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Modeling the Effects of the NMDA Receptor Antagonist MK-801 on Timing in Rats

J. Devin McAuley, Jonathan P. Miller, and Kevin C. H. Pang
Bowling Green State University

The NMDA receptor antagonist MK-801 produces different effects on timing tasks. In particular, MK-801 produces an underestimation of duration when animals are tested with the differential reinforcement of low rate of responding (DRL) schedule and an overestimation of duration when animals are tested with the peak-interval (PI) procedure. The goal of this study was to develop a model-based explanation for this discrepancy. Two computer simulations were conducted via an implementation of scalar expectancy theory (SET). In Simulation 1, SET was used to provide a quantitative account of PI timing data. Simulation 2 used parameter estimates from Simulation 1 to predict effects of MK-801 on the DRL task. DRL predictions provided a close match to previous empirical data. Results of the simulations suggest that differences in the literature are likely due to inherent differences between PI and DRL tasks, rather than fundamental differences in timing. Overall, the role of NMDA receptors in timing appears to be multifaceted, impacting perception, memory, and decision processes.

Keywords: timing, scalar expectancy theory, NMDA receptors, MK-801

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N-methyl-D-aspartate (NMDA) glutamate receptors are important for learning, memory, and synaptic plasticity (Morris, 2003; Morris, Anderson, Lynch, & Baudry, 1986; Shapiro & Caramanos, 1990; Shapiro & O'Connor, 1992). Less is known about their role in timing and temporal processing. Evidence that NMDA receptors influence timing comes from investigations of NMDA antagonists in a differential reinforcement of low rate of responding (DRL) task and a peak-interval (PI) procedure (Miller, McAuley, & Pang, 2006; Sanger, 1992; Stephens & Cole, 1996; Tonkiss, Morris, & Rawlins, 1988; Welzl, Berz, & Battig, 1991).

In the DRL task, chronic intracerebroventricular infusions of the competitive NMDA antagonist D,L-2-amino-5-phosphonopentanoic acid (AP5) decreases efficiency (the number of reinforcements delivered relative to the total number of responses) and produces a leftward shift in the distribution of interresponse times (IRTs; Tonkiss et al., 1988). Similar results are found with acute systemic injections of the noncompetitive NMDA receptor antagonist MK-801 (dizocilpine). The leftward shift in IRT distributions has been interpreted as a disruption in internal timing (Meck, 1996; Tonkiss et al., 1988; Welzl et al., 1991).

From the perspective of scalar timing models, a leftward shift in the IRT distribution (corresponding to underestimation of duration) can arise from an increased speed of an internal clock or a systematic distortion in the memory of the previously rewarded duration such that the subjective experience of the rewarded duration is shorter than the actual duration (Church, 1984; Gibbon, Church, & Meck, 1984; Meck, 1996). However, because MK-801 and other NMDA receptor antagonists can increase general activity (Adriani et al., 1998; Mele et al., 1996; Miller et al., 2006; Tonkiss et al., 1988; Whishaw & Auer, 1989; Wozniak, Olney, Kettinger, Price, & Miller, 1990), an alternative explanation of a leftward shift in IRTs is that it indicates a general reduction in the ability to withhold (inhibit) a response (Wiley, Compton, & Golden, 2000). This alternative explanation is important because DRL performance does not clearly separate changes in internal timing from changes in response inhibition.

However, evidence from signaled and unsignaled DRL tasks suggests that MK-801 affects both response inhibition and timing (Welzl et al., 1991). To further address this issue, Miller et al. (2006) examined the effects of MK-801 on timing using the PI procedure, rather than the DRL task. In the PI procedure, animals must time the duration of a stimulus and develop a memory for this duration, similar to the DRL task. However, unlike the DRL task, animals are free to emit any number of responses without affecting when reinforcement will be delivered. As a result, the peak time of responding (a measure of timing) is dissociable from the overall rate that an animal responds (Roberts, 1981). Similar to DRL performance, Miller et al. (2006) found that for the PI task, MK-801 increased response rate consistent with reduced response inhibition. However, in contrast to DRL performance, the highest tested dose of MK-801 (0.2 mg/kg) produced an overestimation of duration (associated with a rightward shift in peak time), rather than an underestimation of duration. On the basis of this research, MK-801 appears to produce consistent effects on response inhibition across tasks but opposite effects on timing; however,

J. Devin McAuley, Jonathan P. Miller, and Kevin C. H. Pang, J. P. Scott Center for Neuroscience, Mind and Behavior and Department of Psychology, Bowling Green State University.

