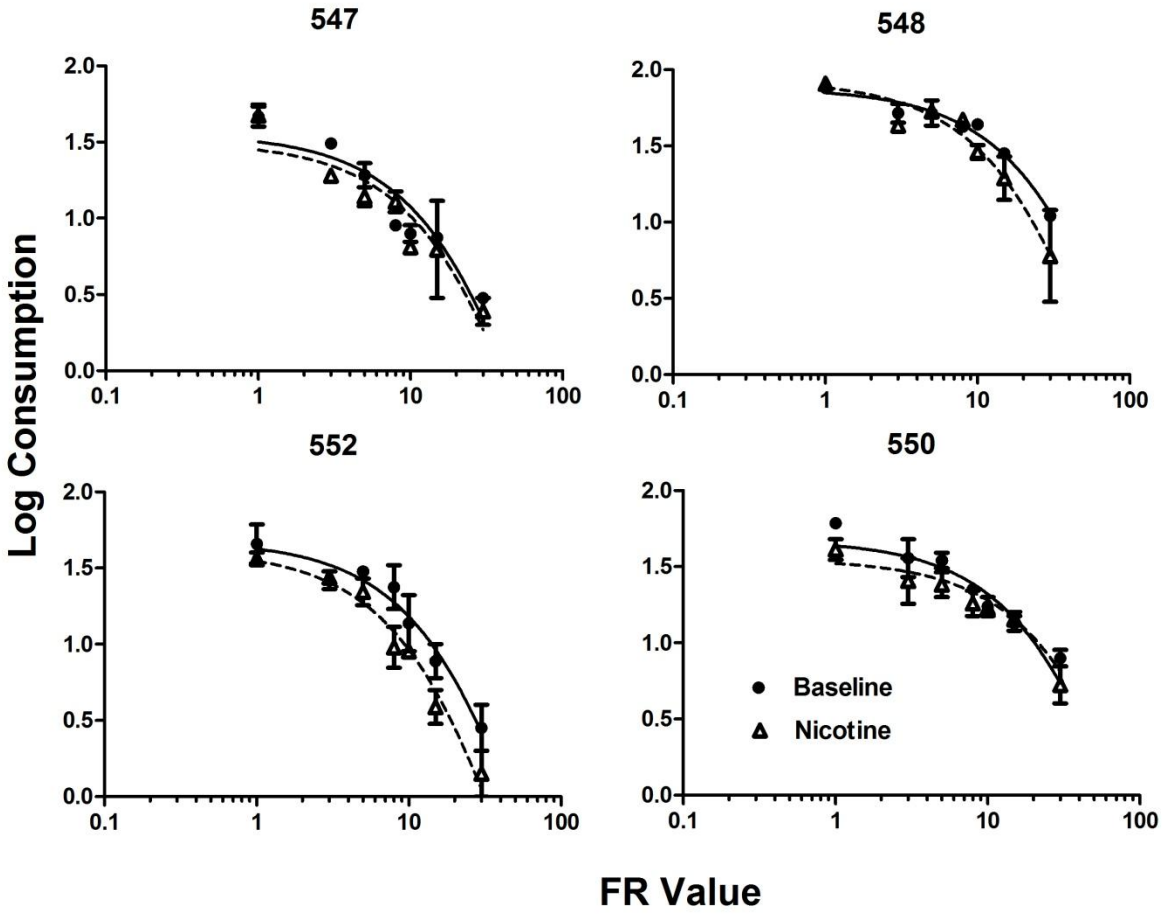

Figure 2-2. The obtained consumption data from both conditions were averaged within subject across each replication. Then, the data were fitted to the Exponential Demand Equation (see text for details).

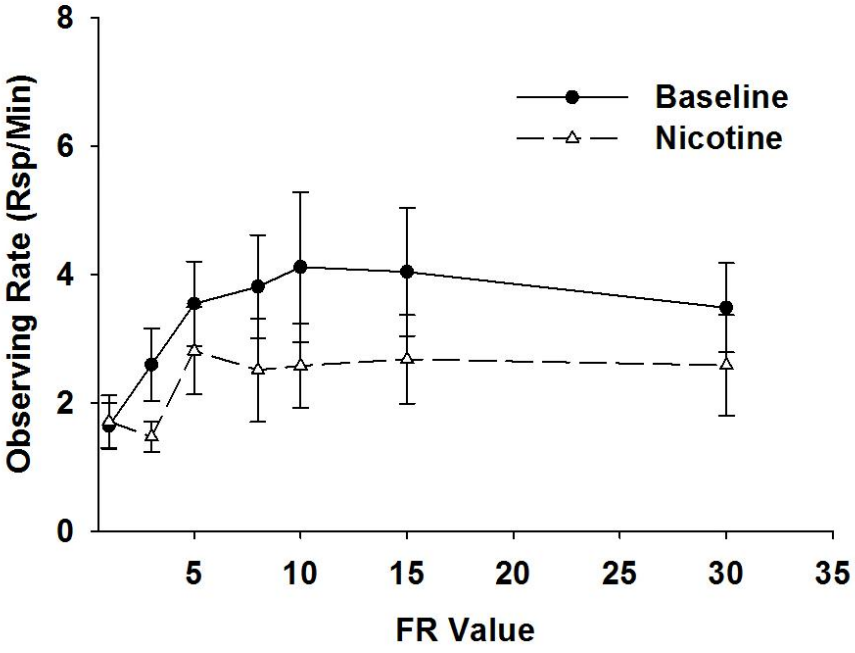

Figure 2-3. The average rate of responses per minute on the observing lever under both baselne and nicotine conditions, averaged across subjects at each FR value. Error bars represent the standard error of the mean.

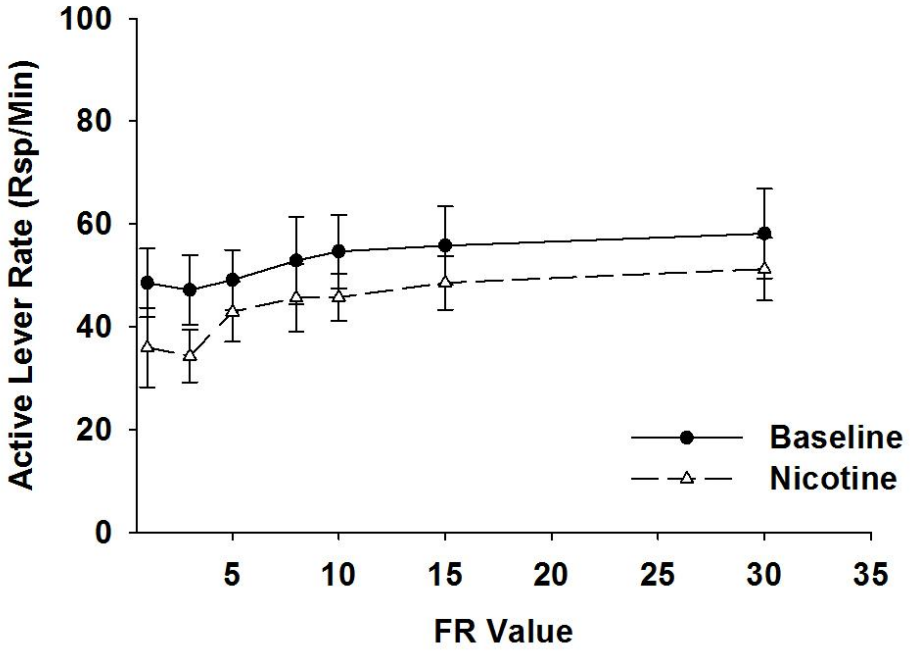

Figure 2-4. The average rate of responses per minute on the active lever under both baseline and nicotine conditions, averaged across subjects at each FR value. Error bars represent the standard error of the mean.

