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

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Effects of MK-801, an N-methyl-D-aspartate antagonist, on short-interval timing were examined using the peak-interval (PI) and PI-gap procedures. Fisher 344 rats were given daily injections of 0.025 mg/kg, 0.05 mg/kg, and 0.2 mg/kg MK-801. The main results were (a) 0.2 mg/kg MK-801 produced an immediate overestimation of the criterion time; (b) MK-801 increased peak rate of responding; (c) 0.2 mg/kg MK-801 produced an increase in variability; (d) during the PI-gap procedure, a *reset pattern* was observed for all rats (MK-801 and saline). Results suggest that MK-801 has at least 2 effects. First, MK-801 interferes with short-interval timing by producing an overestimation of time and a nonscalar increase in variability. Second, MK-801 increases response rate, suggesting a decrease in response inhibition.

Keywords: peak-interval procedure, temporal processing, Fisher 344

Glutamate is a prominent excitatory transmitter found in the central nervous system that interacts with several receptor subtypes (Cotman, Monaghan, Ottersen, & Storm-Mathisen, 1987; Watkins, Krogsgaard-Larsen, & Honore, 1990). The N-methyl-D-aspartate (NMDA) receptor subtype has received much interest because of its role in learning, memory, and synaptic plasticity (Morris, 2003; Morris, Anderson, Lynch, & Baudry, 1986; Shapiro & Caramanos, 1990; Shapiro & O'Connor, 1992). Because of the high concentration of NMDA receptors in the hippocampus (Monaghan & Cotman, 1985), NMDA receptor antagonists often have effects similar to hippocampal lesions (Morris et al., 1986; Tonkiss, Morris, & Rawlins, 1988). Although the study of NMDA receptor involvement in memory has proved very fruitful (Butterfield & Pocernich, 2003; Kumar, 2004; Minkeviciene, Banerjee, & Tanila, 2004; Rogawski & Wenk, 2003), NMDA receptors may also be involved in nonmnemonic cognitive processes.

Evidence that NMDA receptors may be involved in timing and temporal processing comes chiefly from studies in which a differential-reinforcement-of-low-rate-of-responding (DRL) schedule is used (Sanger, 1992; Stephens & Cole, 1996; Tonkiss et al., 1988; Welzl, Berz, & Battig, 1991). In a DRL task (Kramer & Rilling, 1970; Zeiler, 1977), an animal trained to emit an operant response (typically a lever press) after the passage of a target duration following the last response. If the response occurs after the target duration has passed, then the rat receives reinforcement and a new interval begins. If the response occurs before the target duration elapses, then the duration resets and no reinforcement is given.

NMDA antagonists alter DRL performance. Chronic intraventricular infusions of a competitive antagonist of the NMDA receptor D,L-2-amino-5-phosphonopentanoic acid (AP5) increased response rate, decreased efficiency (the number of reinforcements delivered compared with responses made), and shortened the distribution of interresponse times (IRTs; Tonkiss et al., 1988). Upon termination of AP5 administration, the observed impairments disappeared, and rats returned to perform like control rats (Tonkiss et al., 1988). Acute systemic injections of MK-801 (dizocilpine), a noncompetitive NMDA receptor antagonist (Wong et al., 1986), produced impairments similar to those observed with chronic infusions of AP5 (Welzl et al., 1991). Single injections of MK-801 generally increased response rate, reduced efficiency, and caused a shortening, or leftward shift, of the distribution of IRTs. However, the highest dose of MK-801 (.30 mg/kg) depressed response rate below the level of controls and eliminated any observable peak in the distribution of IRTs (Welzl et al., 1991).

Other competitive and noncompetitive NMDA antagonists, including phencyclidine, CGS 19755, eliprodil, memantine, and dextromethorphan, also disrupt DRL performance (Sanger, 1992). Because these NMDA antagonists bind to different sites on NMDA receptors, Sanger (1992) examined the effects of these compounds, in addition to MK-801, on the DRL task. All drugs produced a flattening of the distribution of IRTs, and all except eliprodil produced a leftward shift in the distribution similar to that observed with MK-801 and AP5. The effects of these different drugs on response rate varied, with some increasing response rate, whereas others decreased response rate, depending on the drug and dosage level. These findings suggest that NMDA antagonists consistently disrupt timing behavior on DRL tasks (Sanger, 1992).

