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Revisiting the Effect of Nicotine on Interval Timing

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Abstract

This paper reviews the evidence for nicotine-induced acceleration of the internal clock when timing in the seconds-to-minutes timescale, and proposes an alternative explanation to this evidence: that nicotine reduces the threshold for responses that result in more reinforcement. These two hypotheses were tested in male Wistar rats using a novel timing task. In this task, rats were trained to seek food at one location after 8 s since trial onset and at a different location after 16 s. Some rats received the same reward at both times (group SAME); some received a larger reward at 16 s (group DIFF). Steady baseline performance was followed by 3 days of subcutaneous nicotine administration (0.3 mg/kg), baseline recovery, and an antagonist challenge (mecamylamine, 1.0 mg/kg). Nicotine induced a larger, immediate reduction in latencies to switch (LTS) in group DIFF than in group SAME. This effect was sustained throughout nicotine administration. Mecamylamine administration and discontinuation of nicotine rapidly recovered baseline performance. These results support a response-threshold account of nicotinic disruption of timing performance, possibly mediated by nicotinic acetylcholine receptors. A detailed analysis of the distribution of LTSs suggests that anomalous effects of nicotine on LTS dispersion may be due to loss of temporal control of behavior.

Keywords

Timing; Time Perception; Nicotine; Mecamylamine; Rats; Fixed-interval schedules of reinforcement

Most theories of timing in the seconds-to-minutes timescale—*interval timing*—are based on a simple computational structure (Simen, Rivest, Ludvig, Balci, & Killeen, 2014; Luzardo, Ludvig, & Rivest 2013; Ward, Kellendonk, Kandell, & Nalsam, 2012; Matell & Meck, 2004; Gallistel & Gibbon, 2000; Machado 1997; Killen & Fetterman, 1988; Gibbon, 1977): The onset of a stimulus resets a counter and initiates the emission of pulses from a pacemaker to the accumulator. When the pulse count in the accumulator becomes similar enough to a criterion sampled from memory, a target response (e.g., reporting that 30 s has elapsed) is

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emitted. Upon reinforcement, pulses in the accumulator update the memory criterion. This structure yields a temporal distribution of the target response, typically centered on a proportion of the target interval (Sanabria, Thraill and Killeen, 2009; Simen, Balci, deSouza, Cohen and Holmes, 2011 Machado and Cevik, 1998; Bizo and White, 1995a; quantitative details are provided in Appendix A).

The basic computational structure of interval timing suggests alternative ways in which a drug may interfere with timing performance (see Coull, Cheng, & Meck, 2011 and Meck, 1996 for a review). Here, we focus on two possible changes that nicotine may induce: it may speed up the rate of pulse emissions, and it may lower the threshold for the target response. We refer to the first change as a *clock-speed effect*, and the second one as a *response-threshold effect*. These effects are difficult to disentangle because their immediate behavioral expression is often very similar: both yield premature target responses.¹

Empirical evidence for nicotine-induced clock-speed effects (Hinton and Meck, 1996; Meck and Williams, 1997; Meck, 2007) suggests that nicotine influences timing performance, similarly to other psychostimulants (Maricq, Roberts & Church, 1981; Meck, 2006), through the activation of the mesocortical dopaminergic pathway. This evidence has been obtained primarily using the peak interval procedure. In this procedure, subjects are trained on a fixed-interval (FI) schedule of reinforcement randomly interspersed with probe extinction trials that are 3 to 4 times longer than FI trials. In FI trials the first response after a criterial time since stimulus onset is reinforced. With sufficient training, response rate in extinction trials typically falls under temporal control, peaking close to the time when reinforcement is delivered in FI trials.

The clock-speed effect is supported by leftward shifts in the start- and stop-times of responding, which lead to a corresponding leftward shift in the peak times (see Meck, 1996). It is unclear, however, that psychostimulants actually produce such an effect. D-amphetamine, for instance, appears to influence when animals start responding in probe trials, but not when they stop responding (Saulsgiver, McClure and Wynne, 2006; Taylor, Horvitz and Balsam, 2007); methamphetamine appears to have the opposite effect (Matell, Bateson & Meck, 2006). Regardless of the specific mechanisms that mediate these divergent effects, they suggest that peak-interval start- and stop-times are dissociable and thus likely controlled by distinct neural mechanisms (Balci, Gallistel, Allen, Frank, Gibson and Brunner, 2009; Balci, Ludvig and Brunner, 2011; Ludvig, Balci and Spetch, 2011; MacDonald, Cheng and Meck, 2012).

It is also unclear how a response-threshold effect is expressed in peak performance. With a single threshold for start- and stop-times, a lower threshold should yield shorter stop-times and longer start-times, leading to a broadening of the distribution of responding rather than a leftward shift. Nonetheless, the statistical structure of peak performance parameters suggests separate response thresholds for start- and stop-times (Church, Meck and Gibbon, 1994). If stimulant effects operate only on start-times, then it is not possible to dissociate clock-speed

¹These two effects may also be conceptualized in signal-detection terms (Wickens, 2001). Clock-speed effects are akin to changes in discriminability (increase in clock speed reduces variability in timing; Killeen, 2002) and response-threshold effects are akin to changes in decision bias (lowering the response threshold increases false positives).

from response-threshold effects in peak-interval performance; a leftward shift in start-times is sufficient to produce a leftward shift in peak time (Taylor, Horvitz & Balsam, 2007). These challenges suggest that response-threshold and clock-speed effects are easily conflated in peak performance, thus motivating an investigation of the effect of nicotine on interval timing through alternative behavioral methods.

Nicotinic effects on interval timing have also been examined using the temporal bisection procedure. In this procedure, subjects are trained to make one response after a short-duration stimulus and a different response after a long-duration stimulus; non-reinforced probe tests are conducted in which stimuli of intermediate duration are presented (Stubbs, 1968). Unlike in peak performance, the expression of clock-speed effects in bisection performance is unambiguous: these effects are expressed as a leftward shift in the psychometric function relating the objective duration of the stimulus to the probability of reporting a long duration (Droit-Volet and Wearden, 2002). The evidence for nicotine-induced clock-speed effects obtained from the temporal bisection procedure is mixed at best. One study (Bizot, 1997) reports such an effect. Two other studies (Ward, Barrett, Johnson and Odum, 2009; McClure Saulsgiver and Wynne, 2011) failed to replicate this effect in pigeons; they only report a substantial non-specific effect of nicotine on the discriminability of training durations.

The present study is aimed at testing whether nicotine induces a clock-speed and/or a response-threshold effect. It proposes a methodology previously not implemented to study nicotinic effects on interval timing, based on a well-specified model of response threshold. The model assumes that subjects always have a choice between at least two response actions: “no response” and “response” in the peak interval procedure; “report short” and “report long” in the temporal bisection procedure. Each response is associated with a potential reinforcer: In the peak interval procedure, it is a hypothetical background reinforcer of constant probability (Sanabria et al., 2009) vs. the programmed reinforcer; in the temporal bisection procedure, it is the reinforcer for correct short vs. correct long reports. At any given time, choice between alternative responses is determined by their differences in reinforcement probability and in reinforcement magnitude. The response threshold is the weight of the former relative to the latter. A low threshold means that differences in magnitude supersede differences in probability in controlling behavior.