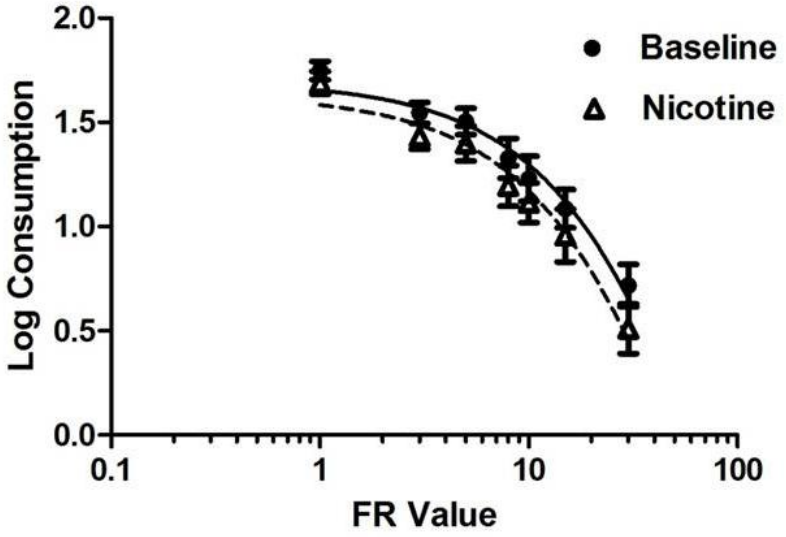

Figure 2-5. All consumption data from all subjects were fit to Equation 1-1 across baseline and nicotine conditions. Data points represent the average absolute consumption in log units, and error bars represent standard error of the mean.

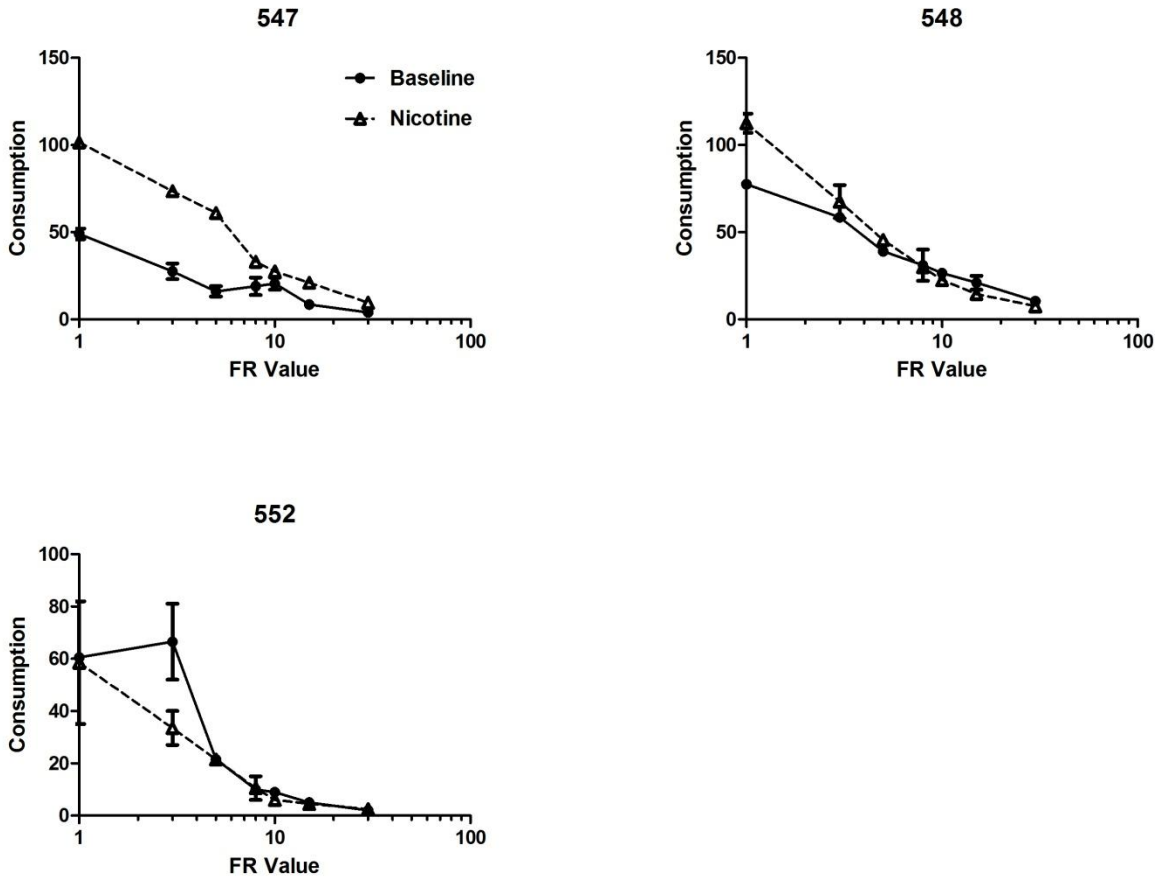

Figure 2-6. The absolute number of stimulus presentations earned for each subject, averaged across replications within subject at each schedule value, across baseline and nicotine conditions. Error bars represent standard error of the mean.

