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Research report

Revisiting the effect of nicotine on interval timing

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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.

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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 pretreatment and nicotine discontinuation 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.

Most theories of timing in the seconds-to-minutes timescale—*interval timing*—are based on a simple computational structure [1–8]. 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 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 [9–12]; 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 [13,14,63,72] 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 [15–17] suggests that nicotine influences timing performance,

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[1] These two effects may also be conceptualized in signal-detection terms [93]. Clock-speed effects are akin to changes in discriminability (increase in clock speed reduces variability in timing [94] and response-threshold effects are akin to changes in decision bias (lowering the response threshold increases false positives).

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similarly to other psychostimulants [18,19,75,76,83], 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 3–4 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 [14]). 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 [20,95]; methamphetamine appears to have the opposite effect [21]. 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 [22,96–98].

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 stop-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 [99]. If stimulant effects operate only on start-times, then it is not possible to dissociate clock-speed from response-threshold effects in peak-interval performance; a leftward shift in start-times is sufficient to produce a leftward shift in peak time [95]. 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 [23,71]. 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 [100]. The evidence for nicotine-induced clock-speed effects obtained from the temporal bisection procedure is mixed at best. One study [24] reports such an effect. Two other studies [25,26] 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 alternatives: “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 [9] 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 [88]. 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. [27]); 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. [28]). 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 drawn from 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 yields 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