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Suppressive and Enhancing Effects of Nicotine on Food-Seeking Behavior

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Abstract

The present study examined how systemic low doses of nicotine affect the microstructure of reinforced food-seeking behavior in rats. Rats were first given an acute saline or nicotine treatment (0.1–0.6 mg/kg, with an inter-injection interval of at least 48 h), and then a chronic saline or nicotine treatment (0.3 mg/kg/day for 10 consecutive days). Immediately after each injection, rats were required to press a lever five times to obtain food that was available at unpredictable times (on average every 80 s) with constant probability. Acute nicotine dose-dependently suppressed behavior prior to the delivery of the first reinforcer, but enhanced food-reinforced behavior afterwards. These effects were primarily observed in the time it took rats to initiate food-seeking behavior. Enhancing effects were also observed in the microstructure of food-seeking behavior, with lower nicotine doses (0.1–0.3 mg/kg) increasing the rate at which response bouts were initiated, and higher doses (0.3–0.6 mg/kg) increasing within-bout response rates. A pre-feeding control suggests that changes in appetite alone cannot explain these effects. Over the course of chronic nicotine exposure, tolerance developed to the suppressive, but not to the enhancing effects of nicotine on food-seeking behavior. These results suggest that (a) lower doses of nicotine enhance the reward value of food and/or food-associated stimuli, (b) higher doses of nicotine enhance motoric activity, and (c) ostensive sensitization effects of nicotine on behavior partially reflect a tolerance to its transient suppressive motoric effects.

Keywords

Nicotine; Food-Seeking Behavior; Rats; Bouts; Variable-interval schedule of reinforcement; Fixed-ratio schedule of reinforcement

Introduction

Tobacco use is linked to diseases of nearly all organs of the body, and to 480,000 deaths per year in the United States (US Department of Health and Human Services, 2014). The main addictive component that maintains tobacco dependence is nicotine (Benowitz, 2010).

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Among other functions, nicotine appears to enhance the reinforcing properties of non-nicotinic stimuli, including food rewards (Chaudhri et al., 2006, 2007; Palmatier et al., 2007; Barr, Pizzagalli, Culhane, Goff, & Evins, 2008; Caggiula et al., 2008; Barret & Bevins, 2012, 2013). Nicotine-induced changes in food-seeking behavior may explain body weight changes often associated with tobacco use (Donny, Caggiula, Weaver, Levin, & Sved, 2011). Although smokers have a lower average body weight than nonsmokers, this difference reverses once smokers quit smoking (Lerman et al., 2004; Pistelli et al., 2009; Aubin et al., 2012). Similarly, rats also have low body weights while on nicotine, but gain substantial weight once nicotine is discontinued (Frankham & Cabanac, 2003). Given these effects, it is particularly important to establish how nicotine affects motivated food-seeking behavior, which may help identify key contributors to the pervasive use of nicotine (Nair, Adams-Deutsch, Epstein, & Shaham, 2009; Donny et al., 2011).

Although nicotinic enhancement of non-nicotine stimuli and rewards is well documented (e.g., see Chaudhri et al., 2006 for a review), such behavior may vary depending on the schedule of reinforcement. Nicotine induces a substantial dose-dependent, but transient, reduction in response rate on both variable-ratio (VR) and variable-interval (VI) schedules of reinforcement (Morrison, 1967). However, nicotine-induced behavioral suppression is typically followed by increased locomotor activity (Clarke & Kumar, 1983a; Perkins et al., 1990). In VI schedules, nicotine-induced suppression of response rate is also typically followed by a dose-dependent increase in response rate. In response-withholding tasks, such as differential reinforcement of low response rates (DRL) and fixed-minimum interval (FMI) schedules of reinforcement, nicotine appears to disrupt performance such that rats are less capable of withholding a reinforced response (Popke et al., 2000; Kirshenbaum et al., 2008; Mazur et al., 2014). Similar disruptive effects are observed in fixed-interval (FI) schedules of reinforcement, wherein response withholding is not required but often emerges (Daniels, et al., 2015; Hinton & Meck, 1996). A disinhibition of reinforced responding is also observed under fixed-ratio (FR) schedules of reinforcement (Barret & Bevins, 2012, 2013; see Caggiula et al., 2009 for a review).

The suppressive effect of nicotine on food-seeking behavior may reflect the malaise typically induced by nicotine at high doses (Etscorn et al., 1987). Such suppressive effect is observed not only in VR and VI schedules of reinforcement, but also in spontaneous locomotion (Clarke & Kumar, 1983a; Nakashima et al., 1988). This effect may be analogous to the initial effects of nicotine in humans, which are typically aversive, but disappear with continued exposure (Srivastava et al., 1991; Perkins et al., 1993; Foulds et al., 1997).

The enhancing effect of nicotine on food-seeking behavior is also observed in nicotine-experienced humans. Under fasting conditions, nicotine increases caloric intake and reduces habituation to food-associated cues (Epstein, Caggiula, Perkins, Mitchell, & Rodefer, 1992; Perkins, 1992; Spring, Pagoto, McChargue, Hedeker, & Werth, 2003; Lerman et al., 2004). Despite the prevalence of these enhancing effects in the literature, it is unclear what components of food-seeking are modulated by the administration of nicotine.

