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Economic demand analysis of within-session dose-reduction during nicotine self-administration

Gregory L. Powell[a,b], Gabriella Cabrera-Brown[a], Mark D. Namba[a], Janet L. Neisewander[b], Julie A. Marusich[c,*], Joshua S. Beckmann[d,*], Cassandra D. Gipson[a,*]

[a] Department of Psychology, Arizona State University, 950 McAllister Ave., Psychology Room 203, Tempe, AZ, 85287 USA
[b] School of Life Sciences, Arizona State University, TEMPE Campus, Mailcode 4701, Tempe, AZ, 85281 USA
[c] Center for Drug Discovery, RTI International, 3040 Cornwallis Rd, Research Triangle Park, NC, 27709 USA
[d] Department of Psychology, University of Kentucky, 741 S. Limestone, B453 BBSRB, Lexington, KY, 40536 USA

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ABSTRACT

Background: This study determined if a within-session dose-reduction design sufficiently captures elasticity of demand for nicotine in male and female rats using environmental enrichment to manipulate demand elasticity.
Methods: Male and female Sprague-Dawley rats were trained to self-administer nicotine (60 μg/kg/infusion). In Experiment 1, rats began daily dose-reduction for nine sessions following acquisition. Rats then underwent a minimum of five within-session dose-reduction sessions where each dose was available for 10 min. In Experiment 2, rats were reared in isolated, social, or enriched housing followed by acquisition of nicotine self-administration. Rats then underwent within-session dose-reduction. Housing environments were then switched, followed by additional testing sessions. Consumption was calculated for each dose and exponential demand curves were fit.
Results: No sex differences in acquisition of nicotine self-administration were detected for either experiment. In experiment 1, demand intensity (Q_0; estimated intake if nicotine were freely available), was higher with between- compared to within-session dose-reduction, although elasticity of demand (α; rate of decline in nicotine intake as a function of increasing unit price), was lower. In Experiment 2, animals reared in enrichment had fewer infusions during acquisition compared to animals in isolation. Enriched males had reduced demand intensity compared to both isolated and social males, whereas isolated females had reduced intensity compared to enriched females.
Conclusions: The within-session dose-reduction procedure for nicotine self-administration replicated effects of environmental enrichment on consumption behaviors. Additionally, this procedure captured differences in nicotine demand due to sex, laying important groundwork for future translational research on mechanisms of nicotine dependence.

1. Introduction

The reinforcing strength of drugs of abuse has been assessed using a variety of methods. In experiments employing nicotine self-administration in rodents, progressive ratio (PR) schedules of reinforcement reflect a persistent motivation for nicotine despite increasing cost (Donny et al., 1995). PR schedules, however, are susceptible to hysteresis and reduce the output of a session to a single data point: the last completed ratio (Bradshaw and Killeen, 2012). Alternatively, applications of behavioral economics as Hursh and Silberberg describe (Hursh and Silberberg, 2008) yield an "essential value" for those drugs, defined as the strength of the reinforcer and quantified as the rate of change in consumption as a function of unit price. Behavioral economic analyses have been employed to examine demand for multiple drugs of abuse, including nicotine, and have helped guide and inform regulatory policy (Bickel et al., 2014; Chetty, 2015; Fowler et al., 2017; Hursh, 1991; Hursh and Roma, 2016).

Many drugs of abuse, including cocaine, methamphetamine, and synthetic cathinones, produce an inverted-U shaped dose-response curve under a low, fixed-ratio (FR) schedule of reinforcement with fewer infusions earned at lower and higher doses compared to middle doses (Grebenstein et al., 2015; Huskinson et al., 2017; Yates et al., 2017). In contrast, the nicotine dose-response curve is relatively flat, with a narrow ascending limb, and large individual differences in intake

* Corresponding authors.
E-mail addresses: jmarusich@rti.org (J.A. Marusich), joshua.beckmann@uky.edu (J.S. Beckmann), cgipsonr@asu.edu (C.D. Gipson).

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at higher doses (Donny et al., 2000, 1995; Matta et al., 2007; Shoaib et al., 1997; Shoaib and Stolerman, 1999; Valentine et al., 1997). Self-administration of different drugs of abuse may result in differently shaped dose-effect curves due to factors such as reinforcing strength, duration of action, and motor impairment, among others. Thus, an alternative metric capable of comparing consumption across doses would prove useful.

The advent and application of behavioral economics theory has facilitated analysis of demand for many drugs of abuse. In order to evaluate changes in consumption across doses, dose can be transformed to "unit price," defined as the response requirement to receive nicotine divided by the nicotine concentration. Demand curves with parameters that reflect intensity and elasticity of demand can then be calculated. Demand intensity, commonly denoted with Q, is defined as consumption of a specific drug, such as nicotine (often calculated at a unit price of zero [Q_0] to represent a theoretical maximum consumption if drug were free). Alternatively, demand elasticity, commonly represented by α, is defined as the change in consumption as a function of unit price (Bickel et al., 2000). Together, these two parameters represent how much work an animal will perform to acquire drug at baseline, and how quickly the animal will stop working when drug becomes more difficult to acquire. Application of these procedures highlights significant distinctions in self-administration procedures and biological factors, such as age and sex. Increasing the response requirement and reducing the available dose are thought to produce similar effects on drug consumption (Bickel et al., 1990), though recent research suggests that alterations of response requirement are not necessarily equivalent to decreases in nicotine content (Smith et al., 2016). Demand analysis for drugs of abuse provides estimates of free consumption and unit price sensitivity, which are dissociable (Oleson et al., 2011; Yates et al., 2017). Additionally, measures such as P_{max} (the unit price at which maximum consumption occurs), O_{max} (the amount of consumption that occurs at P_{max}), and breakpoints can all be estimated using demand curves (Hursh and Roma, 2016; Yates et al., 2017). Together, these studies illustrate how dose-reduction procedures coupled with demand analyses provide additional information beyond traditional approaches such as FR or PR schedules of reinforcement or dose-response curve analysis alone.