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Correspondence concerning this article should be addressed to J. Devin McAuley, Department of Psychology, Bowling Green State University, Bowling Green, OH 43403. E-mail: mcauley@bgnet.bgsu.edu

see Saulsgiver, McClure, and Wynne (2006) for an interpretation of peak time shifts in the PI procedure that does not involve changes in internal timing.

The goal of the present study was to develop a model-based explanation for the observed discrepancy between the effects of MK-801 on PI and DRL task performance. A formal implementation of scalar expectancy theory (SET) was used for two simulations (Church, 1984; Gibbon, 1977; Gibbon et al., 1984). Simulation 1 provides a quantitative description of the effects of MK-801 on PI timing data. Simulation 2 uses the resulting parameter estimates from Simulation 1 to predict the effects of MK-801 on timing in the DRL task.

Formal Implementation of SET

SET is a commonly used information processing model of timing that involves three processes: perception, memory, and decision (Church, 1984; Gibbon, 1977; Gibbon et al., 1984). Perception of time consists of a clock, a switch, and an accumulator. The clock emits a stochastic series of pulses that enter the accumulator via a switch. At any given instant, the number of pulses in the accumulator provides a representation of duration coded as a *count*. Upon delivery of reinforcement, the count in the accumulator is transferred to memory and the accumulator is reset. With training, the memory consists of a distribution of counts associated with the time of reinforcement. The decision process is based on three inputs: the current accumulator count (a), a random sample of the time of reinforcement obtained from memory (m), and a threshold value (b, randomly sampled from a distribution of thresholds). A response is made whenever the absolute difference between the accumulator count (a) and the memory sample (m) is smaller than the threshold value (b), according to the following rule: $|a - m|/m < b$. Otherwise no response is made.

In order to simulate the PI and DRL tasks, we modified a published implementation of SET (Church, 2003). The standard version of SET has seven parameters. The perception process has an associated clock speed (Λ) with standard deviation (σ_Λ). The Λ and σ_Λ parameters determine the average rate at which clock pulses are accumulated and the variability of number of accumulated pulses, respectively. When a reinforcement is delivered, the count in the accumulator is stored in memory following a transformation that multiplies the count by a constant (K^*) with standard deviation (σ_{K^*}). The K^* and σ_{K^*} parameters determine the accuracy and variability of temporal memory, respectively. The threshold value (b) associated with the decision process has standard deviation (σ_b). Together, the b and σ_b parameters determine when a response will be made. Finally, the standard implementation of SET requires a base rate of response parameter (BR) that is greater than 0. This parameter determines the probability of a response independent of timing. In addition to these seven parameters, we added a memory size parameter (N), which determined the maximum number of samples stored in memory. Removal from memory was performed using a first-in/first-out procedure. All simulations were programmed in Matlab (Version 6.5, Release 13.0.1) and run on a Dell (Optiplex GX260) computer with a 2.66-MHz processor and 512 MB of RAM. The Matlab code used for the PI simulation is included in the online supplement to this article.

Simulation 1: Effects of MK-801 on PI Performance

The simulations were designed to match the training and testing procedures of Miller et al. (2006, Experiment 2). Ten simulated sessions of fixed-interval (FI) training on a 12-s FI (≈70 FI trials per session) were followed by 30 simulated sessions of PI training (≈35 FI and ≈35 probe trials per session). Following training, five test blocks of PI trials (5 sessions each) were simulated. The five test blocks corresponded to Days 1–5 (baseline), Days 6–10 (Drug Block 1), Days 11–15 (Drug Block 2), Days 16–20 (Drug Block 3), and Days 21–25 (postdrug) of Miller et al. (2006, Experiment 2). Separate simulations were conducted for each animal in the saline and MK-801 groups. After normalizing the results of each simulation by maximum rate of responding, we averaged temporal response functions across simulated rats for each test block.