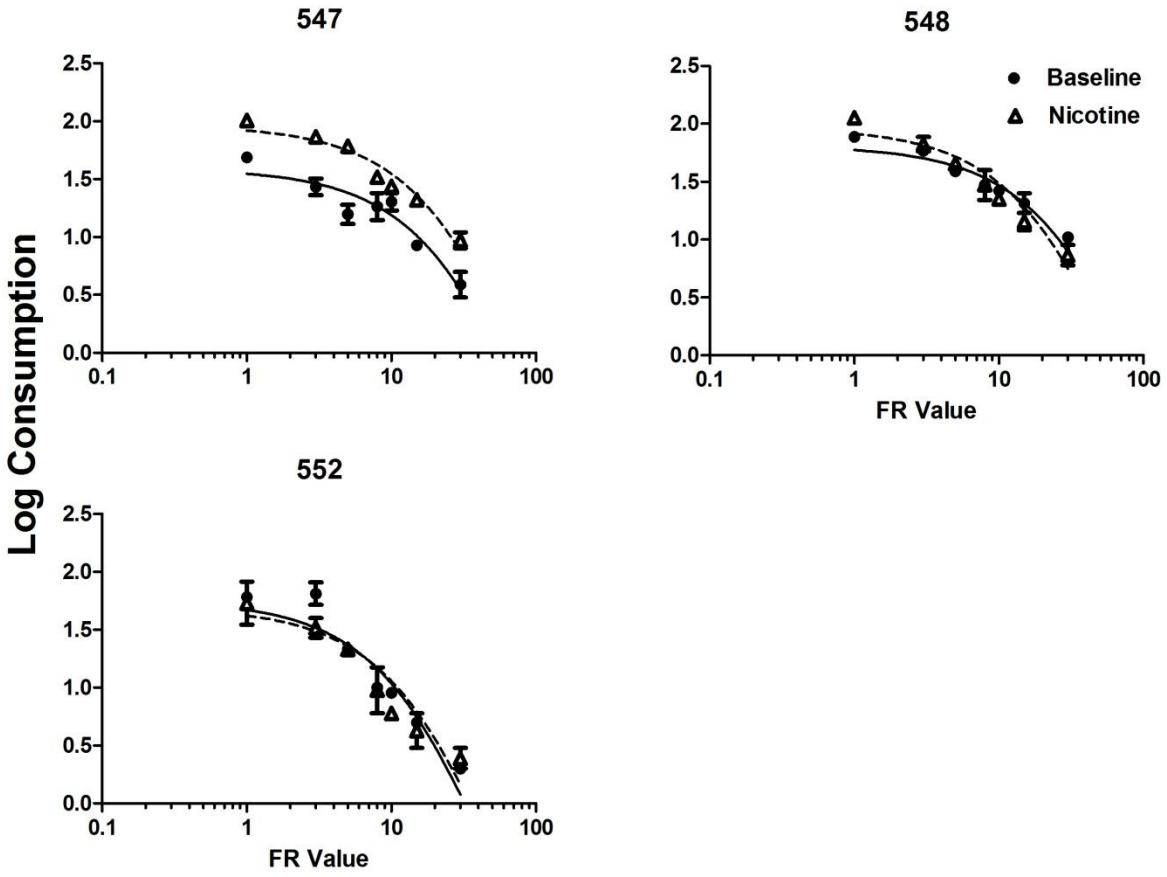

Figure 2-7. The obtained consumption data, averaged across replication within subject, was fit to Equation 1-1. Error bars represent standard error of the mean.

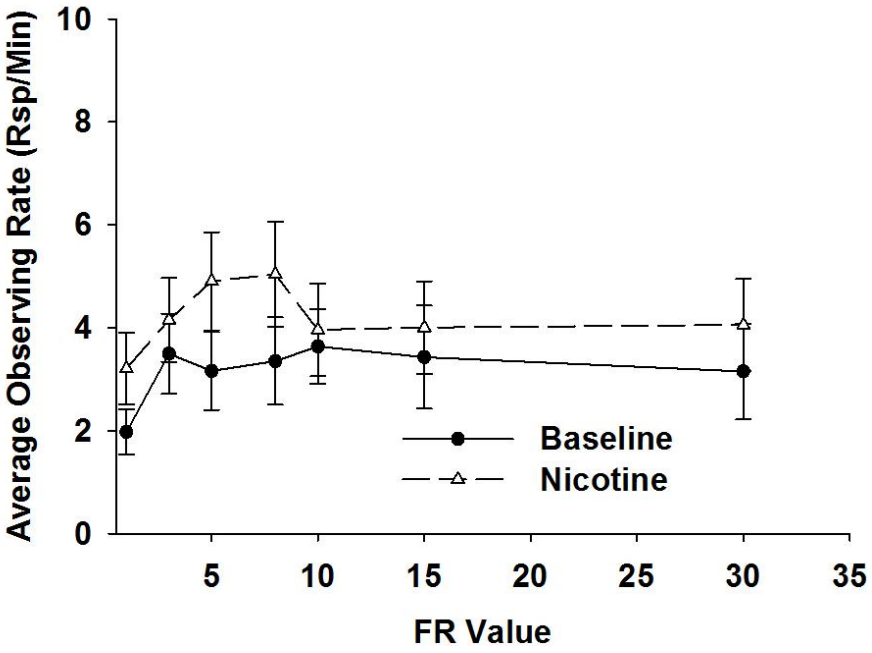

Figure 2-8. The average rate of responses per minute on the observing lever under both baselne and nicotine conditions, averaged across subjects at each FR value. Error bars represent the standard error of the mean.

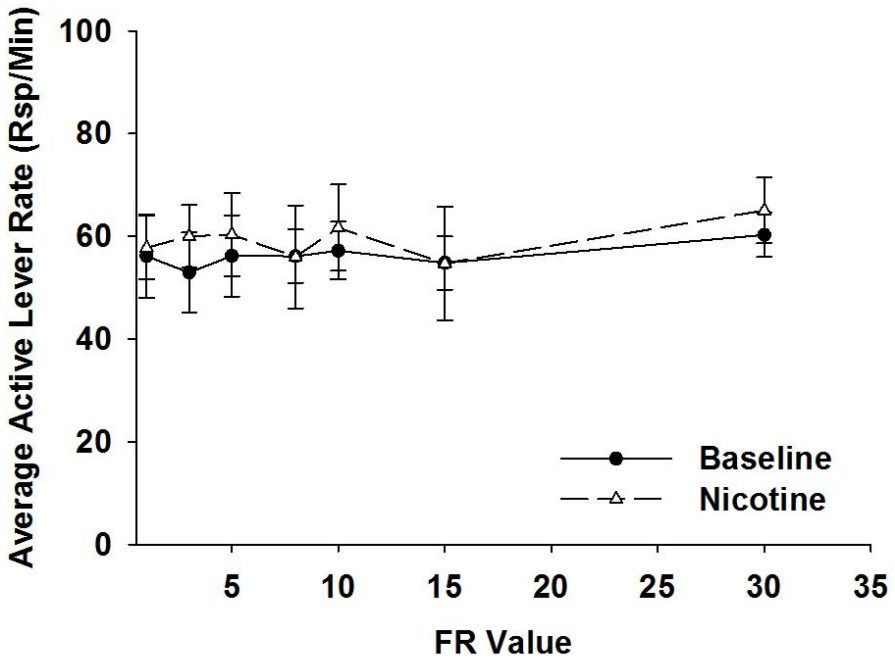

Figure 2-9. The average rate of responses per minute on the active lever under both baseline and nicotine conditions, averaged across subjects at each FR value. Error bars represent the standard error of the mean.