Demand analyses also detect differences in nicotine consumption due to individual characteristics (e.g., sex, age, etc.) and environmental conditions (e.g., exercise, social interaction, etc.). The nicotine self-administration literature is inconsistent regarding sex differences, perhaps attributable to variation in dose and schedules of reinforcement (Chaudhri et al., 2005; Feltenstein et al., 2012; Swalve et al., 2016). Generally, females self-administer more nicotine than males at higher unit doses on low FR schedules (Chaudhri et al., 2005; Flores et al., 2016). Demand curve analysis reveals that sex differences emerge with manipulations of unit price, with female rodents showing less compensatory consumption at higher doses than males during a progressive dose-reduction (Grebenstein et al., 2013). While females self-administer more nicotine during baseline testing than males, both sexes show similar demand elasticity and reinforcement threshold (Grebenstein et al., 2013). Differential housing environment is another commonly used manipulation known to alter motivation for drugs of abuse. For example, an enriched housing environment reduces seeking and consumption of cocaine (Chauvet et al., 2012; Gipson et al., 2011; Nader et al., 2012; Solinas et al., 2010, 2008; Thiel et al., 2012, 2009), amphetamine (Bardo et al., 2001, 1995; Green et al., 2010, 2002), and nicotine (Gomez et al., 2015; Green et al., 2003; Hamilton and Kolb, 2005; Hamilton et al., 2014; Venebra-Muñoz et al., 2014). Furthermore, enriched housing increases elasticity of drug and non-drug reinforcers (Yates et al., 2017), though demand analyses for nicotine and environmental enrichment have not been investigated.

A potential drawback of demand analyses is that commonly used dose-reduction timelines do not allow for efficient within-subject testing because they require more test days, increased volume of drug, and prolonged catheter patency. Alternatively, within-session dose-reduction procedures allow testing across a range of doses while still providing the same information as between-session procedures (Bentzley et al., 2013; Zittel-Lazarini et al., 2007). Within-session dose-reduction procedures have been utilized to assess demand for cocaine, remifentanil, and heroin (Lacy et al., 2019; Lenoir and Ahmed, 2008; Oleson and Roberts, 2009) and to investigate pharmacotherapeutic effects on demand curves (Cox et al., 2017; Oleson et al., 2011), yet this procedure has not been used to assess demand for nicotine. Therefore, the present study first compared between- and within-session nicotine dose-reduction in male and female rats. Then we determined if the within-session dose-reduction procedure is sensitive to sex differences and effects of environmental enrichment on nicotine self-administration.

2. Material and methods

2.1. Experiment 1: comparison of between- and within-session dose-reduction

2.1.1. Animals

Adult male and female Sprague-Dawley rats (males (n = 6): 200–250 g; females (n = 6): arrived pregnant on gestational day (GD) 3; Charles River, San Diego, CA) were housed individually and in separate colony rooms to avoid potential hormonal influences on behavior. Water was available *ad libitum* in the home cage. Males were experimentally naïve, and females had been used as control pregnant dams in a developmental nicotine exposure study (see prenatal nicotine exposure methodology of (Huang et al., 2004)), but were naïve to nicotine prior to being utilized in the current study. Parturition occurred naturally, and pups were allowed to wean through postnatal day (PND) 21. Saline administration in dams ceased on approximately PND 12, an average of 18 days before nicotine self-administration procedures began in the present study. Once pups had weaned, females were single-housed and proceeded with nicotine self-administration. All procedures were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee of Arizona State University. One animal was lost due to attrition in Experiment 1.

2.1.2. Apparatus

All experimental sessions were conducted in operant chambers (MED Associates, St. Albans, VT) housed inside sound-attenuating chambers (MED Associates). Each chamber contained one retractable and one non-retractable lever. A stimulus light was positioned above each lever, and each chamber was equipped with a house light. Fans mounted to the sound attenuating chambers provided ventilation, and infusion pumps (Med Associates) were located outside the chamber. All responses were recorded by MED-PC software (Med-Associates) on a computer in the experimental room.

2.1.3. Food training and surgical procedures

Within one week of arrival for males and following weaning of pups from pregnant females, animals were food restricted (20 g per day) and subsequently trained to respond for food in an operant conditioning chamber for 15 h. An active and inactive lever were present throughout food training. Food pellets (45 mg, BioServ®, Flemington, NJ) were available on a fixed ratio-1 (FR1) schedule of reinforcement. Presses on the inactive lever had no programmed consequence. A house light remained illuminated throughout training. Animals with an active to inactive lever press ratio ≥ 2 were returned to their home environment and food restriction ceased. The remaining animals continued on food restriction and were given a second food training session to meet the same requirement on the following day. All rats successfully completed food training by the end of the second session.

Three to four days following food training, animals underwent surgery to implant a catheter into the jugular vein. Animals were

anesthetized with ketamine (80–100 mg/kg, intramuscular (IM)) and xylazine (8 mg/kg, IM). A small incision was made in the chest over the jugular vein and the vein was isolated. A catheter 13 cm in length (Silastic®, Dow Corning, Midland, MI, USA) with a ball of silicone sealant 2 cm from the end was tunneled subcutaneously from a second incision between the shoulder blades to the visible vein, inserted into the vein, and anchored in place using suture on each side of the ball. The other end of the catheter was attached to a cannula (PlasticsOne®, Roanoke, VA, USA) fitted into a harness (Instech Laboratories, Plymouth Meeting, PA, USA) strapped around the shoulders. Cefazolin (100 mg/kg, intravenous (IV)) and meloxicam (1 mg/kg, subcutaneous) were administered post-operatively for 7 and 3 days, respectively. Additionally, 0.1 ml heparin saline (100 usp/ml, IV) was administered daily to maintain catheter patency throughout the experiment.