In animal models, nicotine may affect food-seeking behavior by altering the reward value of food and associated stimuli, the learned association between food-obtaining responses and

food, and the motoric capacity to produce the food-obtaining response. The purpose of this study is to determine the relative contribution of these factors to nicotine-induced changes of food-reinforced behavior. There are various models that aim at dissociating the contribution of each of these factors to instrumental performance. Some of these models are based on constraints imposed either on the behavioral expression of arousal (Killeen & Sitomer, 2003; Olarte-Sánchez et al., 2015), or on the consumption of the incentive (Barrett & Bevins, 2012; Hursh & Roma, 2013). Although various aspects of these models have been validated, they are not without limitations. Most importantly, these models account only for averaged data, neglecting key behavioral processes that are only visible in the stochastic variability of behavioral data. The methods of the present study aim at overcoming some of these limitations.

In the present study, inferences on reward value, response-outcome association, and motor capacity are drawn from the bout structure of instrumental behavior (Conover, Fulton & Shizgal, 2001; Shull & Grimes, 2003; Brackney et al., 2011; Shull, 2011; Tanno, 2016; Daniels & Sanabria, 2017a, b). This structure is particularly visible in tandem variable-time (VT) FR schedules of reinforcement, in which the probability of reinforcing a train of responses is low and constant over time. Fig. 1 shows a schematic of how responding is organized in each VI trial. Following the onset of cues signaling imminent food, rats wait some time before emitting their first response (latency) and then fluctuate in and out of bouts of responding. Previous work has revealed that the bout-initiation rate is the only parameter of bout structure sensitive to changes in reinforcer efficacy and rate (Shull, Gaynor, Grimes, 2001; Shull & Grimes, 2003; Shull, 2004; Brackney et al., 2011; Daniels & Sanabria, 2017a, b). Other parameters are uniquely sensitive to other manipulations: mean bout length is particularly sensitive to schedule requirements (Brackney & Sanabria, 2015; Daniels & Sanabria, 2017b), and within-bout response rate and response duration reflect the capacity to complete a response (Shull & Grimes, 2003; Brackney et al., 2011; Shull, 2011; Bailey et al., 2015). Latencies, in contrast, appear to be sensitive to various manipulations (Daniels & Sanabria, 2017b).

The present study separately analyzed latencies and run rates (Fig. 1) to identify the locus of the behavioral effect of passively administered nicotine. Run rates were further analyzed to identify potential nicotine-induced changes in bout-initiation rate, within-bout response rate, and response duration, which would indicate changes in reward value, response-outcome association, and motoric capacity.

Methods

Subjects

Twelve male Sprague Dawley rats (Charles River Laboratories, Hollister, CA) served as subjects. Rats arrived on post-natal day (PND) 61 and were immediately pair housed. Rats experienced a 12:12 h light cycle, with lights on at 1900 h. All behavioral training was conducted during their active phase (the dark phase of the cycle). Behavioral training and food restriction began on PND 62. Access to food was reduced daily from 24, to 18, 12, and finally 1 hour a day. Chow was placed on the homecages of the rats 30 min after the end of an experimental session during the dark phase of the cycle (the 30-min interval was meant to

minimize interference of food anticipation on task performance). At the beginning of the next session, weights were, on average, 85% of *ad libitum* weights estimated from growth charts provided by the breeder. Water was always available in home cages. All animal handling procedures used during this study followed National Institutes for Health guidelines and were approved by the Arizona State University Institutional Animal Care and Use Committee.

Apparatus

Experiments were conducted in 12 MED Associates (ST. Albans, VT, USA) modular test chambers (6 chambers were 305 mm long, 241 mm wide, and 210 mm high; 6 chambers were 305 mm long, 241 mm wide, and 292 mm high), each enclosed in a sound- and light-attenuating box equipped with a ventilation fan that provided masking noise of approximately 60 dB. The front and back walls and the ceiling of test chambers were made of Plexiglas; the front wall was hinged and served as a door to the chamber. One of the two aluminum side panels served as a test panel. The floor consisted of thin metal bars positioned above a catch pan. The reinforcer receptacle was a square opening (51-mm sides) located 15 mm above the floor and centered on the test panel. The receptacle provided access to a dipper (ENV-202M-S) fitted with a cup (ENV-202C) that could hold 0.01 cc of a liquid reinforcer (33% sweetened condensed milk diluted in tap water; Kroger, Cincinnati, OH). The receptacle was furnished with a head entry detector (ENV-254-CB). A multiple tone generator (ENV-223) produced a 15-kHz tone at approximately 75 dB through a speaker (ENV-224 AM), which was centered on the top of the wall opposite the test panel and 240 mm above the floor of the chamber. Two retractable levers (ENV-112CM) flanked the reinforcer receptacle. Lever presses were recorded when a force of approximately 0.2 N was applied to the end of the lever. Three-color light stimuli (ENV-222 M) were mounted above each lever; they could be illuminated yellow, green, and red. A house light located behind the wall opposite to the test panel could dimly illuminate the test chambers. Experimental events were arranged via a MED PC® interface connected to a PC controlled by MED-PC IV® software

Drugs

Nicotine hydrochloride tartrate (Sigma, St. Louis, MO, USA) was dissolved in a 0.9% saline solution and pH was adjusted to 7.2. Nicotine and saline were administered subcutaneously in a volume of 1.0 ml/kg. Doses of nicotine ranged from 0.1 mg/kg to 0.6 mg/kg; at these doses nicotine disrupts behavior in a variety of behavioral paradigms (Hinton & Meck, 1996; Kirshenbaum et al., 2008; Mazur et al., 2014; Daniels et al., 2015; Watterson et al., 2015).