In the peak interval procedure, a response-threshold effect is expressed as earlier responding because responding results in larger reinforcement than not responding. In the temporal bisection procedure, if both reinforcers are equal, a lower threshold may be expressed as an exacerbation of idiosyncratic choice biases rather than as a systematic effect on timing performance (e.g. Ward & Odum, 2007); if reinforcement is unequal, such that 4 reinforcers are provided for a correct choice of short and 1 reinforcer for a correct choice of long, a lower threshold would result in a corresponding bias to choose short (e.g. Galtress & Kirkpatrick, 2010). These predictions are consonant with the effect of nicotine on interval timing observed in both the peak interval and temporal bisection procedures.

The proposed model of response threshold makes a previously untested prediction that would explicitly test the hypothesis that nicotine lowers the response threshold. Because a lower threshold is expressed as an exacerbation of the bias to choose the response with the

larger reinforcer, it is expected that nicotine would exacerbate this bias in a choice between unequal reinforcers, but not in a choice between equal reinforcers. In contrast, clock-speed effects are expected to affect both choices similarly.

Clock-speed and response-threshold effects of nicotine are also expected to yield distinct patterns of performance when nicotine is repeatedly administered and subsequently discontinued (see Appendix A for a quantitative description of these effects). A clock-speed effect is expressed as an immediate but transient and proportional decrease in the mean and standard deviation of response times; coefficients of variation are not expected to change. Faster clocks yield larger pulse counts upon delivery of reinforcement, when those counts are transferred to memory. Thus, with sufficient training under nicotine administration, memory updating produces a compensatory change across sessions that yield a progressive full recovery of the mean, a partial recovery of the standard deviation, and a decrease in the coefficient of variation of response times. Discontinuation of nicotine is expected to return the clock speed to baseline levels, immediately producing an increase in the mean, standard deviation, and a decrease in the coefficient of variation of response times, relative to baseline performance.

A response-threshold effect is expressed as an immediate and permanent proportional change in the mean, a small change in the standard deviation, and an increase in the coefficient of variation of response times. To the extent that reinforcement time is independent of response time (as is the case in most timing tasks), memory is not expected to change with a lower threshold. Baseline performance is not expected to recover with repeated administration of nicotine; the accuracy and precision of performance should continue to be disrupted while nicotine is administered. Additionally, because memory is not disturbed, discontinuation of nicotine is expected to immediately recover baseline performance.

The present study implemented two tactics to examine the relative contribution of clock-speed and response-threshold effects to nicotinic disruption of interval timing. First, it compared performance in rats that had equal vs. different incentives for correct reports of short vs. long intervals, and examined the impact of nicotine on the differences in performance between the two groups. Second, it exposed rats repeatedly to nicotine, and then discontinued it. Table 1 presents a summary of predicted effects.

Finally, mecamylamine, a noncompetitive antagonist of nAChRs, was administered to determine the extent to which nicotinic effects of interval timing are mediated by nAChRs. Nicotine has a high affinity for nicotinic acetylcholine receptors (nAChRs). Mecamylamine also has a high affinity for nAChRs, in particular receptors containing subunits $\beta 2$ & $\beta 4$ (Papke, Sandberg, & Shytle, 2001; Chavez-Noriega, Crona, Washburn, Urrutia, Elliott, & Johnson, 1997). Thus, if mecamylamine blocks the nicotine-induced disruption of interval timing, it would suggest that these disruptions are mediated by nAChRs containing $\beta 2$ or $\beta 4$ subunits.

Methods

Subjects

Sixteen male Wistar rats (Charles River Laboratories, Hollister, CA) served as subjects. Rats arrived on post-natal day 60 and were pair-housed immediately upon arrival. Rats were housed on a 12:12 h light cycle, with dawn at 1900 h; all behavioral training was conducted during the dark phase of the light cycle. Behavioral training and food restriction protocols were implemented shortly after arrival. Access to food was reduced daily from 24, to 18, 12, and finally 1 h/day. Chow was placed on the homecages of rats during the dark phase of the light cycle. During behavioral training, food was provided 30 min after the end of each training session, such that at the beginning of the next session weights were, on average, 75% of mean ad libitum weights estimated from growth charts provided by the breeder. Water was always available in home cages. All animal handling procedures in 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 16 MED associates (ST. Albans, VT, USA) modular test chambers (10 chambers measured 305 mm long, 241 mm wide, and 210 mm high; 6 chambers measured 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 (MED Associates, ENV-202M-S) fitted with a cup (MED Associates, ENV-202C) that could hold 0.01 cc of a liquid reinforcer (33% sweetened condensed milk diluted in tap water; Great Value brand, Walmart, Bentonville, AK). The receptacle was furnished with a head entry detector (ENV-254-CB). A multiple tone generator (MED associates, ENV-223) was used to produce a 15-kHz tone at approximately 75 dB through a speaker (MED Associates, ENV-224 AM) 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 (only yellow was used in the present experiment). 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) and mecamylamine hydrochloride (Cayman Chemical Company, Ann Arbor, MI, USA) were dissolved each in a 0.9% saline solution; the solution for nicotine was adjusted to a pH of 7.2. Saline, nicotine,

and mecamylamine were administered subcutaneously (s.c.) in a volume of 1.0 ml/kg. Doses of nicotine and mecamylamine were 0.3 mg/kg and 1.0 mg/kg, respectively. These doses were chosen because of their efficacy in disrupting timing behavior (Mazur, Wood-Isenberg, Watterson, & Sanabria, 2014; Ward et al., 2009; Hinton & Meck, 1996).

Procedure

Overview and Predictions—Fig. 1 provides an overview of the timeline of events. Rats were trained and tested on dependent concurrent fixed-interval 8-s fixed-interval 16-s (FI 8-s FI 16-s) schedules of reinforcement, a procedure similar to the one used by Stubbs and Pliskoff (1969). In this procedure, two levers were extended into the operant chamber on every trial, each associated with a different FI schedule (8- vs. 16-s). On any given trial, only one FI was effective. Subjects sensitive to the timing of reinforcement were expected to respond first on the FI 8-s lever and later change over to the FI 16-s lever (Fetterman and Killeen, 1995). The target response expected to be sensitive to the timing of reinforcement is the first response on the FI 16-s, which we refer to as the latency to switch (LTS).

For half of the rats, the reinforcer was smaller in FI 8-s than in FI 16-s (Group DIFF); for the other half, reinforcers were the same across schedules (Group SAME). The mean LTS was expected to be shorter for group DIFF compared to group SAME. If nicotine increases the speed of the internal clock, it was expected to induce an immediate but transient proportional disruption in timing accuracy and precision in both groups of rats. If nicotine reduces the response threshold, it was expected to induce an immediate but permanent proportional disruption in timing accuracy and precision in group DIFF more than in group SAME (see Appendix A for a mathematical derivation of these predictions). Table 1 summarizes the predictions of the competing hypotheses under evaluation. All training sessions were conducted once daily, 7 days/week.

Phase 1: Box Acclimation and Lever-Shaping—All rats were first acclimated to the chambers for two days. During this procedure the house-light was on for the entire session and reinforcement was delivered on a fixed-time (FT) 60-s schedule, with a 10-s reinforcer. After two days of acclimation a lever-shaping session was implemented. In lever-shaping, the left and right levers were simultaneously inserted 10 s prior to the reinforcer on the same FT 60-s schedule. All rats pressed both levers reliably by the end of the lever-shaping session.