2.1.4. Self-administration

One day prior to nicotine self-administration, animals were again placed on food restriction. Females were allowed to freely cycle, and estrous cycle phase was not monitored. There was no overlap between male and female self-administration operant chamber use. At the beginning of self-administration males were approximately 10–11 weeks old while females were approximately 18–20 weeks old. All rats were given access to 60 μg/kg/infusion of nicotine for self-administration during 2 h sessions. The first three sessions were limited to 30 infusions to prevent aversive effects. An active and inactive lever were present throughout the session, with infusions available on a FR1 schedule of reinforcement on the active lever. There was no programmed consequence for responses on the inactive lever. A response on the active lever produced a 6-s infusion of nicotine. Infusions were paired with a tone (2900 Hz) that sounded for the duration of the infusion, and both stimulus lights were illuminated at the beginning of the infusion and continued during a 20-s timeout, during which active lever presses were recorded but produced no consequences. The acquisition criteria for self-administration were ≥ 10 infusions and ≥ 2:1 active to inactive lever press ratio, both of which needed to be met for 10 sessions.

Following acquisition of nicotine self-administration, dose-reduction protocols were implemented to assess demand across a range of unit prices. Nine doses were tested, and infusion length was altered to modulate dose (see Table 1 for doses with associated unit prices). The duration of the light and tone cues during the infusion were equivalent to the infusion length. Thus, different doses were associated with different durations of cues. Following presentation of the compound stimulus (tone + light), the cue light was presented for another 20-s, regardless of dose. The between-session dose-reduction protocol occurred during 2-hr sessions for 9 days. Doses were presented in descending order, with each dose presented for 1 session. Following completion of between-session dose-reduction, animals were tested using the within-session protocol for a minimum of 5 sessions (see timeline Fig. 2A). Each dose was available for 10 min, and 2-min breaks occurred between doses, during which the active lever was withdrawn. Doses were presented in descending order (Table 1), and total session length for within-session procedures was 1 h 46 min.

Table 1
Nicotine dose, infusion length, and unit price during dose-reduction.

Nicotine dose (μg/kg/infusion)	Infusion length (s)	Unit price
60	6	1
30	3	2
17	1.7	3.53
10	1	6
5.6	0.56	10.71
3	0.3	20
1.7	0.17	35.29
1	0.1	60
0.56	0.056	107.14

2.2. Experiment 2: effects of housing condition on dose-reduction dose-response curve

2.2.1. Animals

Sprague Dawley rats (n = 24 males, n = 18 females; Charles River) arrived on PND 21 and were placed into individual cages. The following day, animals were randomly assigned to one of three housing conditions. The enrichment condition included cohabitation of 4–6 same-sex animals placed in a large home cage (74 × 91 × 36 cm) that contained hard plastic toys, a running wheel, tubes, balls, and other novel interactive toys. Different toy types, i.e., ability to enter the toy, climb, run on the toys, etc., were rotated daily to promote novelty. The social condition included cohabitation of 4–6 same-sex animals in an identical sized home cage as the enriched group, but no toys were available. The remaining animals were kept in standard isolation housing. All animals had *ad libitum* access to food and water until surgical procedures were conducted and were handled daily. Only animals that completed testing in all three housing environments without missing sessions due to patency or health issues were utilized for demand analysis (n = 19; 45%).

2.2.2. Surgical procedures and food training

The experimental timeline for this experiment is shown in Fig. 3A. Catheters were implanted into the jugular vein between PND 52–54 using a similar procedure as described for Experiment 1, except back-mounted catheters were used, in which the cannula was placed subdermally and protruded through a biopsy punch caudal to the shoulders. Post-operative care was the same as described for Experiment 1. All animals remained in isolation housing for 3 days of recovery before returning to their original environments. Subsequently, animals were food restricted (20 g per day) and trained to respond for food in an operant conditioning chamber during a 15 h session. Group-housed animals were not separated during feeding, and no differences or outliers in weight gain among individuals were detected, similar to past studies (Gipson et al., 2011).

2.2.3. Self-administration

On PND 60, animals began acquisition of self-administration as described in Experiment 1. Once acquisition criteria were met (see Section 2.1.4) or up to 21 self-administration sessions had occurred, animals began within-session dose-reduction, as described in Experiment 1. After the 7th session, animals were placed into their assigned housing conditions. Male housing switches consisted of transferring enriched rats to social or isolation housing, isolated to enriched housing, and social to isolation housing, due to noncontiguous timelines of experiments and the necessity to keep group housing above a minimum number of animals. Female rats were split from their original groups, half moving to each other condition using random selection. All rats received 7 sessions of within-session dose-reduction while in their new environment housing. A second switch occurred following the 7th session into the final housing environment and 7 sessions of within-session dose-reduction were given.

2.3. Statistical analysis

Some animals were removed from the study due to catheter patency failure or health concerns. Data from these rats were excluded from graphs and analyses. For Experiment 1, total infusions during acquisition of self-administration by sex were compared using an unpaired t-test. For Experiment 2, total infusions were compared using a two-way ANOVA with sex and housing condition as factors. For both experiments, consumption was calculated by multiplying the number of infusions delivered during a session (or time block) by the dose delivered. Unit price of nicotine was calculated according to the equation:

$$Unit\ Price = \frac{ratio\ requirement}{dose} \quad (1)$$

where reinforcer cost was the ratio requirement for the schedule of reinforcement (e.g., 1 for FR1), and dose was the delivered dose of nicotine. All unit prices were transformed such that the highest dose (60 μg/kg/infusion) was equivalent to 1 (Table 1). The exponentiated form (Koffarnus et al., 2015) of the demand equation:

$$Q = Q_0 \times 10^{k(e^{-\alpha \cdot Q_0 \cdot C} - 1)} \quad (2)$$

where Q represents consumption, Q_0 represents estimated maximum consumption at a unit price of zero (demand intensity), k is a constant defining consumption range, α is the rate of change in consumption as a function of unit price (demand elasticity), and C is unit price. The equation was fit to the data via nonlinear mixed effects (NLME) modeling using the 'nlme' package in *R* (Hofford et al., 2016; Pinheiro et al., 2015; R Core Team, 2018; Yates et al., 2017). The model design included α and Q_0 as free parameters and k as a global constant (best-fit value across all individuals: 3.1 and 1.79 for Experiments 1 and 2, respectively).