Quantitative model fits to the temporal response functions (averaged across simulated rats) were first performed on the baseline data (Days 1–5) of the saline and MK-801 groups. Initial values for the parameters were chosen from previous studies (Church, 2003; Meck, 1983). The maximum size of memory was fixed at $N = 53$ for all simulations; this value was determined from data showing Fisher-344 rats are able to learn a new temporal criterion within approximately 53 FI trials (Miller, 2005). We performed a systematic search of the parameter space to minimize the root-mean-square error of approximation (RMSEA) between the simulated and actual temporal response profiles. After minimizing RMSEA for the baseline data, we held parameter values for the saline group constant across the four test blocks (Drug Blocks 1–3 and the postdrug block). For the MK-801 group, however, we considered the necessary parameter changes needed to account for the effects of MK-801 on PI performance in each of the three drug blocks; parameter values were then returned to baseline values for the postdrug block.

Comparisons of empirical (Miller et al., 2006, Experiment 2) and simulated data from the PI procedure are shown in Figure 1 (Panels A and B show results for the saline group; Panels C and D show results for the MK-801 group). Overall, excellent fits to the empirical data were obtained for both the saline and MK-801 groups. Parameter estimates, RMSEA, and R^2 values for the best fitting model are reported in Table 1. The parameter values that best fit the empirical baseline curves for the saline and MK-801 groups were the same for all of the parameters except the memory storage constant, K^*. Nonetheless, values of K^* for both groups were very close to 1.0, which corresponds to perfect accuracy (peak time = 12 s).

We were particularly interested in whether the effects of MK-801 on PI performance could be explained simply by a general reduction in response inhibition or another single factor. To investigate this possibility, we conducted a series of simulations involving single parameter manipulations, including the base rate parameter, BR; manipulation of the BR parameter would address a potential response inhibition explanation of the PI data. Neither BR nor any other single factor in SET provided a good account of the empirical data; see Miller (2005) for a summary of the results of these simulations and for a discussion of potential single-factor explanations of the effects of MK-801 on PI performance.

To provide a good quantitative account of the effects of MK-801 on PI performance, we had to alter five of the eight parameters. Specifically, the simulation of the effects of MK-801 required a