Procedure

Overview—Sessions were conducted once daily, seven days a week. All sessions began with a 5-min warm-up period during which the house-light was off. After the warm-up period, the session commenced with the illumination of the house-light. Sessions were 55-min long.

Pre-training—Rats were first acclimated to the boxes and the reinforcer, and were shaped to lever press. Reinforcement (10-s activation of the dipper) was delivered on a variable-time (VT) 60-s schedule. Ten seconds prior to reinforcement, the left lever was extended; a single press to the extended lever was reinforced immediately, otherwise reinforcement was delivered without a response requirement. After rats reliably inserted their head into the reinforcer receptacle and were lever pressing, a fixed-ratio (FR) 1 schedule of reinforcement was implemented. After all rats were lever pressing reliably, animals were transferred to baseline training.

Baseline Training—The schedule of reinforcement was progressively adjusted to a tandem VT 80-s FR 5 schedule of reinforcement. This schedule was programmed on the left lever. The terminal FR component was adjusted first, increasing the schedule from FR 1 to FR 2 and finally to FR 5. The initial VT component was then adjusted to VT 10-s, 20-s, 40-s, and finally 80-s. Each trial began with the illumination of the house-light and the insertion of a lever. Completion of the FR requirement at the end of the VT retracted the lever, turned off the house-light, turned on a 1.5-kHz tone for 1 s, and delivered a reinforcer (2.5-s activation of the dipper, counted from lever retraction). Reinforcement was followed by a 10-s inter-trial interval (ITI) during which all stimuli were turned off. Training on the tandem VT 80-s FR 5 continued for a minimum of 20 sessions and until stability was reached for all rats. Stability was defined as a non-significant regression of response rate over 5 consecutive sessions.

Acute Nicotine Injection Cycle—A saline administration period was implemented first to acclimate rats to the injection protocol. Acclimation injections occurred 5 min prior to the beginning of each of 4 consecutive sessions. Nicotine treatment began on PND 116. Treatment sessions were conducted on Mondays, Wednesdays, and Saturdays. Treatment consisted of either saline, 0.1, 0.3, or 0.6 mg/kg of nicotine, a pre-feeding probe, or a no-injection treatment identical to baseline training. Nicotine was administered subcutaneously (s.c.) immediately prior to the corresponding session. During pre-feeding probes, rats were given 1 h of free access to chow in their home cages 1.5 h prior to the test session. Normal sessions, identical to those during baseline training, were conducted on Tuesdays, Thursdays, Fridays, and Sundays. Every treatment was administered twice, each time in identical order, with order counterbalanced across rats following a Latin-square design.

Baseline Recovery—Baseline training conditions were reinstated for a minimum of 10 sessions and until performance stabilized. No nicotine was administered during this phase.

Chronic Administration Test—Rats were assigned to either group Saline (SAL) or Nicotine (NIC), such that the mean stable response rates during baseline recovery were approximately the same for both groups. Group labels denote the substance that was subcutaneously injected 5 min prior to the start of each of 10 consecutive sessions, beginning on PND 153. SAL rats were administered saline and NIC rats were administered 0.3 mg/kg of nicotine, as this dose had a greater effect on behavior than 0.1 mg/kg but not as disruptive as 0.6 mg/kg (see results).

Data Analysis

All measures were log transformed for analysis. Repeated measures ANOVA using JASP (JASP Team, 2016) were conducted on each data set. When an interaction was obtained, the data was further probed with t-tests.

Acute Nicotine Injection Cycle—Data from each dose was pooled across sessions within the same rat. Individual performance was first analyzed at a macro level, tracking 3 dependent measures: mean response rate, median latency, and mean run rate (Fig. 1). Response rate was computed as the number of lever presses divided by the sum of the intervals when effective lever pressing was possible. Median latency was computed as the median time to the first response in each trial. Run rate was the number of effective lever presses divided by the sum of the intervals between the first response in each trial and receipt of the subsequent reinforcer.

The analysis of within-session changes in dependent measures faced two challenges. First, visual inspection of dependent measures as a function of reinforcer suggested potential trends within session, with the greatest change taking place typically between the first and second reinforcer. Second, the total number of reinforcers obtained varied between sessions and rats. Dependent measures were thus organized in three blocks: first reinforcer, middle block of reinforcers, and last block of reinforcers. The first-reinforcer block included only the first trial. The middle block of reinforcers included all the trials after the first reinforcer and up to the highest number of reinforcers that all rats obtained, excluding the last five trials in all sessions within a treatment. If, for example, a rat completed 30 trials after 0.3 mg/kg nicotine, trials 2 through 25 constituted the middle block of reinforcers for the 0.3 mg/kg treatment. The last block of reinforcers was the last 5 trials of each session. Thus, the number of trials in the middle block of reinforcers varied across rats and treatments. However, if there were fewer than five trials completed for the middle block of reinforcers, the rat's middle and last reinforcer block data was excluded from analysis.

Effects of nicotine and pre-feeding on log-transformed dependent measures were analyzed in separate 4 (dose: saline, 0.1, 0.3, 0.6 mg/kg) $\times$ 3 (reinforcer block: first reinforcer, middle, last block of reinforcers) and 2 (feeding treatment: saline vs. pre-feeding) $\times$ 3 (reinforcer block) ANOVAs. Significant main effects of dose and reinforcer-block were followed up with post hoc t-tests comparing saline and each dose data, and between each block of reinforcers. Significant interaction effects were followed up with post hoc t-tests comparing saline and each dose data, or saline and pre-fed data, within each block of reinforcers. All effects and comparisons were evaluated using a significance threshold $\alpha = .05$.