For Experiment 1, session type was considered a nominal, within-subjects factor. Housing environment for Experiment 2 was considered a fixed, nominal within-subjects factor. Subject was defined as a random factor for both experiments. Only animals that experienced all 3 housing environments were utilized in analyses for Experiment 2, and consumption was defined as the average across the last 3 sessions within a housing environment. In order to provide sufficient statistical power for comparisons between housing environment in Experiment 2, data were collapsed across all housing switch orders within sex. Therefore, effects of initial housing condition were not explicitly analyzed. Interactions were followed with Bonferroni-corrected comparisons. All tests were considered significant at $p < 0.05$.

2.4. Drugs

Nicotine tartrate (MP Biomedicals, Solon, OH, USA) was dissolved in 0.9% sterile saline and the pH was adjusted to 7.2. Ketamine (Ketavet, St. Joseph, MO), xylazine (Akorn; Lake Forest, IL), cefazolin, meloxicam, and heparin (all from Henry Schein, Melville, NY) were administered at doses listed previously.

3. Results

3.1. Experiment 1

All rats acquired self-administration of nicotine (60 μg/kg/infusion; Fig. 1A and B) and there were no differences in total infusions earned across acquisition of self-administration due to sex ($t_{10} = 0.4177$, p = n.s.; Fig. 1C). Demand curves are illustrated in Fig. 2B and C for males and females, respectively. NLME revealed a significant effect of session type on demand elasticity (α; main effect of session type: $F_{1,189} = 3.92$, $p < 0.05$), with greater elasticity in the within-session protocol compared to the between-session protocol. Additionally, no significant effects of sex or interactions between session type and sex were observed (Fig. 2B, C). As expected, the within-session procedure reduced demand intensity (Q_0) because duration of exposure to each dose was decreased compared to the between-session procedure (main effect of session type on Q_0: $F_{1,189} = 32.19$, $p < 0.05$). Furthermore, females consumed more nicotine than males, regardless of session type (main effect of sex on Q_0: $F_{1,189} = 10.89$, $p < 0.05$), as indicated by the increase in Q_0 seen in Fig. 2E. There was no significant sex × session type interaction on Q_0 (Table 2).

3.2. Experiment 2

The number of infusions earned during acquisition of nicotine self-administration for Experiment 2 is shown in Fig. 1D and E for male and female rats, respectively. A two-way ANOVA revealed a significant main effect of housing on the total number of infusions earned across acquisition of self-administration ($F_{2,34} = 5.42$, $p < 0.05$; Fig. 3B), and pairwise post-hoc Tukey's test indicated animals raised in enrichment took less nicotine during acquisition of self-administration regardless of sex ($p < 0.05$; Fig. 3C). There was no significant main effect of sex or interaction between housing and sex on the total number of infusions. Following acquisition animals underwent within-session dose-reduction procedures. Demand curves for male and female rats within each environmental condition are illustrated in Fig. 3D and E, respectively, and α and Q_0 values for housing conditions are illustrated in Fig. 3F and G, respectively. Female rats demonstrated less demand elasticity than males as indicated by the smaller α parameter (main effect of sex on α: $F_{1,483} = 14.71$, $p < 0.05$; Fig. 3F). Additionally, a main effect of housing was observed on α ($F_{2,483} = 12.14$, $p < 0.05$). Post-hoc analysis of the significant housing × sex interaction on α ($F_{2,483} = 32.74$, $p < 0.05$) indicates male rats housed in enrichment had a significantly lower α than males in isolation or social housing, as well as female rats in isolation had a lower α compared to those in an enriched environment (Fig. 3F). Females showed significantly greater demand intensity compared to males as indicated by the greater consumption of nicotine regardless of housing environment (main effect of sex on Q_0: $F_{1,483} = 23.26$, $p < 0.05$; Fig. 3G). Furthermore, there was a significant housing effect on demand intensity (main effect of housing on Q_0: $F_{1,483} = 30.82$, $p < 0.05$; Fig. 3G), with animals in isolation demonstrating increased consumption, but there was no significant housing × sex interaction.

Together, the results in Experiment 2 illustrate that female rats have decreased elasticity of demand and increased demand intensity compared to males. Additionally, environmental enrichment significantly affects demand elasticity (α) in both sexes, but in contrasting directions as enrichment decreased demand elasticity in males and increased it in females.

4. Discussion

The present study validated that a within-session dose-reduction protocol produces demand curves for nicotine self-administration that are sensitive to detection of sex and housing condition differences. For both Experiments 1 and 2, no differences in the acquisition of nicotine self-administration were observed between males and females. In Experiment 1, where all rats were housed in isolation, demand elasticity was unaffected by sex but was significantly increased between within- and between-session dose-reduction protocols. However, demand intensity was reduced following a change to within-session dose-reduction, and female rats consumed more nicotine than males across session types. In Experiment 2, rearing animals in differential housing led to differences in nicotine consumption during acquisition, consistent with the literature (Gomez et al., 2015; Venebra-Muñoz et al., 2014), specifically reducing intake in enriched animals compared to those in isolation. Following the switch to dose-reduction procedures in the maintenance phase, female rats had reduced demand elasticity and increased demand intensity compared to males. Specific to housing environment, males in environmental enrichment had reduced elasticity compared to those in social enrichment or isolation housing, whereas females in isolation had reduced elasticity compared to those in enrichment. Finally, during the maintenance phase dose-reduction procedures animals in isolation had greater consumption of nicotine compared to those in enriched housing environments, consistent with consumption behaviors seen in acquisition of self-administration.