Phase 2: Continuous Reinforcement—Each session began with a 3-min warm-up period during which the house-light was on. After completion of this warm-up period, each trial began by turning off the house-light, inserting either the left or right lever (pseudo randomly with $p = .5$, selected without replacement from a 6-item list), and illuminating a yellow light directly above the lever. A single press on the active lever terminated the light above the active lever, retracted the lever, and turned on a 15-kHz tone signaling and lasting throughout reinforcement. Onset of the tone coincided with delivery of a 2.5-s activation of the dipper. Reinforcement was followed by a 5-s ITI, during which the house-light was on. Each session lasted 75 min. Pretraining continued until all rats had been weaned onto the

food restriction protocol (see *Subjects*) and had successfully earned more than 50 reinforcers in at least a single session. These criteria were met after 6 sessions.

Phase 3: Reinforcer Magnitude Manipulation—Rats were randomly assigned to group SAME or DIFF; group assignment remained unchanged for the rest of the experiment. For rats in group SAME ($n = 8$), reinforcement of active lever pressing was increased from 1 to 2 reinforcer deliveries. For rats in group DIFF ($n = 8$) reinforcement increased to 3 deliveries, but only for pressing one of the levers, left or right, when active; pressing the opposite active lever yielded only 1 reinforcer. The larger reinforcer was assigned to the left lever for a random half of the DIFF rats, and to the right lever to the other half. Every dipper activation was 2.5-s long. Consecutive deliveries were separated by a 1-s deactivation of the dipper. A 15-kHz tone was turned on at the beginning of the first reinforcer delivery and was turned off at the end of the last one. Training was conducted for 4 sessions.

Phase 4: FI FI Training—A dependent concurrent FI 8-s FI 16-s schedule of reinforcement was implemented. This schedule modified the *Reinforcer Magnitude Manipulation* schedule by (a) presenting both levers simultaneously, and (b) programming reinforcement according to an FI 8-s schedule on one lever and according to an FI 16-s schedule on the other lever. For Group SAME, assignment of schedule to lever was random; for Group DIFF, the FI 8-s schedule was assigned to the 1-reinforcer lever and the FI 16-s to the 3-reinforcer lever. On any given trial, only one schedule was effective, selected pseudo-randomly without replacement from a 6-item list. The active schedule on any given trial was not signaled. The first press on the active lever after 8 or 16 s (depending on the schedule) was reinforced with 2 reinforcer deliveries for Group SAME, and with either 1 (on the FI 8-s schedule) or 3 (on the FI 16-s schedule) deliveries for Group DIFF. Presses on the inactive lever were recorded but did not have any programmed consequences. Latencies to switch (LTSs; the times between lever insertion and first response on the FI 16-s lever) were recorded on every trial in which the FI 16-s schedule was effective.

FI FI Training continued for a minimum of 21 days and until all rats demonstrated stable temporal control. Stability was determined by a non-significant regression of the median and inter-quartile range (IQR) of LTSs over 7 consecutive sessions.

Phase 5a: Saline Baseline—This condition was identical to the preceding one, except that training sessions were immediately preceded by a s.c. injection of 0.1 mL of saline. Two sessions were conducted; they were labeled “B1” and “B2”. Pooled together, these sessions were labeled “B”.

Phase 5b: Nicotine—This condition was identical to the preceding one, but the pre-session injections were 0.3 mg/kg s.c. nicotine. Three sessions were conducted; they were labeled, “N1”, “N2”, and “N3”. Data for all 3 days is shown, but only N1 and N3 data were analyzed.

Phase 5c: Recovery of Baseline—This condition was identical to *Saline Baseline* training, except that 4 sessions were conducted instead of 2; the first session is labeled “R” and the last session is labeled “LR”.

Phase 6: Reinstatement of Nicotine and Mecamylamine Test—Previous work has suggested that the effect of nicotine on interval timing is, at least in pigeons, not mediated by nicotinic acetylcholine receptors (nAChRs; Ward et al., 2009). To determine whether nicotine-induced effects on interval timing in rats are mediated by these receptors, the noncompetitive nAChR antagonist mecamylamine was administered (1.0 mg/kg, s.c.) in 1 of 2 sessions (both similar to those in Phase 5b), 15 min prior to nicotine administration. The session of mecamylamine administration (first or second) was counterbalanced within each group. Nicotine reinstatement and mecamylamine sessions are labeled “NR” and “NM”, respectively.

Data Analysis (Phases 4 and 5)

The following dependent measures of LTS distribution were obtained: median, interquartile range (IQR = difference between third and first quartile, or $Q3 - Q1$), and coefficient of quartile variation [$CQV = (Q3 - Q1) / (Q3 + Q1)$; Kokoska and Zwillinger, 2000, p. 15]. These measures of central-tendency and dispersion are proportional to the mean, standard deviation, and coefficient of variation in Gaussian distributions, but they are substantially more robust (Huber, 1972). Changes in the median reflect changes in timing accuracy whereas changes in the IQR and CQV reflect changes in timing precision.

The hypotheses in Table 1 were evaluated using ANOVA, with median, IQR, and CQV of LTSs as dependent measures. A significance threshold of $\alpha = 0.05$ was used. When sphericity was violated according to Mauchly's test, a Huynh-Feldt correction was implemented.

ANOVA was implemented to assess the statistical significance of the effects of session (B = saline baseline, N1 = day 1 of nicotine, N3 = day 3 of nicotine, R = recovery of baseline), session-half (half 1, half 2), and group (SAME, DIFF) on median, IQR, and CQV of LTSs in Phases 5a-c. Day 2 of nicotine (N2) was not included as a factor of session because the predicted differences in performance during N2 relative to baseline were similar to those in N3; Day 2 data are, nonetheless, presented graphically. Session-half was included as a factor to detect potential within-session changes due to the short half-life of s.c. nicotine (Ghosheh, Dwoskin, Li & Crooks, 1999). Table 2 lists the comparisons conducted and the significant effects (or absence thereof) predicted by each hypothesis.

Results (Phases 4 and 5a: FI FI Training and Saline Baseline)

FI FI performance in Groups SAME and DIFF stabilized at session 26. Fig. 2 shows for each group the mean ($\pm$ SEM) median LTS for the first and second half of the last 5 of the 7 sessions in which stable performance was detected. Figure 1 also shows data for the two subsequent sessions that were each preceded by a saline injection (B1 and B2). In B1 and B2, a significant difference was detected between groups SAME and DIFF in median [$F(1,14) = 21.016$, $p < .001$], IQR [$F(1,14) = 7.540$, $p = .016$], IQR [$F(1,14) = 5.99$, $p = .028$], and CQV [$F(1,14) = 12.186$, $p = .004$] of LTSs. Additionally, there was a main effect of session-half on IQR [$F(1,14) = 4.618$, $p = .051$] and CQV [$F(1,14) = 4.902$, $p = .044$]. In particular, Group SAME had a longer median LTS than group DIFF, and the dispersion of LTSs decreased from session half 1 to half 2. Increasing the reinforcer magnitude in the

longer FI schedule yielded shorter and substantially less variable LTSs. Because no significant effect of session was detected in median, IQR, or CQV of LTSs, half 1 of B1 and B2 were pooled and treated as half 1 of a single session B in subsequent analyses; half 2 of B1 and B2 were also pooled.

Results (Phase 5: Saline Baseline, Nicotine, and Recovery of Baseline)

Table 2 summarizes the results of Phase 5a-c. Details of the statistical analysis are included below.