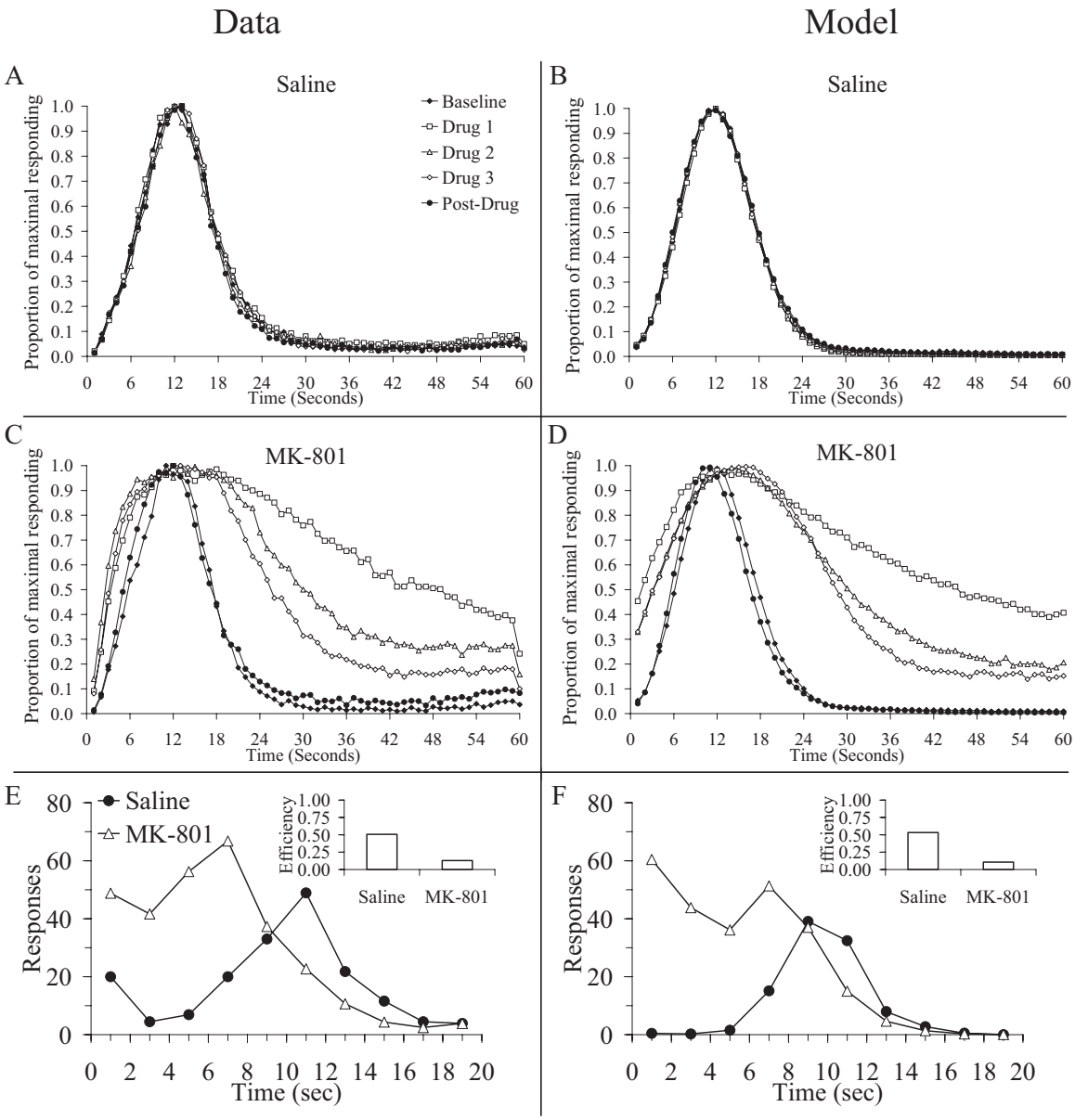

Figure 1. A comparison of observed and simulated temporal response profiles. Panels A–D summarize the results of the peak-interval simulation (Simulation 1), and Panels E and F summarize the results of the differential reinforcement of low rate of responding simulation (Simulation 2).

slower and more variable clock (corresponding to a decrease in mean clock speed and an increase in clock speed variability), a systematic overestimation of time (corresponding to an increase in the memory storage constant, K^*), and a decreased response inhibition (corresponding to an increase in BR and an increase in the mean threshold value). Of these parameters, only clock speed variability was required to vary across drug block to obtain good fits to the empirical data. Changes in variability of clock speed were necessary to account for differences in the tails of the response profiles across drug blocks. Following an initial increase, clock speed variability decreased across drug blocks ($\sigma_\Lambda = 1.450$ for Drug Block 1, $\sigma_\Lambda = 0.600$ for Drug Block 2, and $\sigma_\Lambda = 0.200$ for Drug Block 3; see Table 1). Overall, the results of Simulation 1 suggest that the effects of MK-801 on PI timing are multifaceted, impacting perception, memory, and decision processes.

Simulation 2: Effects of MK-801 on DRL Performance

In Simulation 2, we determined whether parameters obtained from the simulations of the PI procedure (Simulation 1) would accurately predict the pattern of performance observed for the DRL task (Kramer & Rilling, 1970; Zeiler, 1977). In a DRL task, rats are trained to emit an operant response (such as a lever press) after the passage of a fixed amount of time (a target interval).

Table 1
Parameter Estimates, RMSEA, and R^2 Values for a Scalar Expectancy Theory Simulation of Miller et al.'s (2006) Experiment 2

Simulation 1: PI task	Parameter estimates: Clock Λ	Clock σ_Λ	Memory K^*	Memory σ_{K^*}	Decision b	Decision σ_b	Decision BR	Model fit RMSEA	Model fit R^2
				Saline					
Baseline	**5.206**	**0.000**	**0.985**	**0.150**	**0.420**	**0.280**	**0.001**	0.025	0.986
Drug Block 1	5.206	0.000	0.985	0.150	0.420	0.280	0.001	0.047	0.951
Drug Block 2	5.206	0.000	0.985	0.150	0.420	0.280	0.001	0.046	0.948
Drug Block 3	5.206	0.000	0.985	0.150	0.420	0.280	0.001	0.037	0.971
Postdrug	5.206	0.000	0.985	0.150	0.420	0.280	0.001	0.045	0.955
				MK-801					
Baseline	**5.206**	**0.000**	**0.975**	**0.150**	**0.420**	**0.280**	**0.001**	0.023	0.989
Drug Block 1	**2.950**	**1.450**	**1.300**	0.150	**0.700**	0.280	**0.200**	0.079	0.948
Drug Block 2	2.950	**0.600**	1.300	0.150	0.700	0.280	0.200	0.067	0.954
Drug Block 3	2.950	**0.200**	1.300	0.150	0.700	0.280	0.200	0.082	0.917
Postdrug	**5.206**	**0.000**	**0.975**	0.150	**0.420**	0.280	**0.001**	0.053	0.942

Note. Bolded values highlight estimated parameters for saline and MK-801 groups; unbolded values indicate that no subsequent changes were made to parameter values. RMSEA and R^2 are related measures: RMSEA provides an estimate of average error; R^2 provides an estimate of proportion of variance accounted for. RMSEA = root-mean-square error of approximation; PI = peak interval; BR = base rate.