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Because of the shortening of IRTs in DRL tasks, NMDA antagonists have been suggested to alter the short-interval timing system (Meck, 1996; Tonkiss et al., 1988; Welzl et al., 1991). According to this idea, NMDA antagonists may speed up the "clock" or alter the "memory" of the previously rewarded duration such that the subjective experience of the rewarded duration is an underestimate of the actual duration. Alternatively, disruptions observed in DRL tasks with NMDA antagonists could be because of the increased response rate or impairment in the ability to withhold lever responses for the length of the target duration. In order to dissociate an effect on temporal processing/memory from one on response inhibition, the peak-interval (PI) procedure may be useful.

In the PI procedure, rats must time the duration of a stimulus and develop a memory for this duration similar to the DRL task. However, unlike the DRL task, rats are free to emit any number of responses without affecting when reinforcement will be delivered. In the PI procedure, *peak time* is a measure of timing accuracy, whereas *peak rate* is a measure of response rate. These two measures of performance have been shown to be independent (Roberts, 1981). If NMDA antagonists affect the ability to inhibit responding without altering timing ability, then peak rate will be altered but peak time will not. However, if NMDA antagonists alter temporal processing without affecting response inhibition, then peak time should shorten, whereas peak rate may or may not change, similar to hippocampal lesions (Meck, Church, Wenk, & Olton, 1987; Olton, Wenk, Church, & Meck, 1988). It is also possible that both temporal processing and response inhibition could be altered by NMDA antagonists.

Effects of NMDA antagonists on DRL performance have generally been assumed to be because of disruption of hippocampal function for two main reasons (Tonkiss et al., 1988; Welzl et al., 1991). First, NMDA receptors have been found throughout the brain with high concentrations in telencephalic regions and the highest concentrations in the hippocampus (Monaghan & Cotman, 1985). Second, administration of NMDA receptor antagonists results in impairment of spatial leaning (Morris et al., 1986) and temporal processing (Tonkiss et al., 1988) similar to those observed with hippocampal lesions. On the basis of these findings, it has been assumed that the effects of NMDA receptor antagonists are primarily because of a disruption of hippocampal function (Morris et al., 1986; Tonkiss et al., 1988).

A timing task related to the PI procedure that has shown effects of hippocampal lesions is the peak-interval gap (PI-gap) procedure (Meck, Church, & Olton, 1984; Meck et al., 1987; Olton et al., 1988; Roberts, 1981). In this task, a gap (or break in the stimulus) is added to the PI procedure as a test of working memory (Roberts, 1981). Three patterns of response have been previously observed: *run*, *stop*, and *reset* (Meck et al., 1987; Olton et al., 1988; Roberts, 1981). In the run pattern, the rat ignores the gap. For the stop pattern, the rat stops timing when the stimulus goes off and continues timing from that point when the stimulus resumes. The reset pattern supposes that the rat stops timing when the stimulus goes off and begins timing as if a new trial has started when the stimulus resumes. Normal rats typically adhere to a stop, or *partial reset* (a response pattern between stop and reset) pattern, whereas rats with hippocampal lesions typically follow a reset pattern (Buhusi & Meck, 2000; Buhusi, Mocanu, & Meck, 2004; Buhusi, Sasaki, & Meck, 2002; Meck et al., 1987; Olton et al., 1988; Roberts, 1981). If the effect of NMDA receptor antagonists is similar to the effect of hippocampal lesions on timing, then administration of NMDA antagonists should result in rats using a reset pattern instead of a stop pattern in the PI-gap procedure (Meck et al., 1987; Olton et al., 1988).

The effects of an NMDA antagonist, MK-801, on timing performance using the PI and PI-gap procedures were examined in Experiment 1. Performance on the PI and PI-gap procedures was investigated following a 2-week series of daily injections of MK-801 at three doses. We further examined the influence of MK-801 on performance in the PI procedure with only one dose of the drug but with a 3-week treatment that did not include the PI-gap procedure in Experiment 2.