Median of LTSs

Fig. 3 shows for each group the mean ($\pm$ SEM) median LTS for half 1 and 2 of each session. A significant main effect of group and a significant session $\times$ session-half interaction effect were observed when comparing B and N1 [group: $F(1,14) = 16.374$, $p = .001$; session $\times$ session-half: $F(1,14) = 6.008$, $p = .028$], and B and N3 [group: $F(1,14) = 32.355$, $p < .001$; session $\times$ session-half: $F(1,14) = 13.851$, $p = .002$]. Follow-up t-tests revealed that nicotine significantly shortened median LTSs in session-half 1, but not in session-half 2, of N1 [$t(15) = 2.972$, $p = 0.011$] and N3 [$t(15) = 3.660$, $p = .002$]. Additionally, the median LTSs were shorter in session-half 1 relative to session-half 2 for both N1 [$t(15) = 2.759$, $p = .015$] and N3 [$t(15) = 3.273$, $p = .005$]; this was not detected in session B. These results suggest that the difference between groups (median LTS of group SAME $>$ group DIFF) was retained with nicotine administration, that nicotine did not significantly affect the difference between groups, but transiently shortened LTSs in both N1 and N3.

Comparison of sessions B and R revealed only a significant main effect of group [$F(1,14) = 18.549$, $p = .001$] found in prior comparisons. Comparison of N1 and N3 revealed a significant session-half $\times$ group interaction effect, [$F(1,14) = 6.937$, $p = 0.021$]. Follow up t-tests revealed that LTSs were significantly shorter in session-half 1 relative to session-half 2 only for group DIFF [$t(7) = 3.745$, $p = .007$]. Additionally, group SAME had significantly longer LTSs than group DIFF in session-half 1, [$t(14) = 7.32$, $p < .001$], and 2, [$t(14) = 3.218$, $p = .006$]. These effects are consistent with the notion that nicotine transiently shortened LTSs, particularly in group DIFF, and that the discontinuation of nicotine rapidly recovered but did not exceed baseline performance.

Comparison of sessions N3 and R revealed significant session $\times$ session-half [$F(1,14) = 11.22$, $p = .005$] and session $\times$ group [$F(1,14) = 10.340$, $p = .006$] interaction effects. For the session $\times$ session-half interaction follow up t-tests revealed that discontinuation of nicotine significantly lengthened LTSs within session-half 1 [$t(15) = 4.51$, $p < .001$] but not session-half 2. Additionally, LTSs were significantly longer in session-half 2 than session-half 1, in N3 [$t(15) = 3.27$, $p = 0.005$] but not in R. For the session $\times$ group interaction, follow-up t-tests revealed that discontinuation of nicotine lengthened LTSs for group DIFF [$t(14) = 4.56$, $p = .003$] and group SAME [$t(14) = 3.89$, $p = .006$]. Additionally, group SAME had significantly longer LTSs than group DIFF in session-half 1 [$t(14) = 6.39$, $p < .001$] and 2, [$t(14) = 3.63$, $p = .003$]. These effects further suggest that the transient effect of nicotine of LTSs were rapidly reversed by its discontinuation.

IQR of LTSs

Fig. 4 (top panel) shows mean ($\pm$ SEM) IQRs of LTSs within each session-half for each group. A significant main effect of session-half was observed when comparing B and R, [$F(1,14) = 5.785$, $p = 0.031$], and R and N3, [$F(1,14) = 6.435$, $p = 0.024$]; IQRs were significantly larger in session-half 1 compared to session-half 2. Additionally, a significant main effect of group was found when comparing B and R, [$F(1,14) = 6.425$, $p = 0.024$]; IQRs were larger for group DIFF than for group SAME. The comparison of N1 and N3 revealed a significant session-half $\times$ group interaction effect [$F(1,14) = 5.836$, $p = .031$]. Follow-up t-tests revealed that IQRs were significantly larger in session-half 1 than in session-half 2 [$t(7) = 5.399$, $p = .001$] for group SAME but not group DIFF. Additionally, group SAME had a significantly smaller IQR than group DIFF in session-half 2 [$t(14) = 2.784$, $p = .015$] but not in session-half 1. Comparisons of B and N1 and B and N3 revealed no significant effects. These results suggest that the dispersion of LTSs decreased within each session, were smaller when rewards were equal across FI schedules, but were not significantly affected by nicotine.

CQV of LTSs

Fig. 4 (bottom panel) shows the mean ($\pm$ SEM) CQVs of LTSs within each session-half for each group. The pattern of results is similar to that observed for IQRs: Significant main effects of session-half and group were found for comparisons of B and N1, [session half: $F(1,14) = 6.979$, $p = 0.019$; group: $F(1,14) = 10.79$, $p = 0.005$], B and N3, [session half: $F(1,14) = 7.681$, $p = 0.015$; group: $F(1,14) = 10.758$, $p = 0.005$], B and R [session half: $F(1,14) = 4.530$, $p = 0.052$; group: $F(1,14) = 9.362$, $p = 0.008$], N1 and N3, [session half: $F(1,14) = 6.556$, $p = 0.023$; group: $F(1,14) = 13.02$, $p = 0.003$], and N3 and B, [session half: $F(1,14) = 6.908$, $p = 0.015$; group: $F(1,14) = 7.718$, $p = 0.015$]. CQVs were significantly larger in session-half 1 than in session-half 2, and in group DIFF than in group SAME; no significant effect of nicotine on CQV was detected.

Data Analysis and Results (Phase 6)

ANOVA was implemented on dependent measures obtained in Phase 6 to establish whether acute effects of nicotine on timing performance were replicated and to assess the blocking effects of mecamlamine. The factors analyzed were the same as in Phase 5 (session, half-session, and group), except that factor session had 3 levels, LR = last day of return to baseline saline, NR = nicotine reinstatement, and NM = nicotine + mecamlamine. The predicted outcomes of LR vs. NR and NM vs. NR are the same as those listed in Table 2 under B vs. N1.

Median of LTSs

Fig. 5 shows the effect of nicotine and mecamlamine on median LTSs for each group. Comparison of sessions LR and NM revealed only a significant main effect of group [$F(1,14) = 6.579$, $p = .022$] whereas comparing LR and NR revealed a significant session $\times$ group interaction effect [$F(1,14) = 25.764$, $p < .001$]. Follow-up t-tests for the session $\times$ group interaction effect revealed that for both groups SAME [$t(7) = 4.514$, $p = .003$] and DIFF [$t(7) = 6.506$, $p < 0.001$], nicotine significantly shortened LTSs relative to baseline;

this effect was substantially larger in group DIFF. Additionally, LTSs were significantly shorter in group DIFF compared to group SAME in both sessions LR [$t(14) = 3.633$, $p = .003$] and NR [$t(14) = 6.706$, $p < .001$]; this effect was substantially larger under nicotine. These results reproduce the effects observed when sessions B and N3 were compared in Phase 5b.

Comparison of sessions NR and NM revealed a significant main effect of session-half [$F(1,14) = 16.713$, $p = .004$] and a significant session $\times$ group interaction effect [$F(1,14) = 7.456$, $p = .016$] on median LTSs. Main effects of session-half reproduce those observed in Phase 5. Follow-up t-tests for the session $\times$ group interaction effect revealed that administration of mecamylamine significantly lengthened the LTSs for group DIFF [$t(7) = 4.38$, $p = .003$] but not group SAME. Additionally, group SAME had significantly longer LTSs than group DIFF under nicotine alone [$t(14) = 6.706$, $p < .001$] but not when accompanied by mecamylamine. Thus, it appears that mecamylamine reversed the effects of nicotine for group DIFF more robustly than for group SAME.