Chronic Administration Test—Visual inspection of the dependent measures as a function of trial suggested the same potential within-session trends observed during acute administration. However, this phenomenon seemed to only occur in the first session of chronic administration, and only for NIC rats. Also, the total number of reinforcers obtained varied between sessions and rats. Therefore, data were organized into reinforcer blocks as described for acute administration.

Effects of session, drug, and reinforcer block on log-transformed dependent measures were analyzed in a 2 (drug: nicotine, saline) $\times$ 3 (reinforcer block: first reinforcer, middle, last block of reinforcers) ANOVA for the first session (when acute effects were replicated), and an 8 (session: sessions 2 through 10; session 8 was excluded; see results for details) $\times$ 2 (drug: nicotine, saline) $\times$ 3 (reinforcer block: first reinforcer block, middle, last block of reinforcers) ANOVA for subsequent sessions (when chronic effects were detected). Significant interaction effects were followed up with post hoc t-tests comparing NIC and SAL rats within each block of reinforcers, and between blocks of reinforcers within each treatment group. All effects and comparisons were evaluated using a significance threshold $\alpha = .05$.

Distribution of Inter-Response Times (IRTs)—Parameters of the distribution of IRTs were estimated using the Bi-Exponential Refractory Model (BERM; Brackney et al., 2011; Daniels & Sanabria, 2017b). The BERM model assumes that responses are organized in bouts separated by pauses; after each response, there is a probability q of remaining in a bout, and a probability $1 - q$ of exiting a bout. Bout initiations and responses within bouts are generated with a constant probability, so the intervals between bouts and between responses are exponentially distributed. BERM also assumes that, because responses have non-zero duration, the minimum interval between bouts and between responses is also non-zero, and the distribution of IRTs is thus shifted. Therefore, BERM assumes that IRTs are best described as a shifted mixture of two exponential distributions,

$$\begin{aligned} \Pr(IRT = \tau | \tau < \delta) &= 0 \\ \Pr(IRT = \tau | \tau \geq \delta) &= qwe^{-w(\tau-\delta)} + (1-q)be^{-b(\tau-\delta)} \\ \delta &= \min(IRT) > 0; w \geq b > 0; 1 \geq q \geq 0. \end{aligned} \quad (1)$$

In Equation 1, δ is the shift parameter of the distribution, w is the within-bout response rate, and b is the bout-initiation rate.

The present analysis deviates from the conventional BERM-based analysis in one important way. BERM assumes that IRTs are the intervals between the onsets of consecutive responses, when there is no intervening reinforcement. In the present analysis, response durations were measured, and IRTs were defined as the intervals between the *end* of each response and the onset of the following response, barring intervening reinforcement. Therefore, run rate (r) may be recovered from Equation 1 as

$$r = \frac{wb}{qb + (1-q)w + wb(\delta + d)} \quad (2)$$

where d is the mean duration of a response.

For the acute-administration analysis, IRTs were pooled across the two sessions for each treatment, for each rat. The chronic analysis excluded the first session of chronic administration, as it was similar to the acute 0.3 mg/kg dose in a previous phase. Each

chronic session was analyzed separately, with session eight not analyzed due to an anomaly in the data (see results). Estimates of q , b , and w were obtained for each set of IRTs; the median response duration was calculated manually. BERM parameters were transformed to obtain the following dependent measures: the mean length of response bouts [excluding the bout-initiating response, $q/(1 - q)$], the mean bout-initiation rate [$b/(1 + b\delta)$], and the mean within-bout response rate [$w/(1 + w\delta)$]. ANOVA was conducted on log-transformed dependent measures, including median response durations, using the same design implemented for response rates, median latencies, and run rates during acute and chronic nicotine administration.

Results 1: Latencies and Run Rates

Acute Nicotine Injection Cycle

Rats obtained a similar number of reinforcers per session when the nicotine dose was 0.3 mg/kg, 0.1 mg/kg, or saline (mean = 32.72 ± 0.54). Under the 0.6 mg/kg nicotine dose and pre-feeding, rats earned $26.92 (\pm 1.30)$ and $25.00 (\pm 2.23)$ reinforcers per session, respectively. Thus, the 0.6-mg/kg and pre-feeding treatments reduced rate of reinforcement by about 20%.

Saline—Figure 2A–C shows mean ($\pm$ SEM) response rate, median latency, and run rate as a function of reinforcer block under saline. A significant effect of reinforcer block was detected on response rate, $F(2,22) = 16.18$, $p < 0.001$. Response rate decreased significantly between reinforcer blocks, $t(11) = 2.93$, $p < 0.014$.

Response Rate—Figure 2D shows the mean ($\pm$ SEM) difference in response rate relative to saline on each dose of nicotine and following pre-feeding. A significant dose $\times$ reinforcer block interaction effect was detected on response rate, $F(6,66) = 66.86$, $p < 0.001$. Prior to the first reinforcer, the highest doses of nicotine (0.3 and 0.6 mg/kg) reduced response rate relative to saline, $t(11) = 6.06$, $p < 0.001$. During the middle block of reinforcers, the lower doses of nicotine (0.1 mg/kg and 0.3 mg/kg) increased response rate relative to saline, $t(11) = 2.49$, $p < 0.030$. During the last block of reinforcers, all doses of nicotine increased response rate relative to saline, $t(11) = 2.21$, $p < 0.049$. To verify that these effects were not exacerbated by repeated injections, response rate under each dose $\times$ reinforcer block that varied significantly from saline was compared across injections (first vs. second), using t -tests. Of the 7 comparisons, only 2 revealed a significant effect of repeated injections: response rate increased by 50% prior to the first reinforcer, and declined by 22% during the last block of reinforcers, between the first and second administration of 0.6 mg/kg, $t(11) = 3.24$, $p < 0.009$. These effects are in the opposite direction to the effects of nicotine relative to saline, suggesting that repeated injections did not exacerbate the reported nicotinic effects on response rate—if anything, they weakened them. Taken together, these findings suggest that acute nicotine dose-dependently suppresses food-reinforced behavior prior to the first reinforcer, and increases the same behavior afterwards.