Experiment 1

Method

Rats

Thirteen male adult Fisher 344 rats (Harlan, Indianapolis, IN) were subjects for the study, between 2 and 4 months of age at the start of the study, and weighed between 250 and 300 g. Housing was in a room maintained near 22 °C and on a 12-hr light–dark cycle, with lights on at 7 a.m. local time. Rats were housed individually or in pairs. Four groups ($n = 4$) were treated with saline, 0.025, 0.05, or 0.2 mg/kg MK-801. (Three of the rats receiving 0.2 mg/kg had been given saline as part of the control group. All other rats were experimentally naïve at the start of testing.) Prior to training, rats were food restricted until their body weight reached 85% of their ad lib weight. Supplemental food was given so that each rat gained approximately 5 g per week in body weight. Testing sessions were conducted once each day, 5 days per week (Monday–Friday). All procedures used in this study followed National Institutes of Health (NIH) guidelines for handling and caring of animals and were approved by the Bowling Green State University Institutional Animal Care and Use Committee.

Apparatus

Testing was conducted in 16 similar custom-made operant boxes (28 × 28 × 37 cm) constructed of clear acrylic. A hinged door was available on one side of the box, and a water bottle was located next to the door. Sucrose pellets (45 mg, PJFSC-0045; Research Diets, Inc., New Brunswick, NJ) were delivered by a pellet dispenser (ENV-203; MED Associates, East Fairfield, VT) into a food cup on one wall. A response lever (11.0 cm above the floor) was to the right of the food cup, and a stimulus lamp (4.8 W) was positioned directly above the lever (29.0 cm from the floor). Approximately 15 g of force was required to depress the lever. Additional experimental equipment (a sound generator, a stimulus lamp, a small cup for delivery of water, and a response lever) was located on another wall; however, this equipment was not used in the present study and was only present for use in other experiments that were being conducted in the lab. A house lamp (2.8 W) located outside of the operant box provided indirect lighting. A solenoid valve (Z723A; Sirai Elettromeccanica, Bussero, Milano, Italy) was located outside the box to provide an audible click and was activated along with the pellet dispenser to act as a secondary reinforcer.

Each operant box was housed in a larger chamber (61 × 61 × 61 cm) constructed from laminated particle board. This chamber acted to minimize light and sound originating from sources outside of the operant box. A fan provided ventilation to each chamber, and a small peephole could be used to observe the behavior of the rat. A Dell (Optiplex GX240) computer, with a MED Associates SmartCtrl system (MED-PC IV; DIG-716; SG-716; MED Associates, East Fairfield, VT) controlled the presentation of stimuli and delivery of reinforcement and recorded the times of lever responses.

Drug

MK-801 ([+]-5-methyl-16, 11-dihydro-5H-dibenzo[a,d] cyclohepten 5, 10-imine; M-107, Sigma Chemical, St. Louis, MO) was dissolved in physiological saline. Saline or MK-801 (0.025, 0.05, or 0.20 mg/kg, ip) was administered 30 min prior to testing sessions.

Procedure

Rats were first trained to press the lever to receive a sucrose pellet using a continuous reinforcement schedule (CRF, 3–5 sessions). Following the CRF sessions, rats received training on a variable reinforcement schedule (VR-3, five sessions), for which, on average, every third lever press resulted in the delivery of a sucrose pellet. A minimum of one and a maximum of six lever presses were required to obtain a sucrose pellet.

Following the VR-3 sessions, rats were trained on a 12-s fixed-interval (FI) reinforcement schedule. FI trials started with the illumination of a light stimulus. After the 12-s target duration had elapsed, the first lever response resulted in delivery of a sucrose pellet and termination of the light stimulus. Any lever response prior to the passage of the FI duration did not have any effect. If a rat made no lever response after the FI duration, then the stimulus light extinguished after 60 s. Following the completion of an FI trial, an intertrial interval (ITI) began; ITIs were randomly selected from a uniform distribution of times between 30 and 60 s. Any lever response during the final 10 s of the ITI resulted in a 5-s timeout period during which the rat was placed into darkness by extinguishing the houselight. Following the timeout period, the houselight was reilluminated, and a minimum of 10 s without a lever press was required in order to begin the next FI trial. An individual FI session typically lasted 1.5 hr during which a rat would complete approximately 70 trials.