IQRs of LTSs

Fig. 6 (top panel) shows the effects of nicotine and mecamylamine on the IQR of LTSs. Comparison of session LR and NR revealed a significant main effect of session-half, [$F(1,14) = 12.445$, $p = .003$] on IQRs of LTSs. Comparison of session LR and NM revealed significant main effects of session-half [$F(1,14) = 28.566$, $p = .012$] and group [$F(1,14) = 8.091$, $p = .013$]. Comparison of NR and NM revealed a significant session $\times$ session-half $\times$ group interaction effect [$F(1,14) = 6.954$, $p = .021$]. Lower order ANOVAs revealed a simple effect of session-half for group SAME [$F(1,7) = 6.15$, $p = .042$] but not for group DIFF. These effects reproduce the changes in IQR of LTSs observed in Phase 5b, which do not involve nicotine, and were therefore not significantly influenced by mecamylamine.

CQV of LTSs

Fig. 6 (bottom panel) shows the effects of nicotine and mecamylamine on the CQV of LTSs. Significant main effects of session-half and group were found when comparing sessions LR and NR [session-half: $F(1,14) = 16.5$, $p = 0.001$; group: $F(1,14) = 7.738$, $p = 0.015$], and LR and NM [session-half: $F(1,14) = 14.423$, $p = .002$; group: $F(1,14) = 9.204$, $p = .009$]. Comparison of sessions NR and NM revealed a significant session $\times$ session-half $\times$ group interaction effect on the CQV of LTSs [$F(1,14) = 6.436$, $p = 0.024$]. Lower order ANOVAs revealed a significant half $\times$ group interaction within both NR [$F(1,14) = 8.067$, $p = .013$] and NM [$F(1,14) = 17.240$, $p = .001$]. Follow-up t-tests revealed for group SAME a significant difference between session halves within the NR session only [$t(7) = 2.754$, $p = .028$] and for group DIFF revealed a significant difference in session halves within the NM session only [$t(7) = 4.884$, $p = .002$]. In both cases, the CQV decreases from the first to the second session-half. Overall, these effects reproduce those observed in Phase 5b. However, the significant two-way interaction effects suggest that nicotine and mecamylamine may differentially affect the CQV depending on whether reinforcement varies across the two schedules.

Temporal Regulation Data Analysis

The preceding analysis assumes that all LTSs are timed—i.e., generated by the algorithm in Appendix A. There is evidence, however, that random responding sometimes contaminates timing performance (Sanabria & Killeen, 2008; Richards, Sabol, & Seiden, 1993; Lejeune & Wearden, 1991). The Temporal Regulation model (Sanabria and Killeen, 2008) provides an analytical method to dissociate timing from non-timing behavior. This dissociation requires the estimation of distribution parameters from a large number of LTSs. Given that, in Phase 5, no significant session effects were observed across sessions B1, B2, and R, or across sessions N1, N2, and N3, it was assumed that LTSs were sampled from one population in each set of sessions. The Temporal Regulation model was thus applied to each of these sets; the Akaike Information Criterion (Burnham and Anderson, 2002) was used to determine which parameters of the distribution of LTSs were likely to vary between sets of sessions (i.e., between saline and nicotine conditions).

The Temporal Regulation model assumes that at the beginning of every trial the rat either enters a timing state with probability q or enters a non-timing state with probability $1 - q$. When rats are in the timing state they emit gamma-distributed *timed* LTSs, according to the algorithm described in Appendix A. When rats are in the non-timing state they emit responses randomly with a constant probability, thus yielding exponentially-distributed *non-timed* LTSs. Consequently, according to the Temporal Regulation model, underlying the distribution of LTSs is a mixture of two shifted distributions,

$$\begin{aligned} p(LTS=t|t<\delta) &= 0 \\ p(LTS=t|t \geq \delta) &= q\Gamma(t - \delta; \varepsilon, c) + (1 - q) \exp(t - \delta; K) \end{aligned} \quad q \geq 0; \varepsilon > 1; c, k > 0 \quad (1)$$

In Eq. 1, the probability of entering a timing state q is the mixture weight of a gamma distribution with shape parameter ε and scale parameter c . Parameter ε is the proportion of the pulse count in memory needed for emission of a response (mN in Appendix A); response-threshold effects are thus expected to be expressed as reduced estimates of ε . Parameter c is the mean time between pulses (Eq. A1-A3); clock-speed effects are thus expected to be expressed as reduced estimates of c . The probability of entering a non-timing state $1 - q$ is the mixture weight of an exponential distribution with mean K . Changes in estimates of q and K reflect non-timing effects of nicotine. Both the gamma and exponential distributions are shifted rightwards to account for the minimum LTS, δ .

A model comparison approach (similar to Avila et al., 2009) was implemented to select between submodels of Eq. 4. Each submodel specifies which combination of parameters (q , ε , c , K) changes across aggregated saline (B1, B2, and R) and nicotine (N1, N2, N3) sessions within each session half (note that significant session-half effects were observed on nicotine sessions in Phase 5b). The submodel that specifies that no parameter change between saline and nicotine sessions corresponds to the null hypothesis. Each submodel was fit to each rat's data in each session half (DIFF-H1, DIFF-H2, SAME-H1, SAME-H2), via the method of maximum likelihood (Myung, 2003), allowing only changing parameters to vary freely between saline and nicotine sessions. Submodels were then compared using AICc. Briefly, AICc favors submodels that provide superior fitness and fewer free

parameters, i.e., those in which nicotine changes fewer parameters. Given the AICc of each submodel, the selection metric AICc was calculated. AICc of submodel X is the AICc of the most likely submodel (the minimum AICc in the set) minus the AICc of submodel X . Thus, the most likely model has a $\text{AICc} = 0$ and all other submodels have a $\text{AICc} > 0$. Among the submodels with $\text{AICc} < 4$, those with fewest parameters were selected (further details are provided in Appendix B).

Temporal Regulation Results

Figure 7 shows the mean empirical cumulative distribution of LTSs in Phase 5 and the mean fit of the AICc-selected Temporal Regulation submodels for groups DIFF and SAME under saline and nicotine within each session-half. The AICc-selected Temporal Regulation submodels provided an adequate fit to the data.

To the extent that nicotine induces a clock-speed effect, it was expected that the AICc analysis would select submodels that specify a reduction in c in groups DIFF and SAME. To the extent that nicotine induces a response-threshold effect, it was expected that the AICc analysis would select submodels that specify a reduction in ε only in group DIFF.

Table 3 shows AICc from the submodel-comparison analysis. Submodels are identified by the parameters specified to change between saline and nicotine sessions. The AICc of selected submodels is underlined. Table 4 shows the mean estimates of parameters for each group within each session-half, according to the selected submodels. For parameters whose estimates varied with nicotine administration, the estimates under saline and nicotine are reported separately (saline $\rightarrow$ nicotine).

In session-half 1, submodels $q\varepsilon$ and qc were selected for group DIFF, and submodels $q\varepsilon K$ and qcK were selected for group SAME. This selection suggests that nicotine influenced non-timing parameters q and, when reinforcers were equal in both schedules, K . In all submodels, q declined with nicotine, but more markedly for group DIFF (40%) than for group SAME (10%), even though group DIFF had a lower baseline q (.47) than group SAME (.78). Whereas for group DIFF baseline K was high (3.36 s) and not significantly affected by nicotine, for group SAME baseline K was low (~ 1.3 s) and nicotine more than doubled it, approaching estimates of group DIFF. Timing parameters also appear to be affected by nicotine, but it is unclear which parameter is primarily affected, ε or c . All selected submodels suggest that one timing parameter declined with nicotine.

In session-half 2, submodels qK and cK were selected for group DIFF, and submodel εcK was selected for group SAME. This selection suggests that nicotine influenced non-timing parameters K and, when reinforcers were different across schedules, possibly q . For group SAME, nicotine induced an increase in c with a seemingly compensatory reduction of ε to low levels comparable to those of group DIFF. For group DIFF nicotine may have also increased c but without a compensatory change in ε .