A significant feeding $\times$ reinforcer block interaction effect was also detected on response rate, $F(2,22) = 8.68$, $p = 0.002$. Pre-feeding reduced response rate on every reinforcer block, $t(11) = 3.20$, $p < 0.009$, but apparently more so prior to the first reinforcer than on other reinforcer

blocks. This suggests that pre-feeding, unlike nicotine, continuously suppressed behavior throughout the session.

Latency—Figure 2E shows the mean ($\pm$ SEM) difference in latency relative to saline for each dose of nicotine and following pre-feeding. A significant dose $\times$ reinforcer block interaction effect was detected on latencies, $F(6,66) = 33.22$, $p < 0.001$. Prior to the delivery of the first reinforcer, the higher doses of nicotine (0.3 and 0.6 mg/kg) increased latencies relative to saline, $t(11) = 4.15$, $p < 0.002$. During the middle block of reinforcers, all doses of nicotine decreased latencies relative to saline, $t(11) = 2.60$, $p < 0.025$. During the final block of reinforcers, 0.6 mg/kg of nicotine also decreased latency relative to saline, $t(11) = 2.40$, $p = 0.035$. These effects suggest that nicotine dose-dependently increased the time to the first lever press in each session, but decreased the latency to lever press after subsequent reinforcers.

A significant feeding $\times$ reinforcer block interaction effect was detected on latencies, $F(2,22) = 4.21$, $p = 0.028$. Pre-feeding significantly increased latencies relative to saline on the first and middle reinforcer blocks, $t(11) = 3.24$, $p < 0.008$. This suggests that pre-feeding lengthened latencies more persistently than nicotine.

Run Rate—Figure 2F shows the difference in run rate relative to saline for each dose of nicotine and following pre-feeding. No significant effects of dose or reinforcer block were detected on run rate. A significant main effect of feeding, however, was detected on run rate, $F(1,11) = 8.25$, $p = 0.015$. Pre-feeding decreased run rate across reinforcer blocks.

Taken together, these results replicate the time- and dose-dependent suppressive and enhancing effects of nicotine on response rate (Morrison, 1967). These effects are primarily due to changes in latencies. In contrast, a motivational manipulation, pre-feeding, also affected run rate. Therefore, if the post-suppression effects of nicotine reflected an increase in appetite, an increase in run rate would have been expected. The small contribution of run rate on nicotinic effects suggests that either (a) nicotinic enhancement of response rate is not entirely due to changes in motivation, or (b) a ceiling effect: at about 1.5 resp/s, nicotine could not further increase run rate.

Chronic Administration Test

Response Rate—Figure 3A–C shows the mean ($\pm$ SEM) response rate, in each reinforcer block, during the last five sessions of baseline recovery (included for reference only) and in each of the 10 chronic administration sessions. A significant reinforcer block $\times$ drug interaction effect was observed during the first session, $F(2,20) = 16.96$, $p < 0.001$. Prior to the delivery of the first reinforcer in this first session, nicotine reduced response rate, $t(10) = 2.45$, $p = 0.034$. After the delivery of the first reinforcer, nicotine increased response rate, $t(5) = 5.69$, $p = 0.002$. This result replicates the findings from acute administration (cf. Fig. 1D).

A significant main effect of reinforcer block was observed during chronic sessions 2–10, $F(2,18) = 5.45$, $p = 0.014$. Similar to the first session, nicotine increased response rate only after the first reinforcer was delivered, $t(11) = 2.59$, $p = 0.03$, but such increase was

tempered between the middle and last reinforcer blocks. These effects suggest that chronic exposure to nicotine increases food-reinforced behavior after the first reinforcer, without the preceding suppression of behavior induced by acute nicotine administration.

Latency—Figure 3D–F shows the mean ($\pm$ SEM) median latency, in each reinforcer block, during the last five sessions of baseline recovery (included for reference only) and in each of the 10 chronic administration sessions. A significant reinforcer block $\times$ drug interaction effect was observed during the first session, $F(2,20) = 8.08$, $p = 0.003$. Similar to performance in the acute administration phase, nicotine increased the latency to the first response in the session, although the effect in the chronic administration phase was too variable among rats to reach statistical significance. After the delivery of the first reinforcer, nicotine reduced latencies, $t(5) = 3.20$, $p = 0.024$. Although latencies increased in NIC rats during the delivery of the last five reinforcers relative to the middle block of reinforcers, $t(5) = 3.07$, $p = 0.028$, latencies were still shorter than in SAL rats, $t(10) = 2.46$, $p = 0.034$. The nicotine-induced shortening of latencies during the middle of the first chronic-administration session was also observed during the acute administration cycle (cf. Fig. 1E).