After approximately 10 sessions of FI training, rats began the PI procedure. This procedure was the same as the FI procedure, except that half of the trials were probe trials in which a sucrose pellet was never delivered and the stimulus light remained on for the duration of the trial (60 s). During this time, the rat was free to respond. An individual PI session typically lasted 1.5 hr during which a rat would complete approximately 70 trials (approximately 35 FI trials and 35 probe trials). Rats were trained on the PI procedure until the peak of the temporal response function for individual sessions was within 2 s of the target duration (12 s, approximately 30 sessions). At this point, rats were tested for five additional sessions to establish baseline performance.

Following the baseline sessions, rats received injections of either saline or MK-801 for 10 consecutive sessions. After the 10 sessions, injections continued as the rats performed three sessions of the PI-gap procedure. The PI-gap procedure is a modification of the PI procedure in which a random half of probe trials (gap trials) have the light stimulus interrupted. Six seconds after the start of the trial, the stimulus light extinguished for a 6-s gap period and then illuminated again for the remainder of the trial. As with probe trials, no sucrose pellets were delivered during gap trials. After three sessions on the PI-gap procedure, rats were returned to the PI procedure for five additional sessions without injections.

Data Analysis

PI procedure. Data were analyzed in blocks of five sessions: Sessions 1–5 (baseline), Sessions 6–10 (Drug 1), Sessions 11–15 (Drug 2), Sessions 16–18 (PI gap), and Sessions 19–23 (post drug). Only data from probe trials were analyzed. Lever responses were added for each successive 1-s interval (bin) throughout the 60-s signal duration. The total responses in each bin were divided by the total number of trials to determine the mean number of lever responses per trial. The mean lever responses for each bin were plotted as a function of time to create a temporal response function. Response rate was calculated by multiplying the number of responses in each bin by 60 so that response rate could be expressed as responses per minute (Roberts, 1981).

A Gaussian + linear equation (Buhusi et al., 2002) that gave the best fit to the temporal response function was determined by minimizing root-mean-square error using the Solver add-in package for Microsoft Excel, 2002 (Version 10.65, Microsoft Corporation, Seattle, WA). The following was the generalized Gaussian + linear model that was fit to the temporal response function:

$$R(t) = a \times \exp(-.5 \times [(t - t_0)/b]^2) + c \times (t - t_0) + d,$$

where t is the current time bin, and $R(t)$ is the mean response rate at time t. Model fitting determined estimates for the parameters a, b, c, d, and t_O. Peak time was estimated by t_O, peak rate was estimated by $a + d$, and variability was estimated by b^2.

Parameter estimates were obtained for each rat in each session, and then mean parameter estimates were obtained over all sessions within a test block: baseline, Drug 1, Drug 2, and post drug. Data analyses for the PI-gap block are discussed below and are treated separately. Separate mixed model analyses of variance (ANOVAs) were conducted in SPSS for Windows (Version 12.0, SPSS, Inc., Chicago, IL) to examine effects of drug group (saline, 0.025 mg/kg MK-801, 0.05 mg/kg MK-801, and 0.2 mg/kg MK-801) and test block (baseline, Drug 1, Drug 2, and post drug) on peak time, peak rate, and variability. Greenhouse–Geisser corrections were used in all cases in which the assumption of sphericity was violated; for consistency, the degrees of freedom reported in these instances are uncorrected. Post hoc tests for the between-subjects factors were conducted, when necessary, using Tukey's honestly significant difference (HSD) test, with alpha set at .05.

PI-gap procedure. Because the testing procedures during the PI-gap sessions differed slightly from the PI sessions, data from PI-gap block were analyzed separately. Although probe trials were included in this test block as a part of the PI-gap procedure, the primary interest in this procedure is performance on gap trials. Therefore, only data from gap trials were analyzed. Peak time, peak rate, and variability measures were calculated as in the PI sessions with one exception. Because of the small number of gap trials in each session, mean lever response data for each bin were calculated across all trials and sessions prior to parameter estimation using the Gaussian + linear equation.

Separate one-way ANOVAs were conducted in SPSS for Windows for peak time, peak rate, and variability as dependent measures. Drug condition was a between-subjects factor. Post hoc tests, when necessary, were conducted using Tukey's HSD, with alpha set at 0.05.