Taken together, the selected submodels for session-halves 1 and 2 suggest that nicotine reduced the proportion of timed LTSs, and this effect may have lasted longer in the session for group DIFF than for group SAME. Without nicotine, non-timed LTSs lengthened over

the course of the session for group SAME, but were constantly long for group DIFF. Nicotine accelerated this process for group SAME, but also shortened non-timed LTSs later in the session in both groups. The effects of nicotine on the parameters of timed LTSs in session-half 1 do not select between the response-threshold and clock-speed hypotheses, because both are feasible under the selected submodels; the response-threshold hypothesis is supported by the $q\epsilon$ and $q\epsilon K$ submodels of DIFF-H1 and SAME-H1, and the clock-speed hypothesis is supported by the qc and qcK submodels of DIFF-H1 and SAME-H1. In contrast, the parameters of timed LTSs in session-half 2 suggest a late, nicotine-induced deceleration of the internal clock in group SAME and possibly in group DIFF.

Discussion

The primary purpose of the present study was to determine whether the acute administration of nicotine speeds up the internal clock or lowers the threshold of the target timing response, and thus constrain the range of potential neurobiological mechanisms underlying the effect of nicotine on timing. These competing hypotheses were assessed using three dependent measures derived from rats' performance on a concurrent dependent FI 8-s FI 16-s schedule of reinforcement: median LTSs, IQR of LTSs, and CQV of LTSs. The pattern of results obtained largely supports the response-threshold hypothesis of nicotinic effects on timing (Table 2): nicotine induced an immediate and sustained reduction of median LTS, especially when the FI 16-s reinforcer was larger than the FI 8-s reinforcer.

The only effect consistent with the clock-speed hypothesis was a transient reduction in median LTS on the first session of nicotine injections, regardless of the difference in reinforcer magnitude across FI schedules. Further, this effect was not replicated with the first injection following 4 days without nicotine. In that replication, nicotine reduced median LTSs more noticeably when reinforcement was larger in the longer FI schedule. This selective effect of nicotine was also observed when nicotine administration was discontinued (Phase 5c). Additionally, the clock-speed hypothesis predicts that the effect of nicotine should wane over repeated administrations and that, on the first saline session following nicotine administration, the median LTS should exceed baseline levels. Neither of these effects was observed.

Selective nicotine-induced reductions in the central tendency and dispersion measures of LTSs provide ostensible support for the clock-speed hypothesis. If memory is assumed to be quickly reconditioned with new pulse counts, then the clock-speed hypothesis predicts the observed within-session changes in LTS distribution. However, the clock-speed hypothesis does not explain why the effect of nicotine on median LTSs was generally more visible when reinforcement varied between the two schedules. Additionally, it does not explain why within-session changes in timing precision yielded shorter CQVs (the clock-speed hypothesis predicts constant CQVs; the response-threshold hypothesis predicts longer CQVs), and why changes in the dispersion of LTSs occur at baseline. An alternative, simpler, explanation of these effects is that, as nicotine metabolizes (its half-life is roughly 70% of the duration of each session, 52 min, Ghosheh, Dwoskin, Li & Crooks, 1999), baseline performance is recovered.

The reinstatement of nicotine and the mecamylamine test indicates that nAChRs are involved in determining the response threshold. Nicotine selectively reduced LTSs when reinforcers were unequal across schedules and mecamylamine reversed this effect. This reversal suggests that the nicotine-induced reduction in response threshold is mediated by nAChRs, most likely by those containing $\beta 2$ and $\beta 4$ subunits. In other words, it appears that nicotinic cholinergic receptors, aside from possibly modulating the memory of timed intervals (Cheng, Meck, & Williams, 2006; Meck, 2002; Meck & Williams, 1997; Meck & Church, 1987), also modulate the threshold for emitting a response. It is possible that these nAChR-dependent cognitive effects of nicotine are related to the nAChR-dependent enhancement of reinforcer efficacy (Paterson, 2009; Liu, Palmatier, Caggiula, Donny, Sved, 2007; Chen, Nakamura, Kawamura, Takahashi, & Nakahara, 2006). The nature of this relation, however, requires further investigation.

Mecamylamine-induced blocking of nAChRs largely recovered baseline performance, with one exception: the smaller reduction in LTSs induced by nicotine when reinforcers were equal across schedules was not reverted by mecamylamine. Despite the absence of a mecamylamine-induced reversal, this effect may be nAChR-dependent, because mecamylamine binds to allosteric sites rather than to sites for which nicotine has a high affinity. Further research utilizing competitive antagonists (e.g. Charntikov, Swalve, Pittenger, Fink, Schepers, Hadlock, Fleckenstein, Hu, Li, & Bevens, 2013) is needed to determine which receptor types are modulating the response-threshold.

Although many of the effects observed in the present study are consistent with the response-threshold hypothesis, few nicotinic effects on measures of LTS dispersion are consistent with the response-threshold hypothesis (Table 2). That is, the reduction in LTS dispersion predicted to accompany the overestimation of time was not observed. The clock-speed and response-threshold hypotheses predict opposite directions in the effect of repeated nicotine administration on CQVs, so the concurrence of a clock-speed and response-threshold effect may explain the absence of significant effects of nicotine on this dependent measure. However, neither one of these effects, separately or concurrently, may explain the absence of a significant reduction in IQRs with nicotine.

A closer examination of the data suggests that acute nicotine selectively reduced IQRs in the first half of the FI FI sessions of DIFF rats (Figures 3 and 5, top panels). This effect may have been too small for statistical significance, but it was sufficient to compensate for the decline in median LTS, and thus yield relatively unaffected CQVs. Such selective change in IQR would be consistent with the response-threshold hypothesis, and not with the clock-speed hypothesis.

The Temporal Regulation model suggests an explanation for the robustness of LTS dispersion measures against nicotinic disruption. Nicotine appears to have substantial non-timing effects; most noticeable among these effects is an immediate reduction in q , the proportion of temporally-controlled behavior, which is particularly drastic and durable when reinforcers vary across schedules. Based on mean estimates reported in Table 4, while on nicotine in the first half of the session, and regardless of group, the standard deviation of timed LTSs was substantially lower ($\epsilon_c \approx 2$ s) than the standard deviation of non-timed

LTSs ($K \approx 3$ s). This means that a nicotine-induced reduction in the proportion of timed LTSs may have increased the overall dispersion of LTSs. This increase in dispersion induced by the decrease in the proportion of timed LTSs likely compensated for the increase in precision induced by nicotinic effects on timing parameters corresponding to an increase in clock speed (decrease in c) or a decrease in the response-threshold (decrease in ϵ). The reduction in the response-threshold and the increase in clock-speed is supported by different submodels selected for performance in the first half of sessions.

The effects of nicotine on q and K for the selected submodels are consistent with an alternative explanation of the observed effects of nicotine on the distribution of LTSs. According to the rate-dependency hypothesis, the effect of a drug depends on the rate of the behavior in the absence of the drug (Odum, 2002; Dews, 1958, 1981; Byrd, 1979). Specifically, it predicts that drug administration increases low response rates early in the timed interval and reduces high response rates later in the timed interval, resulting in a loss of temporal-control not specific to the timing mechanism (Saulsgiver, McClure, & Wynne, 2006; McClure, Saulsgiver, & Wynne, 2005; Ward et al., 2009; Ward & Odum, 2005; Odum, 2002; Odum, Lieving & Schaal, 2002; White & Ganguzza, 1985). The loss of temporal control suggested by this hypothesis is evidenced in the decrease in q observed for all selected submodels. Taken together, the data are best explained by both the response-threshold and the rate-dependency hypothesis.