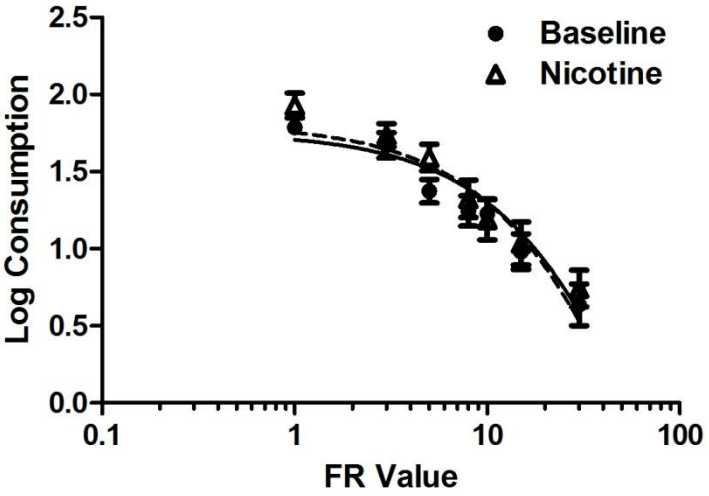

Figure 2-10. All consumption data from all subjects were fit to Equation 1-1 across baseline and nicotine conditions. Data points represent the average absolute consumption in log units, and error bars represent standard error of the mean.

CHAPTER 3
EXPERIMENT 2

The data from Experiments 1a and 1b demonstrate that nicotine does not enhance the essential value of conditioned reinforcers. However, although in Experiment 1a no enhancement of any kind was seen, in Experiment 1b a dissociation between observing response rate and essential value was observed. Thus, one variable that may contribute to nicotine's enhancement effect – measured in terms of rate – is method of drug administration. Indeed, in previous experiments using the observing response procedure to show nicotine's enhancement effect on observing response rates, injected nicotine was used. However, previous studies also differed from the present studies along another dimension: the schedule of food presentation on the active lever.

Previous experiments, which showed enhancement of observing responding by nicotine using this approach, arranged a variable interval 15 second (VI 15s) schedule of food presentation (e.g., Raiff & Dallery, 2008), while in Experiments 1a and 1bfood was available under a VR 10 schedule. It is plausible that the schedule of alternative reinforcement affects enhancement by nicotine. Therefore, we decided to investigate this phenomenon when food was available on a VI, as opposed to a VR, schedule.

Experiment 2 Materials and Method

Subjects

Six male Long-Evans rats, obtained from Harlan Laboratories, maintained at 85% of their free-feeding weight served as subjects. The subjects were individually housed in a windowless colony room and had unrestricted access to water in their home cages. The colony room had a 12:12 hour light/dark cycle, and subjects received any extra-session

feeding in their home cages. Two additional subjects experienced training and baseline procedures; however, their data was excluded due to a faulty feeder mechanism in their experimental chamber that inconsistently delivered pellets.

Apparatus

Three MED-PC aluminum and Plexiglas rodent operant chambers, with dimensions and specifications as described in Experiment 1a, were used as experimental chambers.

Discrimination Training

Discrimination training was conducted as described in Experiment 1a. During discrimination training, components of fixed ratio (FR) 1 reinforcer availability alternated with components of extinction during each session. The schedule then increased to a variable interval 5 second schedule, and then a variable interval 15-second (VI 15s) final schedule of food availability was reached. Sessions lasted 60 minutes, and continued until the stability criteria outlined in Experiment 1 had been met. Following discrimination training, the animals began the observing response procedure.

Observing response procedure

As in Experiments 1a and 1b, at this time, the S+ and S- were only presented after an observing response press, which illuminated the S+ or S-, depending on the current schedule, for fifteen seconds (Shahan, 2002). The terminal schedule parameters were: a VI 15s food schedule which alternated with periods of extinction approximately every 60 s (VI 60s component duration), and conditioned reinforcing stimuli presented for 15 s beginning on an FR 1 schedule. Each session lasted for 1hr.

Baseline

Following establishment of FR 1 observing lever responding, the schedule in place on the observing lever increased across days according to the following sequence: FR 1,

FR 2, FR 3, FR 5, FR 7, FR 10. Each FR was in place for one session. The curves were re-determined a minimum of three times until two of the curves met the F-test criteria specified in Experiment 1.

Nicotine Administration

Nicotine (nicotine hydrogen tartrate salt; Sigma, St. Louis, MO) was dissolved in potassium phosphate vehicle and administered via subcutaneous injection at a dose of 0.3 mg/kg. Nicotine was administered for three curve determinations, with a minimum of three days between redeterminations. Vehicle administrations consisted of subcutaneous injections of potassium phosphate at the same volume (1 ml/kg) as nicotine doses. Vehicle injections were administered for two curve determinations. Data from only the second two nicotine curves were included to equalize the number of data points across both conditions.

Experiment 2 Results & Discussion

Figure 3-1 shows the number of stimulus presentations earned by each subject across all FR values under both vehicle and nicotine conditions. As in the previous experiments, the demand curves are sharply downward-sloping. In terms of absolute consumption, compared with the previous experiments' data, consumption was in the same general range; however, the average consumption was lower, and the highest FR value that would support a minimum of responding was lower (FR 10 as opposed to FR 15 and 30). For all subjects, nicotine increased consumption of the conditioned reinforcers.

Figure 3-2 shows the data from Figure 3-1 fit to Equation 1-1. For all subjects, the nicotine curve significantly differs from the vehicle curve. This visual analysis is again confirmed by the F-test data, shown in Table 3-1, which indicates that for all six

animals, the curves were different enough that the α values were not shared across data sets. As is also evident from Table 3-1, in all cases the model accounted for more than 60% of the variance of the data. Additionally, the α values listed in Table 3-1 confirm that the shift depicted in Figure 3-2 represents an increase in essential value of the conditioned reinforcers when nicotine is present.

The increase in response rate on the observing lever as a function of nicotine administration can be seen in Figure 3-3. The data are from all subjects, averaged within each FR value, and are representative of individual animals. Response rates increased across all FR values when nicotine was administered compared to rates under vehicle administration. This effect is consistent with an enhancement interpretation. The observing rate data and the essential value data agree in this case, which is in contrast to the results from Experiment 1b. In the previous experiment, response rates increased on the observing lever as a function of nicotine, but essential value did not.

Nicotine also increased food responding somewhat, which is shown in Figure 3-4. This increase is comparable in magnitude to the slight increase in food responding as a function of nicotine found in Experiment 1b. These data raise the possibility that nicotine increased all types of responding, without reflecting any corresponding change in value. However, while in Experiment 1b both observing response rates and active lever response rates were increased, essential value was not changed; whereas in the present experiment, observing response rates were increased and essential value *was* increased as a function of nicotine (as shown in Figure 3-5), while food rates were also

slightly increased. Therefore, changes in response rates do not always coincide with changes in essential value.

In the current study, response rates and the essential value of the stimuli were compared to response rates and essential value when vehicle was presented. That is, the only difference between the conditions was the presence of nicotine. This makes the conclusion from this study with regard to nicotine's effects stronger than comparing to a baseline condition alone. In the previous experiment using injected nicotine, vehicle comparisons were not possible due to time constraints and the advancing age of the rats. Therefore, in Experiment 1b, the observed effect of nicotine on response rates could have been due to the injection procedure alone. Similarly, in Experiment 1a, a within-subject vehicle comparison was not possible, as multiple survival surgeries are not possible on a within-subject basis. However, given that no expected effects of nicotine were found, an across-group vehicle comparison was not necessary to rule out the effect of surgery alone. However, future research investigating nicotine's enhancement effect using injected nicotine should compare vehicle rates to drug rates.