Results

PI Procedure

During baseline sessions, temporal response functions for all rats peaked near the 12-s target duration (see Figure 1). Peak times were not altered by saline, 0.025 mg/kg, or 0.05 mg/kg MK-801 (see Figure 2A). However, the 0.2 mg/kg dose of MK-801 produced a dramatic lengthening of peak time during Drug 1 sessions. During Drug 2 sessions, peak times began to return to the target time, although they remained longer than baseline values. Peak times for this group returned immediately to baseline levels following cessation of the drug, post drug: mean difference = 0.10 s, $t(15) = 0.66$, $p > .05$. These observations were confirmed by the ANOVA on peak times, which showed a main effect of session block, $F(3, 36) = 30.01$, $p < .001$; a main effect of drug group, $F(3, 12) = 5.71$, $p < .05$; and a Drug Group × Session Block interaction, $F(9, 36) = 22.30$, $p < .001$. Post hoc tests on drug group revealed that the 0.2 mg/kg MK-801 group had significantly longer peak times than the saline group ($p < .05$), the .025 mg/kg MK-801 group ($p < .05$), and the 0.05 mg/kg MK-801 group ($p <$

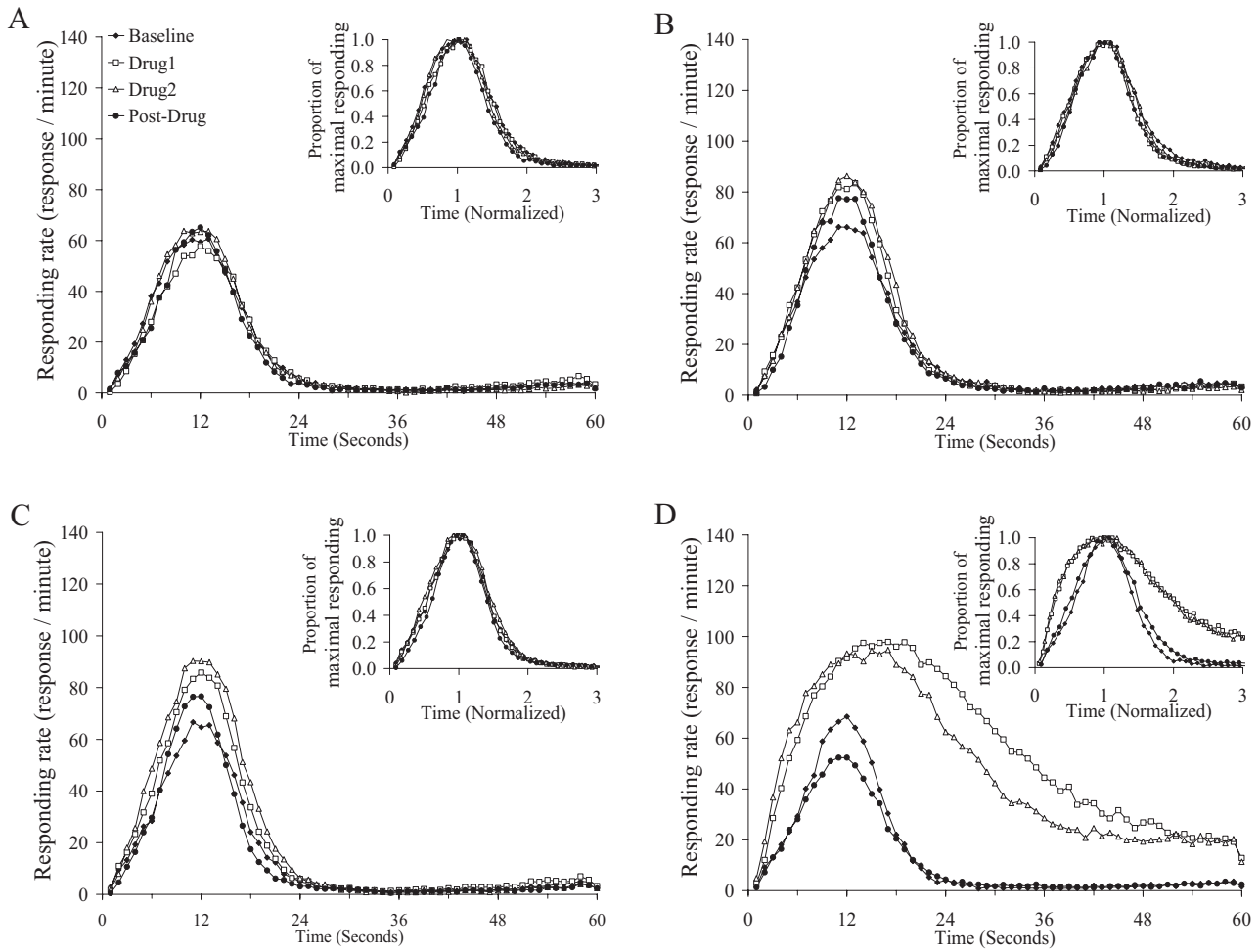

Figure 1. Temporal response profiles for each drug condition across testing blocks. Inset figures are response profiles normalized by both peak rate and peak time. A: saline. B: 0.025 mg/kg MK-801. C: 0.05 mg/kg MK-801. D: 0.2 mg/kg MK-801.

.05). No other significant differences in peak time were found between drug groups.

Peak rate remained stable across all test session blocks for the saline groups (see Figure 2B). However, MK-801 groups increased response rate upon receiving the drug injections (see Figure 2B, Drug 1). This increased response rate was maintained throughout Drug 2 sessions. Upon the termination of drug injections, response rate for the 0.025 mg/kg and 0.05 mg/kg MK-801 groups remained somewhat elevated above baseline levels, although these differences were not statistically