A significant reinforcer block $\times$ drug interaction effect was also observed during chronic administration sessions 2–10, $F(2,18) = 4.93$, $p = 0.020$. No significant effect of nicotine was observed on the latency to the first response of each session or after the delivery of the first reinforcer. However, NIC latencies were shorter than SAL latencies during the middle reinforcer block, $t(10) = 3.13$, $p = 0.011$. Although latencies increased in NIC rats during the delivery of the last 5 reinforcers, $t(5) = 2.89$, $p = 0.035$, latencies were still shorter than in SAL rats, $t(10) = 2.67$, $p = 0.024$. Taken together, this pattern of results suggests a rapid and selective development of tolerance to the suppressive effect of nicotine on food-seeking behavior prior to the first reinforcer. In contrast, the excitatory effect of nicotine, expressed as shorter latencies after the first reinforcer, was maintained even after 10 daily administrations.

Run Rate—Figure 3G–I shows the mean ($\pm$ SEM) run rate, in each reinforcer block, during the last 5 sessions of baseline recovery and in each of the 10 chronic administration sessions. No significant reinforcer block or drug effects were detected during the first session. A significant main effect of reinforcer block was observed during chronic administration sessions 2–10, $F(2,18) = 2.16$, $p = 0.009$. The run rate prior to the first reinforcer in session 8 increased relative to sessions 7 and 9, $t(11) = 2.48$, $p < 0.031$. However, this is likely to reflect an anomaly in data collection. Upon further inspection, the anomaly seems to be driven by two cage mates from each group, all injected simultaneously. When session 8 was removed from analysis, a main effect of reinforcer block was detected, $F(2,18) = 17.11$, $p < 0.001$. Run rate increased after the delivery of the first reinforcer, $t(11) = 4.62$, $p < 0.001$ and decreased during the delivery of the last five reinforcers, $t(11) = 5.17$, $p < 0.001$.

Taken together, these results suggest that nicotine-induced behavioral suppression prior to the first reinforcer weakens rapidly over sessions. In contrast, nicotine-induced behavioral facilitation after the first reinforcer, which peaks near the middle of the session, is substantially more persistent. This pattern of effects is primarily driven by changes in

latencies to respond after session onset and after each reinforcer, and not by subsequent responses.

Results 2: Microstructural Analysis of Run Rates

Figure 4A–B shows the mean distribution of cumulative IRTs, using percentiles, in each of the 5 treatments (saline, 3 nicotine doses, and pre-feeding) and in the chronic nicotine treatment, expressed as semi-log survivor plots (proportion of IRTs shorter than x). The broken-stick patterns shown in Figure 4 reflect a mixture of two exponential distributions, as predicted by BERM (Equation 1). The steeper leftmost portion of the curves represents the distribution of within-bout IRTs, whereas the shallower rightmost portion of the curves represents the distribution of between-bout IRTs (Shull et al., 2001; Brackney et al., 2011; Daniels & Sanabria, 2017a). The curves in Figure 4A–B are mean traces of Equation 1 fit to each distribution of IRTs. The fits adequately describe the data, suggesting that responses were organized in bouts.

Acute Nicotine Injection Cycle—Table 1 shows mean ($\pm$ SEM) BERM parameter estimates and median response durations under each treatment. Under saline, rats produced bouts at a rate of about 0.15 per second (9 per minute). Each bout comprised 7–8 responses, each about 0.15-s long. Once a response was completed, the following response within the same bout was produced very quickly, at a rate of about 11–12 per second (an average of 86 ms between consecutive responses).

Neither nicotine nor pre-feeding had a significant effect on mean bout length. A significant effect of nicotine dose was observed on the estimates of bout-initiation rate, $F(3,33) = 7.16$, $p < 0.001$. The lowest doses of nicotine (0.1 and 0.3 mg/kg) increased bout-initiation rate relative to saline, $t(11) = 3.61$, $p < 0.004$. A significant effect of nicotine dose was observed on the estimates of within-bout response rate, $F(3,33) = 6.51$, $p = 0.001$. The highest doses of nicotine (0.3 and 0.6 mg/kg) increased within-bout initiation rate relative to saline, $t(11) = 2.56$, $p < 0.026$.

Pre-feeding reduced both bout-initiation rate, $F(1,11) = 24.62$, $p < 0.001$, and within-bout response rate, $F(1,11) = 14.10$, $p = 0.003$. Pre-feeding also increased the median response duration, $F(1,11) = 19.07$, $p = 0.001$.

Although no significant effect of acute nicotine was observed on run rate (Fig. 1F), a closer analysis of the components of run rate suggests that lower doses of nicotine increased the rate at which response bouts were initiated within runs, and higher doses of nicotine increased the response rate within those bouts. Variance in nicotine-robust components of run rate, such as bout length and response duration, may have obscured these effects when assessed on run rate.

Chronic Administration Test—Table 2 shows means ($\pm$ SEM) BERM parameter estimates for SAL and NIC rats. A chronic nicotine regimen had a similar impact as on estimates of bout length, bout-initiation rate, and within-bout response rate as acute injections of 0.3 mg/kg nicotine (cf. Table 1). However, whereas acute-nicotine effects on

bout-initiation and within-bout response rates were statistically significant, chronic-nicotine effects on these parameters were not statistically significant. This discrepancy likely reflects a difference in statistical power across analyses: the within-subject design of the acute injection cycle was more powerful than the between-subject design of the chronic injection cycle.