Table 3-1. The fitted α parameters and percent variance accounted for by Equation 1-1 for each replication of the demand curve, under both vehicle and nicotine conditions, for all subjects. Also shown are the results of an extra-sum-of-squares F-Test (see text for details).

Subject	224	225	227	228	229	231
Vehicle α	0.001344	0.0007658	0.001217	0.0001743	0.00159	0.004378
values	0.001058	0.001051	0.0007286	0.0001977	0.000672	0.002949
Vehicle R^2	0.87	0.94	0.86	0.95	0.74	0.91
	0.99	0.82	0.91	0.94	0.87	0.95
Nicotine α	0.0005068	0.0002734	0.0005123	0.0000704	0.0007188	0.001248
values	0.0004689	0.0003297	0.0003101	0.0001247	0.0004175	0.0008987
Nicotine	0.82	0.66	0.91	0.62	0.77	0.88
R^2	0.96	0.95	0.98	0.96	0.88	0.98
F-Test	α not	α not	α not	α not	α not	α not
result	shared	shared	shared	shared	shared	shared

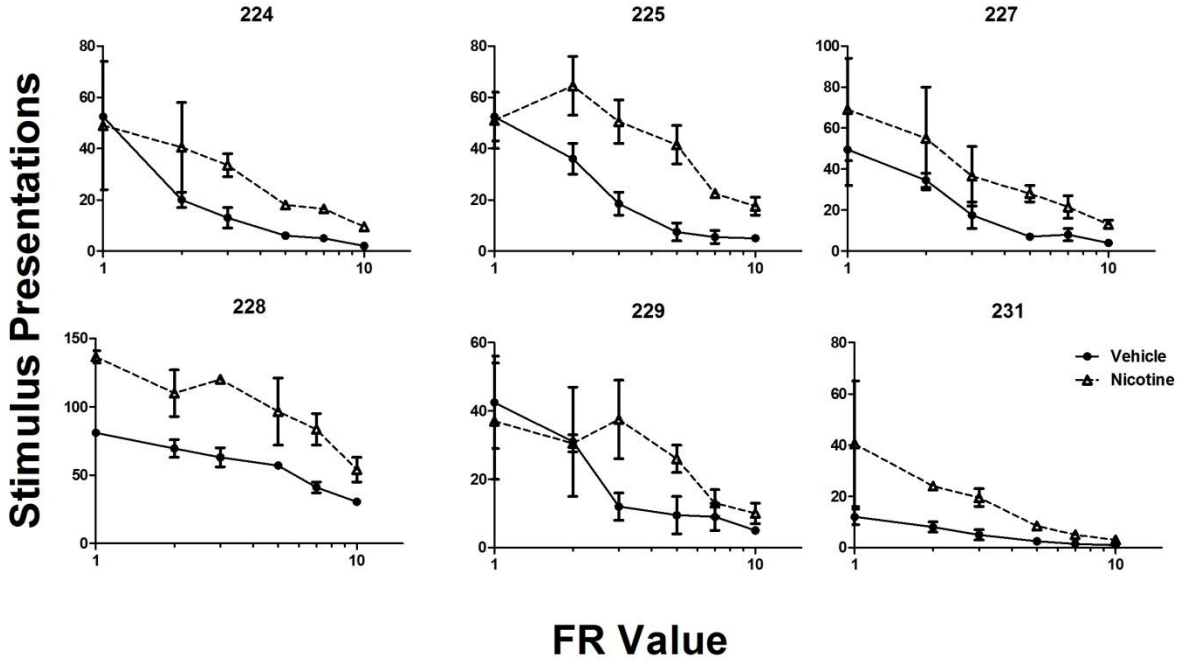

Figure 3-1. The absolute number of stimulus presentations earned for each subject, averaged across replications within subject at each schedule value, across vehicle and nicotine conditions. Error bars represent standard error of the mean.

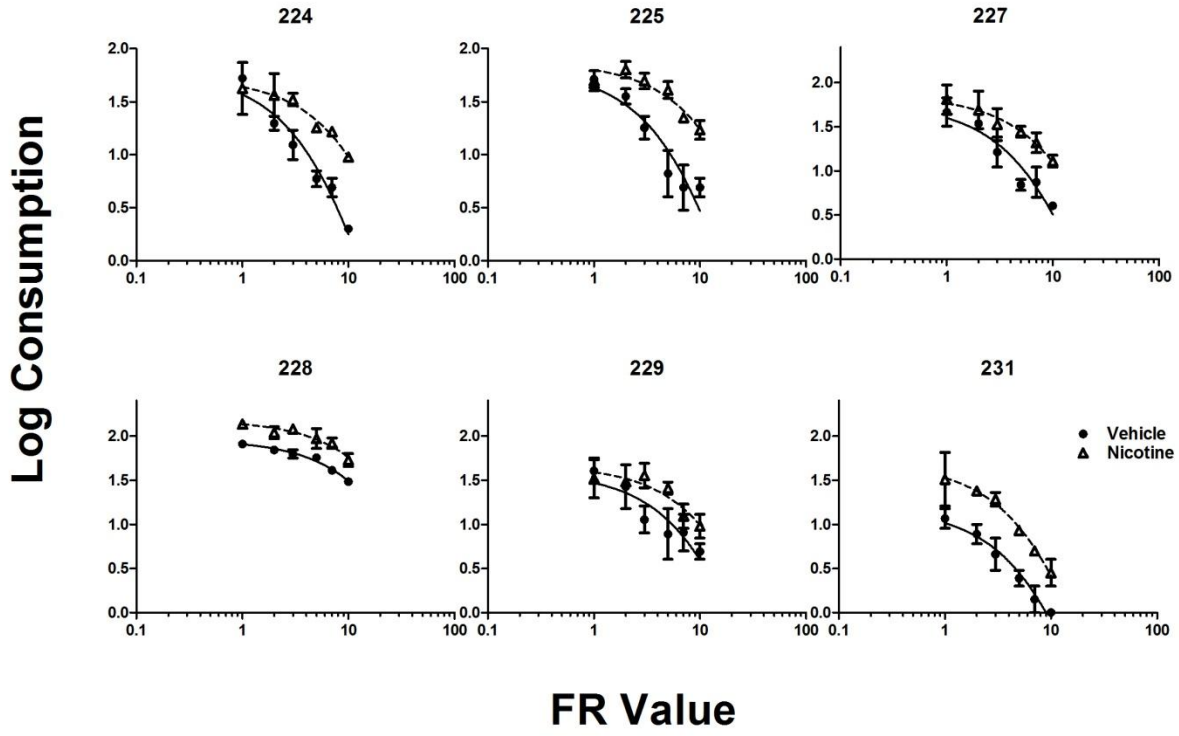

Figure 3-2. The obtained consumption data, averaged across replication within subject, was fit to Equation 1-1. Error bars represent standard error of the mean.