Reinforcement (e.g., a food reward) is given whenever a rat successfully waits to make a response until after the target interval has elapsed. If a rat responds before the target interval has elapsed, then the trial restarts without reinforcement. In general, accurate DRL task performance requires infrequent responses that are timed appropriately.

Simulations of DRL performance were structured to correspond to the procedures used in Welzl et al. (1991). Simulations matched both the number of training sessions and number of trials within individual sessions (200 trials per session). The sequence of events was as follows: training (20 sessions), testing (5 sessions), and drug testing (1 session). Training and testing were simulated with the parameter estimates from the fits to the baseline data of Simulation 1, with the following exceptions. For DRL training, threshold parameters b and σ_b were set to 0.12 and 0.02, respectively. This decrease in the parameter values for the decision component of SET was necessary to accurately simulate the low rate of responding associated with the DRL schedule, in which there is a penalty for an early response (Kramer & Rilling, 1970; Zeiler, 1977).

The test sessions verified that the performance criterion used by Welzl et al. (1991) was met in the simulation. Welzl et al. used a performance criterion in which the efficiency score was at least 0.50 (number of reinforcements received/number of responses). Following adequate performance on test sessions, a drug test session was conducted to examine the effects of MK-801 on DRL performance. The clock and memory parameters used in the drug test session were obtained from the simulation of effects of MK-801 on PI performance (Simulation 1). Separate simulations were performed to mimic different animals in the saline and MK-801 groups; temporal response functions and efficiency scores were then averaged for each test session.

Empirical DRL data from Welzl et al. (1991) and predictions from DRL simulations can be seen in Figures 1E and 1F, respectively. Overall, DRL predictions provided a good match to the empirical data for both the saline and MK-801 groups. It is important to note that the predicted and observed DRL data showed similar patterns despite the fact that clock and memory parameters produced overestimation, not underestimation, in the simulations of the PI task. Similar to the simulation of the PI task, it was necessary to increase both the response threshold, b, and response base rate, BR, from their baseline values to improve the quantitative match between data and model; final values for the MK-801 simulation of DRL were $b = 0.45$ and BR = 0.065.

The BR parameter used to model the effects of MK-801 on DRL performance was substantially lower than that used to model PI performance. One reason for this difference is attributable to different characteristics of DRL and PI tasks. In the DRL task, animals are penalized for responding early, whereas in the PI procedure there is no such penalty. A second reason for the difference in BR values across tasks may be due to idiosyncratic differences between animal strains used in the two experiments that we modeled; some evidence suggests that the function of glutamatergic receptors differs between strains (Manahan-Vaughan & Braunewell, 2005).

An additional noteworthy finding was that the SET parameters for the PI baseline data provided an average efficiency criterion score for the five test sessions of DRL that was nearly identical to the value reported by Welzl et al. (1991; $M_{\text{Sim}} = 0.53$ vs. $M_{\text{Data}} \approx 0.51$); moreover, MK-801 produced a similar magnitude reduction in the predicted efficiency ($M_{\text{Sim}} = 0.11$ vs. $M_{\text{Data}} \approx 0.13$). With respect to the predicted and observed IRTs, the parameter values that produced a rightward shift (overestimation) in the PI task accurately predicted a leftward shift (underestimation) in the DRL

task. Overall, the results of Simulation 2 suggest that reported differences in the effects of MK-801 on timing are likely due to a task difference, rather than an inherent difference in timing.

Discussion

Previous studies have reported different effects of MK-801, an NMDA receptor antagonist, on timing and temporal processing. In particular, MK-801 produced an overestimation of duration in the PI procedure and an underestimation of duration in DRL. The main question addressed in this study was whether these disparate results represented different effects of MK-801 on timing or whether the results were due to inherent procedural differences in the two tasks. In this study, we used SET to develop a model-based explanation of the effect of MK-801 on timing in rats. Simulation 1 provided a quantitative account of the effects of MK-801 on the PI procedure (Miller et al., 2006, Experiment 2). Simulation 2 used the clock and memory parameters from Simulation 1 to predict the effects of MK-801 on the DRL task.