A significant session $\times$ group interaction effect was detected on median response duration, $F(7,70) = 2.898$, $p = 0.010$. Nicotine decreased median response duration between sessions 2 and 3, $t(5) = 2.992$, $p = 0.030$. This effect suggests that nicotine may only induce a reduction in response duration after repeated administrations.

Discussion

In the present study, the effects of acute and chronic nicotine administration on the structure of food-seeking behavior were investigated to determine the relative contribution of motivational, learning, and motoric factors to the nicotine-induced enhancement of food-reinforced behavior. Consistent with prior research, the acute administration of nicotine transiently suppressed behavior (Morrison, 1967; Clarke & Kumar, 1983a). Once this effect subsided, food-reinforced behavior rebounded above baseline levels (Figure 2D; Morrison, 1967; Clarke & Kumar, 1983a). These effects were largely driven by an initial and substantial lengthening of latencies—the intervals between reinforcement and subsequent food-seeking behavior—followed by a more moderate shortening of latencies (Figure 2E). Selective changes in latencies are often detected with changes in food deprivation (Blakely & Schlinger, 1988; Shull, 2004; Brackney et al., 2011; Daniels & Sanabria, 2017a, b), and were replicated here, albeit with a small but noticeable effect on run rate (Figure 2E–F). With chronic administration, rats developed a tolerance to nicotinic latency lengthening, emitting short latencies throughout each session (Figure 3D–F). Latency shortening may reflect nicotine-induced enhancement of reinforcer efficacy, but latencies are sensitive to a broad range of effects (Daniels & Sanabria, 2017b). A microstructural analysis of food-seeking behavior was aimed at verifying this hypothesis.

Food-seeking behavior was organized in bouts, consistent with prior research (e.g., Brackney et al., 2011; Shull, 2011; Daniels & Sanabria, 2017b). The lowest dose of nicotine tested (0.1 mg/kg) selectively raised the rate at which bouts were initiated (Table 1). This selective effect is typically observed in variable interval schedules when the efficacy of reinforcers is enhanced (Shull & Grimes, 2003; Brackney et al., 2011; Daniels & Sanabria, 2017a, b). The opposite effect was observed with pre-feeding (Table 1), reducing bout-initiation rate by less than half. Pre-feeding, however, also resulted in a smaller reduction in within-bout response rate (<11%) and a smaller increase in response duration (<14%); these effects are consistent with the notion that pre-feeding reduces motoric capacity (Belke, Pierce, & Jensen, 2004; Daniels & Sanabria, 2017b). The highest dose of nicotine tested (0.6 mg/kg) selectively raised the rate of responding within bouts (Table 1). This variable appears to be controlled primarily by the physical characteristics of the response device (Shull & Grimes, 2003); in the absence of changes to the operandum, this variable is indicative of changes in motoric capacity. Interestingly, the intermediate dose of nicotine (0.3 mg/kg) showed both a higher bout-initiation and within-bout response rate, an effect replicated

during chronic administration (Table 2). Consistent with prior findings (Barret & Bevins, 2013), whereas low doses of nicotine appear to selectively enhance reinforcer efficacy, higher doses appear to enhance motoric capacity. Tolerance does not appear to develop to either the motivating effects of lower nicotine doses, or to the motoric effects of higher nicotine doses.

It is important to note that inferences on motivational and motoric effects are based on the distribution of inter-response times (IRTs). Although these inferences are well validated (Brackney et al., 2011, 2017; Brackney & Sanabria, 2015), they hinge on key assumptions about the distribution of IRTs, which the present data appear to meet (Figure 4). Nonetheless, recent research suggests that IRT distributions are generated from processes more complicated than those assumed here (e.g., Tanno, 2016). Novel techniques that empirically disentangle bout-initiation rates from within-bout response rates (e.g., Daniels & Sanabria, 2017b) may be helpful for future research.

The steady decline in lever pressing for food when rats were just administered saline (Figure 2A) may reflect satiation (Bizo, Bogdanov, & Killeen, 1998) or a habituation of the reinforcing properties of food (McSweeney & Murphy, 2009). Nicotinic effects on motivation may be mediated by disruptions in either process (cf. Epstein et al., 1992).

Prior research suggests a particularly noticeable effect of nicotine on sucrose consumption. When nicotine is on board, both humans and rats decrease their consumption of sweet foods (Grunberg 1982); when it is no longer on board, sucrose consumption increases (Jias & Ellison, 1990). Changes in taste perception appear to mediate nicotine-induced changes in sucrose consumption. Nicotine concentrates in the salivary glands and in the fundus of the stomach of rats, causing disruptions in taste perception (Wager-Srdar et al., 1983). In addition, human smokers have a higher threshold for the perception of bitter and sweet solutions (Wager-Srdar et al., 1983). It appears that nicotine increases the “wanting” of the reinforcer, in that, under nicotine, rats seek out the reward more (enhanced food-seeking behavior), but does not affect or even reduces the “liking” aspect of the reinforcer (reduced feeding behavior; Berridge, 2007). The effect of nicotine on the seeking and consumption of sweet flavors may have important implications for research and policy regarding electronic nicotine delivery systems (ENDS), given their additive flavors (Harrell et al., 2017). Future research may aim to determine if a reduction in “liking” at high doses of nicotine yields a decrease in total consumption (e.g., Chen et al., 2011).