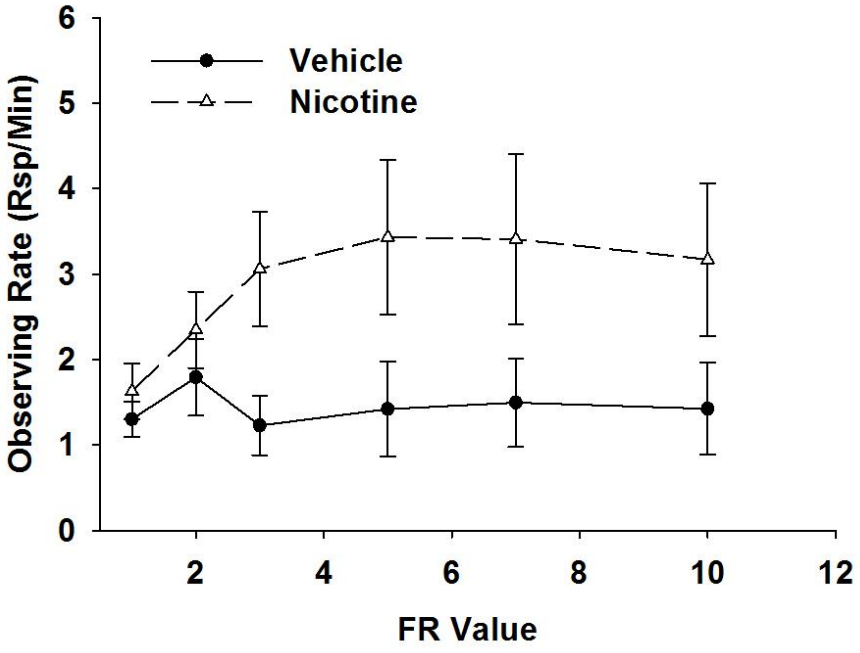

Figure 3-3. The average rate of responses per minute on the observing lever under both vehicle and nicotine conditions, shown as an average across subjects at each FR value. Error bars represent the standard error of the mean.

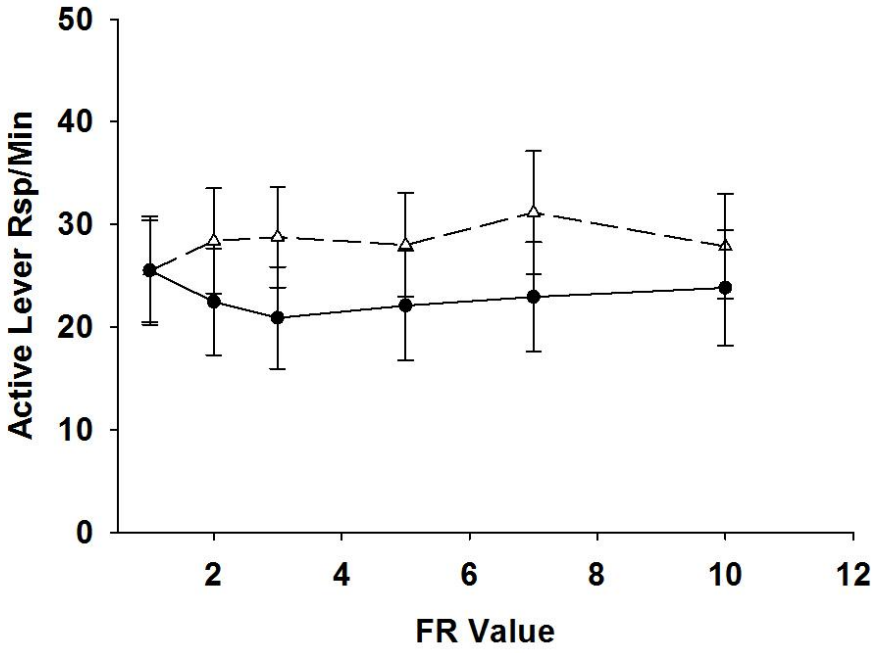

Figure 3-4. The average rate of responses per minute on the active lever under both vehicle and nicotine conditions, shown as an average across subjects at each observing FR value. Error bars represent the standard error of the mean.

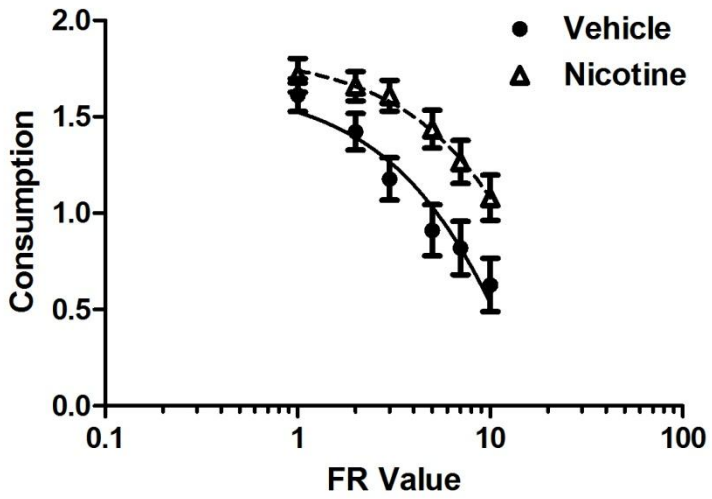

Figure 3-5. All consumption data from all subjects were fit to Equation 1-1 across baseline and nicotine conditions. Data points represent the average absolute consumption in log units, and error bars represent standard error of the mean.

CHAPTER 4
GENERAL DISCUSSION

The present experiments demonstrated the feasibility and utility of using a behavioral economic approach to investigate nicotine's value-enhancement effect. All the studies used a modified observing response procedure to generate a demand curve for food-associated conditioned reinforcers. In Experiment 1, food was available according to a VR schedule which alternated with periods of extinction, and presses to the observing lever illuminated schedule-correlated stimuli after completion of a fixed ratio schedule. The fixed ratio schedule varied across session, thus creating a demand curve which was fit to behavioral economic equation to determine the elasticity (or essential value) of the function. In Experiment 1a, nicotine was administered surgically, and essential value was not changed as a function of nicotine administration. In Experiment 1b, nicotine was administered via subcutaneous injection, and although increases in response rate on the observing lever occurred, essential value was again unchanged as a function of nicotine administration. In Experiment 2, the same basic procedure was used. However, the schedule of food availability was changed to a VI 15s schedule. Nicotine was administered via subcutaneous injection, and under these conditions both an increase in essential value and an increase in observing response rate was seen. Therefore, under at least some conditions, nicotine enhances the value of conditioned reinforcers.

Taken together, the observing response rate data and essential value data from Experiments 1b and 2 tell an interesting story. The two measures, essential value and rate of observing responding, generally changed in the same direction; however, in Experiment 1b, rate increases were observed that did not correspond to changes in

essential value. Other examples exist of variables that result in changes in response rate for a good without a corresponding change in the essential value of that same good (see Hursh & Silberberg, 2008). Particularly relevant to the present experiments are data showing that although nicotine decreased rates of responding for food, the essential value of food was unchanged by nicotine (e.g., Cassidy & Dallery, 2012). Such data underscore the promise of behavioral economic approach to understanding changes in reinforcer efficacy: a change in response rate for a good as a function of drug administration *may or may not* reflect a change in the form of the function relating price to consumption, which is captured by the essential value parameter.