The interference of nicotine-induced non-timing effects on timing performance is not unique to the concurrent FI FI paradigm. These effects are also visible in the temporal bisection procedure (Ward et al., 2009; McClure et al., 2011). It is likely that these effects are also present in the peak interval procedure. In peak interval performance, Roberts (1981) identified a linear increase in response rate over time since the last reinforcer; this pattern appears to be insensitive to the target interval. These components of peak-interval performance are rarely disentangled, which undermines the interpretation of peak interval performance in terms of timing, as suggested by research on the effects of motivational manipulations on peak-interval performance (Sanabria et al., 2009; Ludvig, Conover, Shizgal, 2007; Galtress & Kirkpatrick, 2009).

The observed effect of nicotine on the response-threshold is also consistent with the effects of nicotine on the performance of rats in other timing tasks that involve response withholding, such as the lever-holding task (Popke, Mayorga, Fogle, & Paule, 2000), the fixed-minimum interval schedule of reinforcement (Mazur et al., 2014), and the differential reinforcement of low rates schedule (Kirshenbaum, Jackson, Brown, Fuchs, Miltner, Doughty, 2011; Kirshenbaum, Johnson, Schwarz, & Jackson, 2009; Kirshenbaum, Brown, Hughes, Doughty, 2008; Popke et al., 2000). In these tasks, animals must withhold a response for a fixed interval to obtain reinforcement, and typically produce withholding intervals that are close to the withholding requirement. These withholding intervals are reduced immediately upon the administration of nicotine, and do not return to baseline levels with repeated administration (Kirshenbaum et al., 2008).

In conclusion, the present data suggests that clock-speed accounts of nicotine effects on timing are incomplete, at best. The reported effects of nicotine, and its discontinuation, on

timing accuracy (median LTSs) provide more support for a response-threshold account of timing under nicotine, mediated by nAChRs. The latter account is consistent with the notion that nicotine is detrimental to response-withholding capacity (e.g., Mazur et al., 2014; Kirshenbaum et al., 2008; Popke et al., 2000) and suggests the involvement of nAChRs in this capacity. The reported effects of nicotine, and its discontinuation, on timing precision (IQR and CQV of LTSs) are inconsistent with current timing models. Furthermore, although analysis of LTSs with the Temporal Regulation model did not differentiate between the clock-speed and response-threshold hypotheses, it suggest an explanation for the robustness of timing precision against nicotinic disruption, which is inconsistent with the clock-speed or response-threshold hypotheses. These results show that appropriate behavioral paradigms, such as the concurrent FI FI, accompanied by model-driven analysis, can isolate timing from non-timing components of performance, and may guide future research to empirically isolate pharmacological effects on timing capacity.

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Appendix A

The basic computational structure of interval timing has the following components:

- (1) A pacemaker that emits pulses. Inter-pulse intervals are sampled from an exponential distribution with mean c .
- (2) An accumulator of pulses.
- (3) A long-term memory of pulse counts. Upon reinforcement (i.e., positive feedback) the value of the accumulator updates memory and the accumulator is reset. The mean pulse count in memory is m .
- (4) A response threshold N . When the pulse count in the accumulator is mN , the target response is emitted.

A well-trained algorithm with a low memory-updating rate would maintain a constant mean pulse count in memory of m . Under this assumption, the algorithm yields an Erlang distribution of response times, with parameters

$$\mu = mNc, \quad (\text{A1})$$

$$\sigma = \sqrt{(mN)} c, \quad (\text{A2})$$

and

$$CV = \sigma / \mu = \sqrt{(1/mN)}. \quad (\text{A3})$$

If non-integer pulse counts are allowed, these parameters correspond to those of a gamma distribution (Forbes et al., 2011).

Speeding up the clock (i.e., reducing c) and lowering the response threshold (i.e., reducing N), both result in shorter mean response times (i.e., lower μ) with reduced dispersion (i.e., lower σ). Speeding up the clock, however, does not affect the coefficient of variation (CV), whereas lowering the response threshold yields a higher CV .

Training with a faster clock yields a higher pulse counts in the accumulator upon reinforcement, thus progressively increasing m in memory relative to baseline (when the clock ran slower). Thus, over the course of training under a faster clock, m is expected to increase such that baseline μ is eventually recovered, baseline σ is partially recovered, and CV declines over training. Once μ , σ , and CV are stabilized under fast-clock training, a return to baseline speed of the clock would result in an immediate increase in μ and σ beyond baseline levels, but no immediate change in CV . Discontinuation of fast-clock training yields pulse counts in the accumulator upon reinforcement that are lower than those in memory, yielding a progressive decline of m . Thus, over the course of training following the discontinuation of fast-clock training, μ and σ progressively decline toward baseline levels, and CV progressively increases toward baseline levels.

In contrast, training with a lower response threshold does not affect the pulse counts in the accumulator, and therefore does not affect memory. Thus, over the course of training under a lower response threshold, μ and σ are expected to remain low and CV is expected to remain high. Discontinuation of low-threshold training is expected to recover baseline performance immediately.

Appendix B

The submodel with $AICc = 0$ was constrained such that free parameters across rats changed in the same direction between saline and nicotine conditions. For example, if the most likely model was qK , then one potential constrained submodel would specify that nicotine decreases q and increases K for all rats and another might specify that nicotine increases q and increases k for all rats. If the constrained submodel had a higher $AICc$ than other, unconstrained submodels, then those submodels were constrained for further comparison. This analysis specified $2^4 \text{ parameters} = 16$ unconstrained submodels plus up to $3^4 = 81$ constrained submodels. The constrained submodel with the lowest $AICc$ and fewest free parameters was selected as providing the best balance between fit and parsimony. However, other models were considered just as likely if they had the same number or fewer free parameters as the selected constrained submodel and $AICc$ was not larger than 4 units. Note that this threshold is recommended by previous researchers because a submodel with $AICc = 4$ is e^2 or roughly 7 times less likely than a submodel with $AICc = 0$ (Brackney, Cheung, Neiswander, & Sanabria, 2011; Burnham & Anderson, 2002).

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Highlights

- Tested two competing hypotheses of nicotinic disruption of interval timing in rats
- Timing was permanently disrupted under a regimen of acute nicotine administration
- Mecamylamine reverses the observed disruption of timing behavior
- Nicotine appears to decrease the threshold for responding in a timing paradigm

Figure 1.

Timeline of events. Rats arrived on post-natal day (PND) 60; after a two-day acclimation period to the colony room, rats were acclimated to the operant chambers for two days beginning on PND 62. Lever press was shaped on PND 64, and reinforced on a continuous reinforcement schedule on PND 65. Training with different reinforcer magnitudes began on PND 71, which was followed by training on a dependent FI 8 s FI 16 s schedule of reinforcement beginning on PND 75. After 26 sessions of FI FI training, a saline baseline (B) was established on PND 101-102, nicotine testing (N1-N3) began on PND 103, followed by a return to saline baseline (R) on PND 106. PND 109 was the last day of saline baseline (LR); it was followed by reinstatement of nicotinic disruption of interval timing (NR) and antagonism of nicotinic disruption by mecamylamine administration (NM). The order of NR and NM was counterbalanced across rats.

Figure 2.

Mean ($\pm$ SEM) latency to switch (LTS) for each group within each session half. Sessions -5 through -1 are the last 5 of the 7 sessions in which stability was detected. Sessions B1 and B2 are baseline saline sessions.