significant, $t(3) = -2.18$, $p > .05$; and, $t(3) = -1.06$, $p > .05$, respectively. The 0.2 mg/kg MK-801 group displayed a much sharper drop in peak rate than the other two drug groups, returning to baseline levels during the postdrug sessions, $t(3) = 1.68$, $p > .05$. To further analyze the peak rate data, the results for each test block were normalized by animal relative to their baseline block peak rate, (Normalization relative to baseline levels effectively eliminated the large individual differences in overall response rate typically observed between rats.) An ANOVA was then performed on the normalized peak rate data with the baseline block omitted (for the baseline block, all rats were necessarily at 100% of baseline performance levels), which resulted in a change in degrees of freedom for the analysis of peak rate. This analysis showed a main effect of session block, $F(2, 24) = 9.08$, $p < .001$; no main effect of drug group, $F(3, 12) = 0.881$, $p > .05$; but a significant Drug Group $\times$ Session Block interaction, $F(6, 24) = 3.72$, $p < .01$.

Variability remained stable across test blocks for the saline, 0.025 mg/kg, and 0.05 mg/kg MK-801 groups (see Figure 2C). However, the 0.2 mg/kg MK-801 group displayed a dramatic increase in variability during Drug 1 sessions. Variability decreased during Drug 2 sessions, although variability was still larger than during baseline sessions, $t(3) = -3.55$, $p < .05$ (see Figure 2C). Variability for this group returned to baseline levels upon termination of the drug, $t(3) = -2.56$, $p > .05$. These observations were confirmed by the ANOVA on variability, which revealed a significant main effect of session block, $F(3, 36) = 12.76$, $p < .001$; a main effect of drug group, $F(3, 12) = 33.52$, $p < .001$; and a significant Drug Group $\times$ Session Block interaction, $F(9, 36) = 11.19$, $p < .001$. Post hoc tests on the drug groups indicated that the 0.2 mg/kg MK-801 group had significantly greater variability