The data from Experiment 2 indicate that nicotine did in fact change the form of the function relating the price of conditioned reinforcers to rats' consumption of these reinforcers. Nicotine changed the slope of the function, making responding more inelastic to increases in price. In other words, nicotine enhanced the value of these stimuli. Why, then, did nicotine not increase the value of the conditioned reinforcers used in Experiments 1a and 1b? Route of drug administration alone is not the whole story, as nicotine was delivered via injection in Experiment 1b and, while changes in response rate were found, nicotine did not alter essential value. Rather, the key difference between the two experiments was the schedule of food presentation on the active lever.

The change from a VR to a VI schedule of food presentation had several potential impacts on observing responding and/or essential value. First, the change from a VR to a VI schedule resulted in lower obtained rates of food reinforcement. The rates of food reinforcement across all three experiments under baseline/vehicle and

nicotine conditions are shown in Figure 4-1. This lower rate of obtained reinforcement affected the schedule of conditioned reinforcement presentation, as conditioned reinforcers associated with a lower rate of primary reinforcement did not support responding at the higher FR values that conditioned reinforcers associated with a VR schedule did. Thus, the highest FR value in Experiment 2 that supported responding on the observing lever was FR 10, as opposed to FR values of 15 and 30 that maintained responding in Experiment 1. This difference was also reflected in the baseline essential values of the conditioned reinforcers: in Experiment 1, the conditioned reinforcers were relatively more valuable than the conditioned reinforcers used in Experiment 2.

The difference in value of the conditioned reinforcers across Experiments 1 and 2 points to an interesting hypothesis about the nature of nicotine's enhancement effect. The conditioned reinforcers used in Experiment 1 were more valuable than in Experiment 2, yet nicotine only increased the essential value of those in Experiment 2. These data support to the hypothesis, put forth by Raiff & Dallery (2008), that nicotine may enhance the value of moderately valuable reinforcers. That is, nicotine enhancement may be seen only along a part of the continuum of essential values that reinforcers can generate. This hypothesis suggests that nicotine will enhance primary visual stimuli, such as those used by Barrett & Bevins (2012), which have relatively small essential values, without enhancing the essential value of stronger reinforcers such as food (as demonstrated by Cassidy & Dallery, 2012). What is interesting about the present studies in terms of this hypothesis is that these data seem to show a specific quantitative value after which nicotine enhancement is unlikely to be seen. Evidence of this is shown in Table 4-1.

Table 4-1 lists four data sets that have used Equation 1-1 to quantify nicotine's enhancement effect. The studies are listed in order of increasing essential value of the stimuli prior to nicotine injection (recall that smaller α values indicate a *higher* essential value). The relatively low essential value of the stimuli in Experiment 2 is comparable to the essential value of primary reinforcing visual stimuli, which were available without any alternative source of reinforcement (data from Barrett & Bevins, 2012). In these two cases, moderately reinforcing stimuli were enhanced by nicotine. The next two data sets reflect the essential value of the conditioned reinforcing stimuli used in Experiment 1a, and the very high essential value of food available under 24-hour closed economy conditions (data from Cassidy & Dallery, 2012, Experiment 2). In these two cases, nicotine did not alter essential value. Thus, this approach allows us to more precisely predict which stimuli nicotine may be likely to enhance, and to further specify the conditions under which enhancement is likely to be seen.

Table 4-1 also raises a potential limitation of the stimuli used in Experiment 2. Why were these conditioned reinforcers similar in essential value to the primary reinforcing visual stimuli used by Barrett & Bevins (2012)? Is it possible that the visual stimuli were acting only as primary reinforcers, and not as conditioned reinforcers? This possibility can be examined by looking more closely at the data from Barrett & Bevins (2012). While essential value was similar, the absolute values of the stimuli earned were far lower. Under vehicle conditions, an average of only 16 stimulus presentations were earned at FR 1; and at the halfway point along the demand curve, the average number of stimulus presentations had declined to 4. In contrast, in the present Experiment 2, the average number of stimulus presentations earned at FR 1 was 50, and along the

halfway point of the demand curve, approximately 20 stimulus presentations per session on average we earned. Thus, the greater absolute number of stimulus presentations earned tells us that the stimuli used in the present stimuli were of a larger scalar value – that is, the demand curve for these stimuli is higher in absolute terms than the demand curve for the stimuli used by Barrett & Bevins (2012)- even though the essential values were very similar. Additionally, the value of the Barrett & Bevins (2012) stimuli may have been heightened due to the fact that no alternative reinforcement was available, in contrast to the present studies.

In addition to the lower rate of obtained reinforcement in the presence of the stimuli in Experiment 2 versus Experiment 1, the change from a VR to a VI schedule may also have affected the value of the stimuli through other mechanisms. Another difference between the VR and VI schedules used in the present experiments is the amount of effort required to produce each reinforcer. The VR schedule is response-dependent; therefore, higher rates of responding result in higher rates of reinforcement, and the upper limit of obtained reinforcer rate is determined by the animal's motoric capacity combined with the schedule value (Soto, McDowell, & Dallery, 2006). Thus, this type of schedule engenders higher response rates and requires more responses per reinforcer. Under a VI schedule, in contrast, there is an upper limit of response rate past which further responding will not result in higher rates of reinforcement due to time-based nature of the schedule, even if the animal can physically respond at a higher rate (Baum, 1973; Herrnstein, 1970). Thus a VI 15s schedule, compared to a VR 10, requires fewer responses per unit time to earn each reinforcer. That is, the two schedules differed in the amount of effort required, and this may have contributed to the

differences observed across Experiments 1 and 2. We have already seen that the increased effort required under the VR did not lead to a decreased essential value of the observing stimuli; however, it is possible that the competing alternative responding required by the VR disrupted the extent to which nicotine enhanced the essential value of these stimuli. Future research should investigate this question by equating the rates of reinforcement under a VI and VR schedule such that the only difference between the two schedules would be the amount of effort required. The results of such a study would demonstrate the relative contribution of effort alone, as opposed to changes in obtained reinforcement, to nicotine's enhancement effect.

The present series of experiments both confirm quantitatively that nicotine enhances the value of conditioned reinforcers, while also suggesting constraints on the conditions under which enhancement may be seen. In addition to the schedule of alternative reinforcement discussed above, another constraint suggested by the present experiments is the method of administration: in the present experiments, no nicotine enhancement – either as judged by rates or by essential value changes- was seen when nicotine was administered via osmotic minipumps. In contrast, when nicotine was injected, rates increased in both Experiments 1b and 2 and in Experiment 2, essential value was also changed. Injected nicotine rapidly delivers a bolus of nicotine to nicotine receptors in the central nervous system (Gourlay & Benowitz, 1997; Rose, Behm, Westman, & Coleman, 1999). Nicotine acts on nicotinic acetylcholinergic receptors such that initially, dopamine is quickly released; however, following chronic administration these receptors become desensitized and less dopamine is released (Balfour, 2004; Laviolette & van der Kooy, 2004; Pidoplichko et al., 2004). Furthermore, dopamine

appears to be a crucial neurotransmitter involved in learning, particularly in associating arbitrary stimuli with biologically important events (Balfour, 2004; Everitt et al., 2008; Schultz, 2001). Therefore, the initial burst of dopamine release that is associated with injection of nicotine may lead to a nicotine enhancement, while nicotine presented chronically may not.