Figure 3.
Mean ($\pm$ SEM) median LTS for each group within each session half within sessions B (saline baseline), N1, N2, N3 (0.3 mg/kg s.c. nicotine), and R (recovery of baseline).

Figure 4.

Top Panel: Mean ($\pm$ SEM) interquartile range (IQR) of LTSs as a function of session (B = baseline, N = 0.3 mg/kg s.c. nicotine, R = recovery of baseline), for each group (SAME and DIFF) within each session half. Bottom Panel: Mean ($\pm$ SEM) coefficient of quartile variation (CQV) of LTSs as a function of session, for each group within each session half.

Figure 5.

Mean ($\pm$ SEM) median LTSs for each group within each session half as a function of session (LR = baseline, NR = 0.3 mg/kg s.c. nicotine, NM = nicotine + 1.0 mg/kg s.c. mecamylamine).

Figure 6.

Top Panel: Mean ($\pm$ SEM) interquartile range (IQR) of LTSs as a function of session (LR = baseline, NR = 0.3 mg/kg s.c. nicotine, NM = nicotine + 1.0 mg/kg s.c. mecamylamine), for each group (SAME vs. DIFF) within each session-half. Bottom Panel: Mean ($\pm$ SEM) coefficient of quartile variation (CQV) of LTSs as a function of session, for each group within each session half.

Figure 7.

Empirical cumulative distributions of LTSs presented separately for each drug (saline vs. nicotine, in separate curves) in each group $\times$ session-half cell (DIFF-h1, DIFF-h2, SAME-h1, SAME-h2), along with corresponding mean fits of the most likely submodel of the TR model (Eq. 1 and Table 3). In cases where two submodels were equally likely, the submodel with the smallest AICc was fit to the data. Data are organized in 40 equally sized bins. The TR model provides an adequate fit to the data.

Table 1

Predictions of clock-speed and response-threshold hypotheses

Hypothesis		Immediate Effect		After Training		Upon Discontinuation	
Group		SAME	DIFF	SAME	DIFF	SAME	DIFF
Clock-speed							
Accuracy	μ	↓	↓	=	=	↑	↑
Precision	ρ	↓	↓	↓	↓	↑	↑
	CV	=	=	↓	↓	↓	↓
Response-Threshold							
Accuracy	μ	=	↓	=	↓ _a	=	=
Precision	ρ	=	i	=	i	=	=
	CV	=	↑	=	↑	=	=

Note. Symbols indicate direction of change in dependent measures of the distribution of LTSs (μ = mean, ρ = standard deviation, CV = coefficient of variation = μ/ρ) relative to baseline. ↓ means reduced; = means no change; ↑ means increased.

Table 2

Predicted outcome of Planned Comparisons for Phases 5a-c

		Comparison				
Hypothesis		B vs. N1	B vs. N3	B vs. R	N1 vs. N3	N3 vs. R
Clock-speed						
Accuracy	median	B > N1 [*]	n.s.	B < R	N1 < N3	N3 < R
Precision	IQR	B > N1	B > N3	B < R	N1 < N3	N3 < R
	CQV	n.s.	B > N3	B > R	N1 < N3	n.s.
Response-Threshold						
Accuracy	median	B > N1 (DIFF) [‡]	B > N3 (DIFF)	n.s. [*]	n.s. [*]	N3 < R (DIFF) [*]
Precision	IQR	B > N1 (DIFF)	B > N3 (DIFF)	n.s. [*]	n.s. [*]	N3 < R (DIFF)
	CQV	B < N1 (DIFF)	B < N3 (DIFF)	n.s. [*]	n.s. [*]	N3 > R (DIFF)

Note. “X > Y” indicates a significant difference between levels X and Y of factor session (B = saline baseline, N1, N3 = first and third day of 0.3 mg/kg s.c. nicotine, and R = recovery of baseline), and the direction of the effect. “X > Y (DIFF)” indicates a significant session x group interaction effect, whereby the difference between levels X and Y is larger in level DIFF than in level SAME of factor group. IQR = interquartile range. CQV = coefficient of quartile variation. n.s. = no statistically significant difference.

^{*}Data in Phase 5 was consistent with predicted outcome.

[‡]Data in Phase 6 was consistent with predicted outcome (B vs. N1 only).

Table 3

δ AICc for submodels of each group within each session-half.

Model	Group			
	DIFF-H1	SAME-H1	DIFF-H2	SAME-H2
None	187.94	240.45	14.16	473.85
q	9.62	224.38	12.25	219.49
ε	61.06	77.72	11.01	51.97
c	62.62	77.66	11.33	126.29
K	86.32	227.21	6.54 (29.27)	367.36
q, ε	<u>0.00 (1.44)</u>	63.77	11.37	55.33
q, c	<u>0.07 (1.23)</u>	63.39	11.29	101.71
q, K	7.19	169.52	<u>0.06 (3.12)</u>	175.16
ε, c	60.27	35.63 (123.98)	21.70	16.18
ε, K	68.33	69.85	4.70 (39.44)	25.92
c, k	70.15	67.94	<u>4.99 (4.99)</u>	95.84
q, ε, c	18.82	22.19 (102.01)	12.52	19.71
q, ε, K	1.25	<u>47.11 (47.11)</u>	0.00 (46.42)	25.13
q, c, K	1.15	<u>43.94 (43.94)</u>	0.00 (19.29)	70.80
ε, c, K	112.55	18.86 (103.29)	13.01	<u>0.00 (9.38)</u>
q, ε, c, K	51.40	0.00 (59.64)	2.93	3.11 (9.17)

Note. Submodels are labeled with the parameters that could vary freely between saline and nicotine conditions (row headers). δ AICc is indicative of the relative likelihood of a submodel within each session-half (column headers); lower δ AICc indicate higher relative likelihood. δ AICc in parentheses is the δ AICc of the constrained version of that submodel (see Appendix B). Selected submodels (those with lowest number of free parameters among those with δ AICc < 4) are underlined.

Table 4

Mean (+/- SEM) estimates of distribution parameters of LTS for each group within each session-half.

Group	Model	Parameters				
		q	ε	c (ms)	K (ms)	δ (ms)
DIFF-H1	q, ε	.47(.03)→.28(.04)	43.79(6.96)→41.28(7.07)	31(4)	336(49)	19(6)→23(3)
	q, c		43.08(7.04)	31(4)→29(3)		
SAME-H1	q, ε, K	.78(.05)→.70(.05)	41.55(2.99)→37.89(2.92)	33(4)	137(24)→289(39)	23(5)→39(12)
	q, c, K		39.01(2.78)	35(4)→31(3)	129(19)→300(41)	
DIFF-H2	q, K	.53(.05)→.46(.04)	34.61(5.05)	37(5)	402(55)→357(55)	27(4)→29(6)
	c, K	.53(.05)		37(5)→46(4)		
SAME-H2	ε, c, K	.80(.03)	56.9 7(6.05)→32.54(4.75)	24(4)→35(3)	350(108)→186(42)	28(4)→135(102)

Note. Parameter estimates are based on AIC-selected submodels for each group within each session-half. Two submodels are shown for DIFF-H1, SAME-H1, and DIFF-H2 because their likelihood was similar. The arrows indicate likely changes in the mean estimates of a parameter between conditions (Saline → Nicotine); absence of arrows indicates that mean parameter estimates were likely constant across saline and nicotine conditions. Parameter δ is the minimum LTS in the data set and thus not a free parameter. Units of free parameters are in parentheses in column headers.