The use of within-session dose-reduction procedures has become more frequent in recent years as researchers attempt to expand experimental testing using an abbreviated timeline. The experiments performed here, particularly Experiment 1, have attempted to validate the use of the within-session procedure for nicotine self-administration. We observed a significant increase in demand elasticity (Fig. 2D) and a significant reduction in demand intensity (Fig. 2E) using the within-

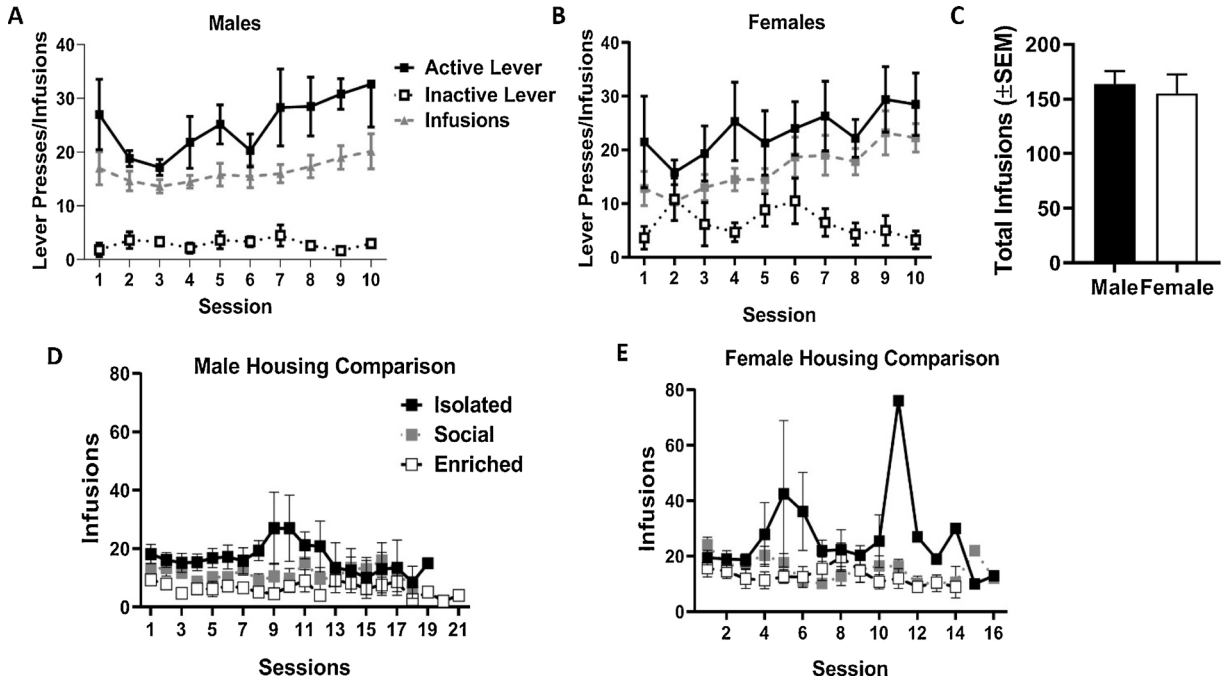

Fig. 1. Acquisition of self-administration as a function of session for Experiment 1 **(A)** males **(B)** and females, total number of infusions earned during acquisition in Experiment 1 **(C)**, and acquisition data as a function of session for Experiment 2 **(D)** males **(E)** and females. Mean lever presses and infusions (± SEM) are shown across 2-h session during which animals self-administered 60 μg/kg/infusion on a FR1 schedule of reinforcement. (n = 6 for Panels A, B, and C; n = 5–11/group for Panel D; n = 6/group for Panel E).

session dose-reduction compared to the between-session dose-reduction protocol, thus indicating that demand for nicotine is altered by the type of session utilized. A reduction in demand intensity is not unexpected given the reduction in nicotine availability going from a 2-hr session for each dose down to 10-min/dose in the within-session procedure. However, the increase in elasticity seen with the within-session procedure indicates that demand for nicotine decreases much more rapidly than when rats are given one dose per day. This is also not unexpected, as animals were only exposed to each unit price once during the between-session dose-reduction procedures as opposed to multiple times