It is also possible that stimuli associated with food (test chamber, house-light, lever insertion) mediated the nicotinic effects on motivation. Nicotine enhances the incentive value of such stimuli, facilitating a conditioned approach to them (*sign tracking*, Palmatier et al., 2013; Overby et al., under review). In the presence of the lever press-food contingency, it is likely that such approach would be directed to the lever. Therefore, nicotine-sensitive neural mechanisms that modulate sign tracking may be involved in the nicotinic enhancement of motivation for rewards. These mechanisms include corticosterone release (Pentkowski et al., 2011), prefrontal norepinephrine and serotonin signaling (Shearman et al., 2008), dopamine transmission in the nucleus accumbens shell (Pontieri et al., 1996), and

GABA interneuron activity in the anterior cingulate cortex (Liu et al., 2005; for a review, see Tomie et al., 2008).

The motoric effects that were observed in this study are similar to those observed in open-field locomotion. Nicotine seems to affect locomotion in a bidirectional and temporally dependent manner that is initially suppressive and then enhancing (Clarke & Kumar, 1983a; Domino, 2001). In addition, tolerance seems to develop to these motoric suppressive effects (Clarke & Kumar, 1983a; Clarke & Kumar, 1983b; Morrison & Stephenson, 1972; Domino, 2001). During the acute-administration phase of the present study, higher nicotine doses (0.3 and 0.6 mg/kg) initially suppressed reinforced behavior, and then enhanced it after the delivery of the first reinforcer. During the chronic phase, only the first session showed an initial suppression of behavior, which disappeared as the sessions progressed (Figure 3A).

In conclusion, the present study provides converging evidence that low doses of nicotine induce (a) a disruptive but transient motoric effect on food-seeking behavior, and (b) long-lasting enhancing effects on food-seeking behavior (Morrison, 1967). These enhancing effects appear to reflect elevated motivation at the lowest doses, and motoric facilitation at higher doses. Motivational effects may in part reflect a disruption of reinforcer habituation in rats, as seen in humans (e.g., Epstein et al., 1992). These results suggest that ostensive sensitization effects of nicotine on behavior may partially reflect a tolerance to its suppressive motoric effects.

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Figure 1.

The microstructure of response rate found in a typical VI trial. Response rate is composed of latency and run rate, where $\text{response rate} = \text{run rate} \times (1 - \text{mean latency}/\text{VI requirement})$, assuming independence of latency and run rate. Run rate is composed of bout length, within-bout response rate, bout-initiation rate, and response duration. Each component is differentially sensitive to changes in motivation, response-outcome learning, and motoric capacity; see text for details.

Figure 2.

Effects of acute saline and nicotine administration, and pre-feeding on macro measures of food-seeking behavior. Mean ($\pm$ SEM) response rate (Panel A), median latency (Panel B), and run rate (Panel C) under saline, and the mean ($\pm$ SEM) nicotine- (0.1 [black circles], 0.3 [white circles], and 0.6 [grey circles] mg/kg) and pre-feeding-induced (black crosses) changes in response rate (Panel D), median latency (Panel E), and run rate (Panel F) as a function of reinforcer block. Note that, in Panel E, there is a break in the x-axis.

Figure 3.

Effects of chronic saline and nicotine administration on macro measures of food-seeking behavior. Mean ($\pm$ SEM) response rate (Panels A–C), median latency (Panels D–F), run rate (Panels G–I), in each reinforcer block, during the last 5 sessions of baseline recovery (BL), and in each of the 10 chronic administration sessions for SAL (black circles) and NIC rats (white squares).

Figure 4.

Effects of acute saline and nicotine administration, pre-feeding (Panel A), and chronic saline and nicotine (Panel B) on the microstructure of food-seeking behavior. Mean semi-log survival plots of IRTs in saline (black circles), nicotine doses (0.1 [white squares], 0.3 [black triangles], 0.6 [white diamonds] mg/kg), and pre-feeding (black crosses). Continuous lines are mean traces of BERM (Eq. 1). Survival plots were constructed individually for each rat by organizing data into 40 equally sized bins with approximately an equal number of IRTs in each bin.

Table 1

Mean ($\pm$ SEM) BERM parameter estimates during the acute nicotine injection cycle

Parameters	Treatment				
	Saline	0.1 mg/kg	0.3 mg/kg	0.6 mg/kg	Pre-feeding
Mean Bout Length (resp)	7.45 (0.44)	7.28 (0.33)	6.26 (0.38)	6.75 (0.69)	7.50 (0.31)
Mean Bout-Initiation Rate (resp/s)	0.15 (0.04)	0.20 (0.04)*	0.21 (0.04)*	0.16 (0.03)	0.07 (0.02)*
Mean Within-Bout Response Rate (resp/s)	11.67 (1.41)	12.21 (1.36)	13.96 (1.65)*	14.41 (1.98)*	10.44 (1.25)*
Median Response Duration (s)	0.15 (0.02)	0.16 (0.02)	0.17 (0.02)	0.19 (0.03)	0.17 (0.02)*

* Significantly different from Saline, $p < .05$.

Table 2Mean ($\pm$ SEM) BERM parameter estimates during the chronic nicotine injection cycle

Parameters	Group	
	SAL	NIC
Mean Bout Length (resp)	7.82 (0.39)	6.72 (0.40)
Mean Bout-Initiation Rate (resp/s)	0.12 (0.05)	0.28 (0.05)
Mean Within-Bout Response Rate (resp/s)	10.09 (1.45)	15.76 (2.53)
Median Response Duration (s)	0.17 (0.003)	0.14 (0.002)*

Note. Estimates are averaged across chronic administration sessions.

* Significant session $\times$ group interaction effect, $p < .05$