The results of Simulation 1 provided an excellent quantitative fit to the empirical PI data. Effects of MK-801 were associated with a slower and more variable clock, increased memory storage constant that yielded systematic overestimation of time, a wider response threshold window, and an increased response base rate. With respect to Simulation 2, we were primarily interested in whether we would be able to predict DRL performance using the clock and memory parameter estimates obtained from the PI task. Indeed, an excellent match between the DRL predictions and the empirical data was obtained for both the saline and MK-801 groups. This is especially noteworthy because the direction of change in clock speed and memory storage constant obtained from the SET simulation of DRL is in the opposite direction to that inferred from descriptive interpretations of empirical DRL data.

Overall, the reported simulations suggest that what appear at first glance to be conflicting findings with the PI and DRL procedures are in fact consistent (Sanger, 1992; Stephens & Cole, 1996; Tonkiss et al., 1988; Welzl et al., 1991). Previous results from the PI procedure indicate that MK-801 produces a rightward shift in peak time (overestimation of duration), whereas results from the DRL task show that MK-801 produces a leftward shift in the IRT distribution (underestimation of duration). Results from our simulations suggest that differences observed between DRL and PI performance are not due to differences in timing per se but are due in part to a general reduction in response inhibition associated with MK-801; in the context of the DRL task, a reduction in response inhibition results in a leftward shift in the IRT distribution that is not easily separated from timing; see Wiley et al. (2000) for a recent empirical study that supports this view.

Our results with a formal implementation of SET suggest that MK-801 affects both timing and nontiming abilities. With respect to timing, the slower clock speed associated with MK-801 is similar to that observed with dopamine antagonists (Hinton & Meck, 1997; Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; Matell, King, & Meck, 2004; Meck, 1983, 1986, 1996). MK-801 also increases the memory storage constant similar to the increase observed with administration of cholinergic antagonists (Meck, 1983, 1996; Meck & Angell, 1992; Meck & Church, 1987). With regard to nontiming abilities, our simulations suggest that MK-801 increases the response base rate and the width of the response threshold window; both of these results are consistent with a general decrease in response inhibition typically found in animals treated with MK-801 (Ford, Sanberg, Norman, & Fogelson, 1989; Welzl et al., 1991; Whishaw & Auer, 1989). The reduction of response inhibition may involve the hippocampal system, consistent with the high concentration of NMDA receptors in this brain region (Jarrard, 1973; Monaghan & Cotman, 1985; Tracy, Jarrard, & Davidson, 2001). An important outcome of our simulations is that from the perspective of SET, changes in both response inhibition and timing are required to account for the effects of MK-801 on DRL and PI performance.

Additional empirical evidence supporting the perspective that MK-801 affects both response inhibition and timing comes from Welzl et al. (1991). In a comparison of signaled and unsignaled DRL performance, Welzl et al. showed that MK-801 increased response rates and decreased efficiency for the signaled DRL task but that these effects were dramatically less than those reported for the unsignaled DRL task; moreover, the leftward shift in IRT distributions in the unsignaled DRL task was not present in signaled DRL task. Assessments of responses per opportunity (which take into account the unequal probability of responding at a given time inherent in the DRL task) also showed a leftward shift in the peak of the IRT distribution following MK-801 administration that was not present in the signaled DRL task. Welzl et al. concluded that these findings support a disruption in timing that is in addition to effects of MK-801 on response inhibition. If MK-801 alters timing abilities per se, an important question that remains unresolved is whether the rightward shift in peak time associated with MK-801 is scalar. Future research addressing this issue will provide important constraints for models and help in our understanding of the exact nature by which NMDA receptors are involved in timing.

In conclusion, this research highlights the value of quantitative modeling. Previous interpretations of the effects of MK-801 on DRL performance suggested that MK-801 produces an underestimation of duration (Sanger, 1992; Stephens & Cole, 1996; Welzl et al., 1991), whereas PI performance suggested an overestimation of duration (Miller et al., 2006). From the perspective of SET, the simulations reported in this article demonstrate that a single explanation can resolve these apparent discrepant results. We cannot rule out the possibility that a different timing model might be able to provide a different quantitative account of PI and DRL data that does not involve changes in internal timing (e.g., Saulsgiver et al., 2006). Nonetheless, the current study provides the first unified quantitative account of effects of MK-801 on timing.

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