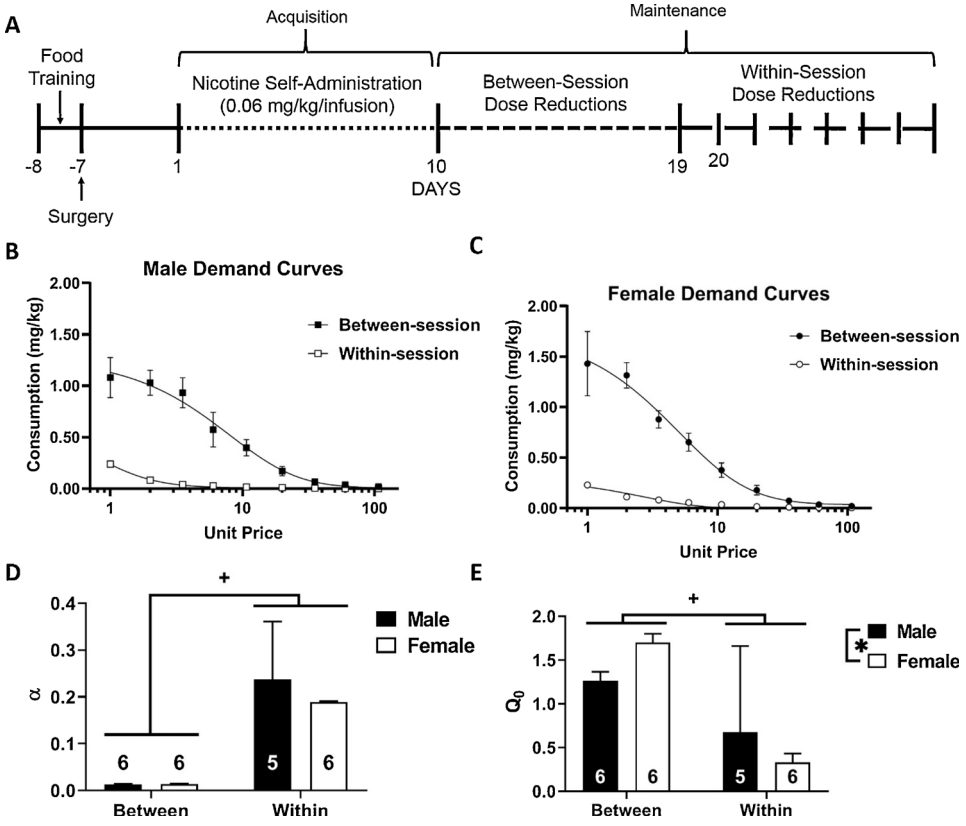

Fig. 2. (A) Timeline for Experiment 1. Mean consumption (mg/kg, mean ± SEM) of nicotine as a function of unit price in **(B)** male and **(C)** female rats, comparing between- and within-session dose-reduction procedures. Lines represent the best-fit curves determined from the demand equation. **(D)** Mean ± SEM α values from male and female rats. **(E)** Mean ± SEM Q_0 values in male and female rats. Numbers on or above bars indicate the number of subjects. $*p < 0.05$, significant sex difference in Q_0. $+p < 0.05$, significant difference in α **(D)** or Q_0 **(E)** due to session type.