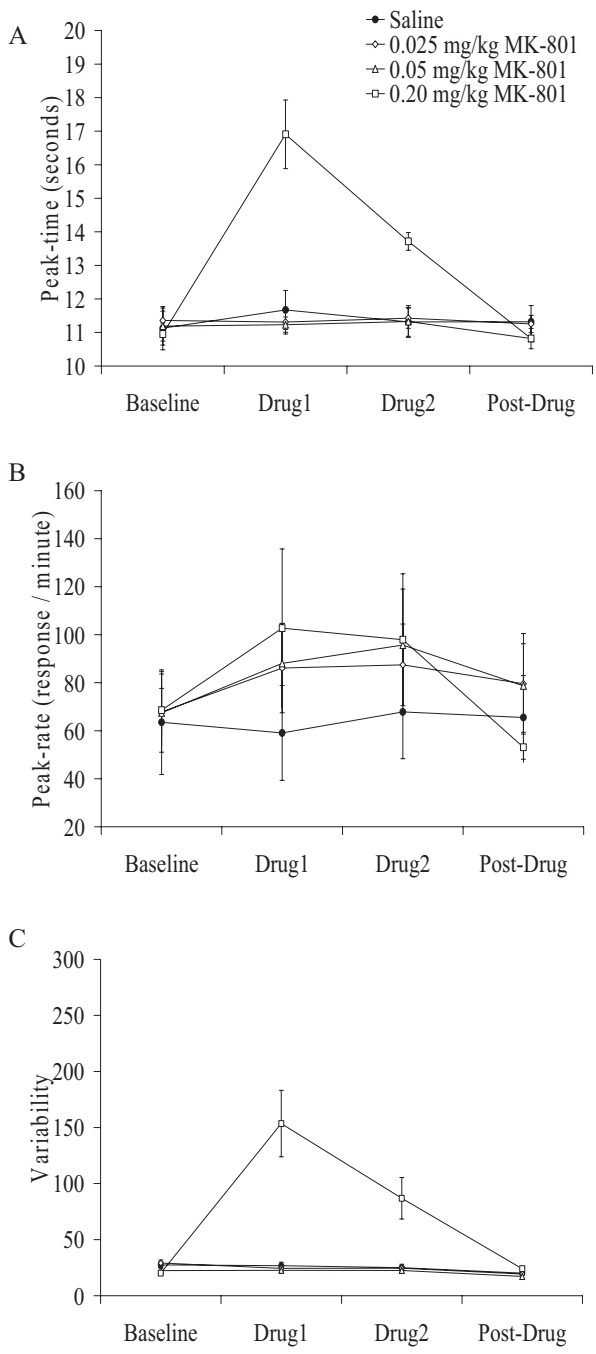

Figure 2. Peak time (A), peak rate (B), and variability (C) plotted by drug group (saline, 0.025 mg/kg MK-801, 0.05 mg/kg MK-801, and 0.2 mg/kg MK-180) and by test block (baseline, Drug 1, Drug 2, and postdrug). Error bars are expressed as standard error of the mean.

than the saline group ($p < .05$), 0.025 mg/kg MK-801 group ($p < .05$), and the 0.05 mg/kg MK-801 group ($p < .05$). No other significant differences in variability were found between drug groups.

Because the highest dose of MK-801 increased peak time, a proportional increase in variability would be expected on the basis of scalar timing (Gibbon, 1977; Gibbon, Church, & Meck, 1984). In order to determine whether increases in variability observed for the 0.2 mg/kg MK-801 group were consistent with scalar timing (i.e., Weber's law), the data were plotted using a normalized time scale. Temporal response functions were also normalized with respect to peak rate in order to facilitate comparisons between blocks. Results of this analysis are displayed in the inset graphs found in Figure 1A–1D. Response functions of Drug 1 and Drug 2 sessions for the saline, 0.025 mg/kg, and 0.05 mg/kg groups (see Figure 1A–1C) superimposed, whereas functions for 0.2 mg/kg MK-801 group did not. These results demonstrate that the increase in variability observed in the 0.2 mg/kg MK-801 is greater than would be expected on the basis of scalar timing.

PI-Gap Procedure

No differences between drug groups were observed in the PI-gap procedure for peak time, $F(3, 15) = 0.73$, $p > .05$. All groups displayed a pattern of responding that was consistent with a reset pattern. In addition, no differences between drug groups were observed for either peak rate, $F(3, 15) = 1.40$, $p > .05$, or variability, $F(3, 15) = 0.90$, $p > .05$. The findings for peak rate and variability for the PI-gap procedure contrast with those observed for the standard PI procedure.

Discussion

Effects of the NMDA antagonist MK-801 on timing were examined using the PI procedure and the PI-gap procedure for three drug doses (0.025 mg/kg, 0.05 mg/kg, and 0.2 mg/kg). Four main results were observed. First, injections of 0.2 mg/kg MK-801 produced an immediate lengthening of peak time that attenuated with continued training. This result was not observed at lower doses. Second, injections of MK-801 increased peak rate of responding. Third, injections of the highest dose (0.2 mg/kg) resulted in an increase in variability, beyond that expected from Weber's law; this increase in variability was not observed at lower doses of MK-801. Finally, during the PI-gap procedure a reset pattern was observed for all rats (MK-801 and saline), and the findings for peak rate and variability during PI-gap performance differed from those observed for the standard PI procedure.