Inhaled nicotine functions much like injected nicotine in that it delivers a quick bolus of drug to the brain, particularly the first cigarette of the day for smokers (Balfour, 2004). However, generally smokers then continue to smoke throughout the day, during which their nicotinic receptors undergo desensitization and their blood cotinine levels resemble those of rats who have been implanted with continuous-release osmotic minipumps (Matta et al., 2007). Therefore, the current data is equivocal as to whether human smokers may experience nicotine enhancement and under what conditions. However, other studies using human participants have looked for evidence of nicotine enhancement in smokers.

The data on nicotine enhancement in humans is equivocal. One study, which had smokers respond for money, music and termination of an aversive sound, saw no enhancement of these responses when nicotine was administered (Perkins, Grottenthaler & Wilson, 2009). In contrast, a later study found that nicotine did enhance responding for music rewards, but not for money rewards (Perkins & Karelitz, 2013). Despite these data, Dawkins, Powell, West, Powell, & Pickering (2006) demonstrated that nicotine enhanced the subjective value of a monetary reward. Nicotine has also been shown to increase smokers' ratings of the attractiveness of faces, which may be taken as an indication of value enhancement (Attwood, Penton-Voek, & Munafò, 2009).

In short, the extent to which nicotine's value enhancement effect is seen in human smokers, and the degree to which value enhancement may play a significant role in nicotine addiction, remains to be seen.

Nicotine's value enhancement effect has the potential to help answer many unsolved questions about the persistence of nicotine addiction. The current studies used a behavioral economic approach, which holds promise for characterizing the effects of nicotine, and other drugs, on the value of other reinforcers. The data from current studies demonstrated that nicotine does enhance the value of stimuli in the environment. However, the present data also raise a number of caveats about nicotine enhancement and the conditions under which it is likely to occur. Although nicotine enhancement may a somewhat limited phenomenon, understanding and quantifying this phenomenon in humans and animals remains a worthwhile endeavor.

Table 4-1. A brief summary of the relationship between α value and nicotine enhancement in studies using Equation 1-1 to quantify nicotine's value – enhancement effect.

Study	Stimuli	Average pre-Nicotine α value	Nicotine Enhancement?
Present Exp. 2	Conditioned reinforcing visual stimuli-associated with VI 15s schedule of food presentation	0.0014	Yes
Barrett & Bevins (2012)	Primary reinforcing visual stimuli	0.0035	Yes
Present Exp. 1a	Conditioned reinforcing visual stimuli-associated with VR 10 schedule of food presentation	0.00031	No
Cassidy & Dallery (2012)	Food pellets	0.0000017	No

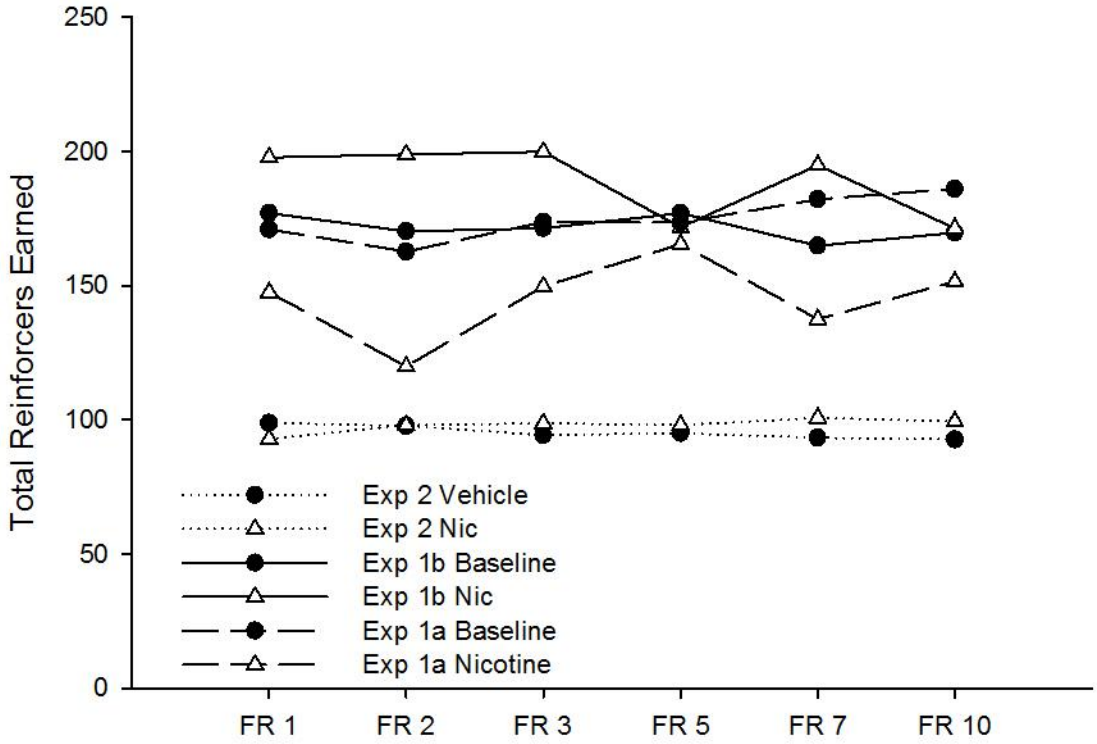

Figure 4-1. Total reinforcers earned on the active lever, averaged across subjects, as a function of observing FR value under baseline/vehicle and nicotine conditions of each of the present experiments.

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BIOGRAPHICAL SKETCH

Rachel Cassidy was born in 1986, in Fort Myers, Florida. She graduated from Fort Myers High School with an International Baccalaureate Degree in 2004. She then attended the University of Florida, where she was indicted in to Phi Beta Kappa as a junior and graduated Magna cum Laude with a bachelor of science in psychology and in sociology in 2008.

Rachel began her research career in behavior analysis in 2006, when she presented a poster at the UF Psychology Undergraduate Research Forum and was awarded Outstanding Poster. In 2007, her application was accepted for the competitive University Scholars Program, which awards stipends to undergraduate researchers. Her final project was published in the Journal of Undergraduate Research. She presented her first poster at a national conference in 2007.

Upon completion of her bachelor's degree Rachel was accepted in to the UF Behavior Analysis Ph.D. program as a student of Dr. Jesse Dallery. In May of 2010, Rachel gave her first paper presentation at a national conference of Behavior Analysts in San Antonio, Texas. In 2013, she received an Outstanding Graduate Student Teaching award, as well as an award for Excellence in Research in Behavior Analysis. She received her doctorate in August 2013 and accepted an NIH postdoctoral fellowship appointment at Brown University researching novel treatments for substance abuse.