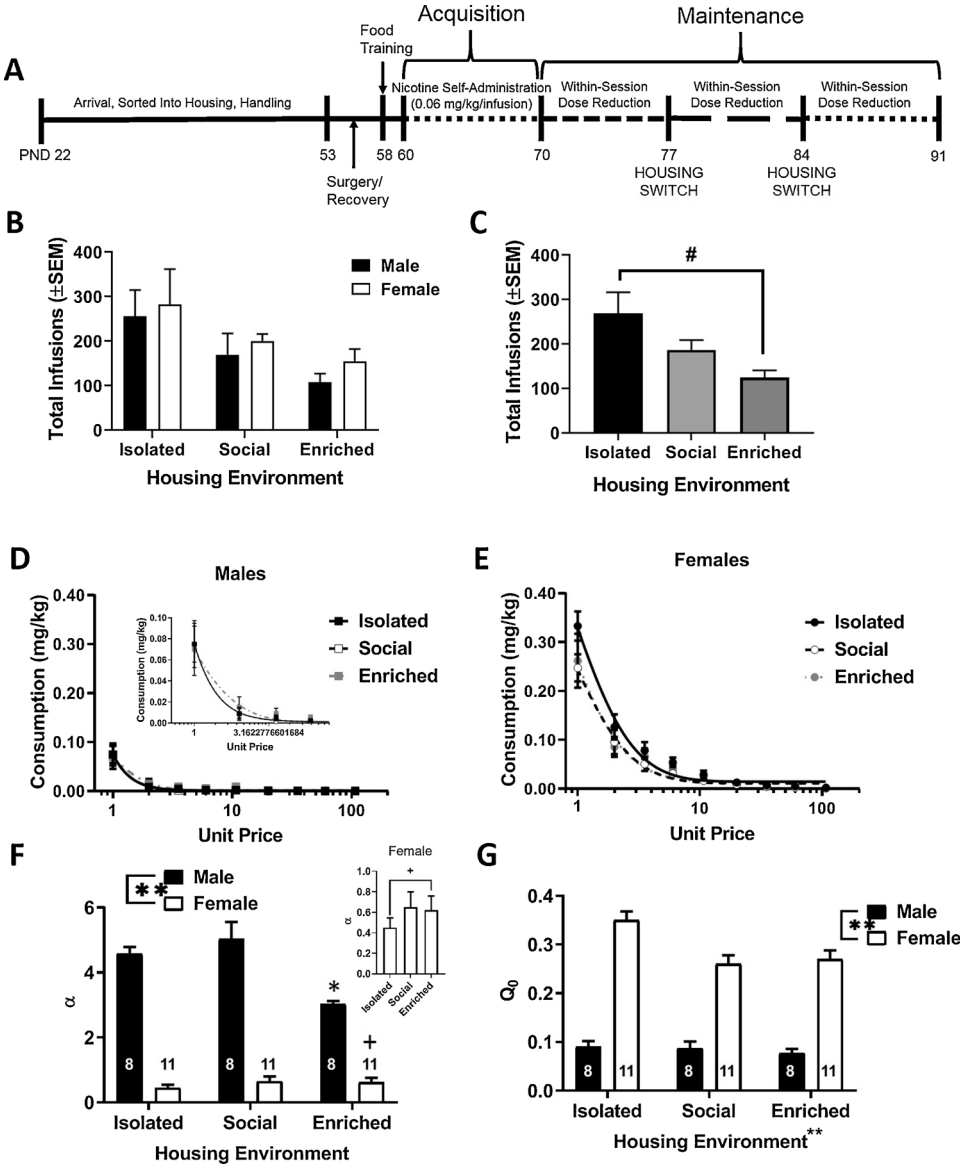

Fig. 3. (A) Timeline for Experiment 2. **(B)** Total infusions earned during acquisition self-administration prior to within-session dose reduction procedures. **(C)** A significant main effect of housing was observed, and pairwise comparisons of each housing condition collapsed across sex indicate that rats in environmental enrichment consumed less nicotine than those in isolation. Mean consumption of nicotine (mg/kg, mean ± SEM) as a function of unit price in **(D)** male **(E)** and female rats for within-session dose-reduction across housing environments. Magnified data at low unit prices for male rats are shown in panel **D** insert. Lines represent the best-fit demand curves for each housing condition. **(F)** α values for each housing environment from best-fit demand curves (mean ± SEM). α values for each housing environment for females (mean ± SEM) are shown in panel **F** insert. **(G)** Q_0 values for each housing environment (mean ± SEM). Numbers on or above bars indicate the number of subjects.
$\#p < 0.05$, significant difference in total infusions between isolation and environmental enrichment.
$*p < 0.05$, significantly different than α of isolated and socially-housed males.
$+p < 0.05$, significantly different than α of isolated females.
**p < 0.05, significant main effect.

during the within-session dose-reduction procedures. With this additional training, we would expect greater discrimination across unit price in the within-session dose-reduction procedure. In Experiment 2, when male and female rats were reared in variable housing conditions and only experienced the within-session dose-reduction procedure, the results demonstrated that this abbreviated procedure was still sensitive to the environmental conditions as well as to sex differences. Thus, future research must assess if the alterations in the demand curve due to session type observed here could potentially necessitate the use of one of the dose-reduction procedures over the other based on experimental timelines.

Previous experiments utilizing within-session dose-reduction procedures observed a loading effect within the first 10 min time block (Ahmed and Koob, 1999; Lynch and Carroll, 2001; Oleson et al., 2011), during which blood levels of the self-administered drug peaked and then consumption decreased and stabilized during the remainder of the session. After this initial loading period, consumption during blocks 2–4 and the calculated Q_0 were highly correlated, indicating that the calculated Q_0 and actual consumption during blocks 2–4 are congruent (Oleson et al., 2011). Although not measured here, levels of nicotine in

Table 2
Summary of results from Experiments 1 and 2. Q_0: demand intensity. α: demand elasticity. IC: isolated condition. SE: social enrichment. EE: environmental enrichment. Between: Between-session dose-reduction. Within: within-session dose-reduction.

Experiment	Acquisition of Self-administration Results	Behavioral Economics (Maintenance) Results	
		α	Q_0
2	Main effect of housing on total infusions earned Environmental enrichment decreased infusions	Between < Within Male ≈ Female Male > Female Male EE < Male IC, Male EE < Male SE Female IC < Female EE	Between > Within Male < Female Male < Female IC > SE, IC > EE

the blood were potentially titrated and subsequently reflected in demand intensity during dose-reduction sessions. Furthermore, recent investigations have shown that mice titrate the number of nicotine infusions earned during self-administration, but when α5 nicotinic acetylcholine receptors in the medial habenula are genetically eliminated this titration ability disappears and consumption increases at higher unit doses (Fowler et al., 2011). Patterns of nicotine consumption potentially differ between the dose-reduction protocols utilized here due to the nicotine pharmacodynamics and the control of the titration setpoint, leading to differences in demand intensity.

The significant effect of session type on demand elasticity in Experiment 1 is similar to prior research where animals trained to self-administer methamphetamine on a between-session protocol showed a near four-fold increase in demand elasticity when switched to a within-session paradigm (Cox et al., 2017). Importantly, Cox et al. detected consistent sex differences in methamphetamine demand elasticity in both the between- and within-session paradigms, demonstrating the high potential value of the within-session procedure in examining male and female consummatory behaviors. Elsewhere, session length has been shown to affect response rates, but when response rates and demand functions from shorter sessions are compared with those from longer sessions, those differences collapse (Foster et al., 2011). For example, Foster and colleagues (2011) observed similar demand elasticity (α) when comparing total session data of various lengths in domestic hens responding for wheat in 10, 40, 60, or 120-min sessions. Little work comparing the between- and within-session dose-reduction protocols has been performed, and thus the effects of session type on nicotine demand elasticity are novel.

We predicted that environmental enrichment would increase demand elasticity for nicotine as has been previously found for cocaine (Yates et al., 2017; though see Hofford et al., 2016, for different results with cocaine and morphine). In Experiment 2, nicotine demand in enriched female rats was more elastic than isolated females; however, enriched male rats demonstrated less elastic demand than isolated males (Fig. 3F). Visual inspection of the first few price points for the male demand curves in Experiment 2 (Fig. 3D inset) indicate a rapid decline in consumption within the first 4 doses. Of interest, the first test of the within-subjects dose-reduction procedure occurred in the first housing condition, which was approximately 8–9 weeks in duration. Subsequent housing environments were only utilized for 7 sessions, thus limiting the potential impact of the change in housing condition. As such, demand intensity and elasticity may reflect alterations in consumption behaviors due to different experimental conditions, including differential housing and the change between environments that occurred only in Experiment 2. Our studies are the first to reveal possible interactions between sex and environmental conditions that may modulate changes in the demand for nicotine.

Marked sex differences have been found in the acquisition and maintenance of self-administration for other drugs of abuse (see review by Roth et al., 2004), however, few studies have utilized behavioral economics to examine sex differences (Grebenstein et al., 2013). As well, inconsistent sex differences in acquisition of nicotine self-administration and intake have been found for rodents, which may be dose- and reinforcement schedule-dependent (Chaudhri et al., 2005; Donny et al., 2000; Feltenstein et al., 2012; Peartree et al., 2017; Swalve et al., 2016). Of note, no sex differences in acquisition of nicotine self-administration were observed in either Experiment 1 or 2, in line with our recent results (Goenaga et al., 2019). Furthermore, in Experiment 1 no sex differences were found in elasticity of demand for nicotine (α), indicating that nicotine consumption in males and females was equally sensitive to price changes, as corroborated by previous reports (Grebenstein et al., 2013). However, in Experiment 2, females demonstrated increased demand intensity and reduced demand elasticity compared to males (Fig. 3F and G). Previous research with rats has shown that novelty-induced and cocaine-stimulated locomotor activity are affected by differential housing conditions during adolescence, with male rats increasing activity when housed with social companions but female rats decreasing activity with social or environmental enrichment (Zakharova et al., 2012). Similarly, Elliott and Grunberg found that physical or social enrichment reduced habituation time in an open field task, and therefore increased information-processing, in males compared to females (Elliott and Grunberg, 2005). Alternatively, nicotine intake during acquisition can be enhanced in males, but not females, during the initial self-administration training session when a social partner is introduced (Peartree et al., 2017). The results seen here indicate that housing environment may induce differential effects on nicotine demand intensity and elasticity by sex, and that a within-session dose-reduction protocol can detect such differences. Given that little work has been published utilizing females and environmental enrichment beyond the current results, future studies should investigate potential interactions of sex differences and differential housing.

Use of a within-session dose-reduction procedure yields benefits, such as reduced experimental duration for acute pharmacotherapy testing and reduced attrition rates throughout the experiment. However, the increased efficiency of within-session dose-reduction was paired with reduced demand intensity and demand elasticity compared to the between-session procedure. One additional limitation of the present study was the use of post-infusion timeouts during the within-session dose-reduction protocol. Use of a 20-s timeout limited the number of infusions that could be earned, potentially capping the number of infusions available during a 10-min block. However, no animal in the within-session dose-reduction protocol reached the estimated maximum number of infusions per time block (ranging from 23 to 30, depending on dose). The 20-s timeout also occurred during between-session dose-reduction, but the extended session duration increased the theoretical maximum number of infusions beyond concern.

Demand analysis of nicotine self-administration in rats has translational value, as it is utilized in clinical research. For example, demand analysis indicates that e-cigarettes may aid smoking reduction and cessation, perhaps more so than nicotine gum (Johnson et al., 2017). These findings highlight how behavioral economics can address questions in tobacco research such as substitutability. Furthermore, behavioral economics can be used to assess the development and treatment of maladaptive operant behavior (Bickel et al., 2014). For example, drug abuse is frequently characterized by excessive valuation of drug and excessive delay discounting. Previous research in humans has shown that abstinence from nicotine increases impulsivity, while having no effect on the purchase of any commodity in a behavioral economic task (Field et al., 2006). In the same experiment, however, increases in cigarette price were paired with increased money spent on cigarettes, though ultimately at an inelastic rate (Field et al., 2006). Behavioral economic procedures also provide translational value for studies of sex differences. Here, we observed a decrease in α and an increase in Q_0 for females compared to males in Experiment 2, consistent with clinical research on female smokers indicating that women have increased difficulty abstaining from smoking compared to men (Japuntich et al., 2011; Saladin et al., 2014; Ward et al., 1997; Weinberger et al., 2014). The use of an abbreviated dose-reduction paradigm, as demonstrated here, has great potential to cross this translational gap and provide a foundation for sculpting policy, taxation, and law regarding drugs of abuse beyond nicotine (Hursh and Roma, 2016; Smith et al., 2014).

Because nicotine is the primary psychoactive alkaloid in tobacco responsible for maintaining smoking behavior in humans (Stolerman and Jarvis, 1995), future behavioral economic studies of nicotine and tobacco products can focus on different clinical populations to better understand how unit price and elasticity interact to render nicotine a highly challenging drug to quit. Initial investigations determined that the reinforcing value of cigarette-smoking depends on short-term smoking history, response requirements, and availability of alternative reinforcers (Bickel et al., 1991; Epstein et al., 1991). Additional studies found that de-nicotinized cigarettes share similar reinforcing efficacy

with control cigarettes, but only when subjects are not given a choice. Nonetheless, these findings highlight the conditioned reinforcing effects of non-nicotine tobacco constituents (Shahan et al., 1999). Moreover, conditioned and non-nicotine tobacco constituents may underlie findings that nicotine gum is a less effective alternative reinforcer than denicotinized cigarettes (Johnson and Bickel, 2003). Preclinical research utilizing behavioral economics can include extensive neurobiological and neurophysiological testing that would be difficult to perform in clinical research. Strengthening these models may improve translation, and thus enhance drug development efforts to decrease use of nicotine and other drugs of abuse. Furthermore, additional preclinical research on nicotine and tobacco products using demand analysis can guide formation and execution of policy and regulatory science (LeSage et al., 2018; Smith et al., 2014).

5. Conclusions

Here we compare the use of within- and between-session dose-reduction procedures to produce demand curves for nicotine self-administration, extending previous findings with other drugs of abuse. Within-session dose-reduction increases the efficiency of self-administration experiments while conferring the benefits improved statistical power and reduced number of animals of the within subject design but do produce significantly different demand curves compared to the between-session dose-reduction procedures. These aspects of the present model increase its utility for use with neuroscience techniques, particularly for studies that require data collection on a specific day. We demonstrate here that a within-session dose-reduction protocol of nicotine self-administration is sensitive to modifiers of elasticity such as sex and environmental enrichment. Interestingly, sex differences in nicotine self-administration are sensitive to changes in reinforcement schedule, and the within-session procedure here can be altered to increase unit price using changes in reinforcement schedule in the future. Although additional research is needed, abbreviated economic demand protocols represent a promising avenue of research across various substance use disorders.

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Contributors

GLP, JLN, JAM, JSB, and CDG designed the studies. GLP, JAM, JSB, and CDG analyzed data. GLP, MDN, and GCB performed research. GLP, JSB, JAM, and CDG wrote the paper. All authors contributed edits and revisions to the paper. All authors read and approved the final manuscript.

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