Overall, the present results are only partly consistent with the results reported in previous studies using the DRL task. MK-801 increases responding in the DRL task, which is consistent with our finding of an increase in response (peak) rate in the PI procedure. Moreover, an increase in behavioral activity is common in studies using MK-801 (Ford, Sanberg, Norman, & Fogelson, 1989; Welzl et al., 1991; Whishaw & Auer, 1989). Although this is not a new finding, the increase in peak rate in the PI procedure for the two lowest doses of MK-801 (0.025 mg/kg and 0.05 mg/kg) indicate that the drug doses were of a sufficient level to alter some aspects of behavior but not other measures (peak time and variability).

The effect of MK-801 on peak time was different than that reported for DRL performance. In the present study, injections of MK-801 at the highest dose (0.2 mg/kg) produced an abrupt lengthening (rightward shift) of peak time in the PI procedure, unlike the shortening (leftward shift) of the IRT distribution during DRL (Sanger, 1992; Stephens & Cole, 1996; Tonkiss et al., 1988; Welzl et al., 1991). The finding of a nonscalar increase in vari-

ability at the highest drug dose may partially explain some of the differences found in performances of the DRL and PI procedures. Examination of the temporal response profiles in Figure 1 revealed that rats given the 0.2 mg/kg dose of MK-801 started to respond sooner and continued to respond longer than control rats. This type of early responding in the PI procedure would manifest itself as a shortening of the IRTs in DRL. Taken together, our findings with peak time and variability suggest that the shortening of the IRTs in the DRL task is not because of a timing problem but more likely because of the inability to inhibit responding.

The effect of MK-801 on peak times was also different from previous reports of the effect of hippocampal lesions. Lesions of the hippocampal system have been observed to produce a gradual and permanent leftward shift in peak times, whereas we observed an abrupt rightward shift that appeared to partially renormalize with continued training (Meck et al., 1987; Olton et al., 1988). According to scalar expectancy theory, the type of gradual and permanent shift in peak time associated with hippocampal lesions has been attributed to alterations in "memory storage," whereas an abrupt but transient shift in peak time has been previously attributed to a change in "clock speed" (Church, 2003; Meck, 1994, 1996; Meck et al., 1984, 1987).

The issue of hippocampal involvement is potentially addressed by the PI-gap procedure, as previous reports in the literature have found that control rats typically display a stop or partial-reset pattern, whereas rats with hippocampal lesions typically follow a reset pattern (Buhusi et al., 2002, 2004; Cabeza de Vaca, Brown, & Hemmes, 1994; Meck et al., 1987; Olton et al., 1988; Roberts, 1981). However, in the present study, saline control rats, as well as those receiving MK-801, displayed a reset pattern, limiting the value of the PI-gap procedure in terms of evaluating the effects of MK-801 on hippocampal function. The factors influencing whether rats reset or stop during a gap are difficult to tease apart. Animal species (i.e., rat vs. pigeons) and strain (i.e., pigmented vs. albino rats), stimulus modality, and intensity have been shown to affect pattern of responding to gaps (Buhusi, Perera, & Meck, 2005; Buhusi et al., 2002). Buhusi et al. (2005) concluded that albino rats (Sprague–Dawley) usually demonstrate a stop pattern during a gap in a visual stimulus. However, we found that Fisher 344 rats, also an albino rat strain, followed a reset pattern during a gap in a visual stimulus in the present study. It is possible that other experimental design characteristics, such as duration of target interval, gap location, gap duration, length of probe trials, and duration of the ITI, may all be influencing the response strategy of our control rats (Buhusi et al., 2005, 2002; Cabeza de Vaca et al., 1994). Overall, it is clear that additional research is needed to disentangle the various factors responsible for response strategy shifts in the PI-gap procedure and the influence of NMDA receptor function in the PI-gap procedure.

Supporting the view that MK-801 mediates clock function, the present results are similar in some ways to distortions in timing reported with dopamine antagonists (Meck, 1983, 1986, 1996; Meck & Church, 1987). Like the effects of MK-801, dopamine antagonists produce an immediate rightward shift in the peak time that gradually returns toward its predrug value with continued training on the drug (Maricq, Roberts, & Church, 1981; Meck, 1996). In addition, continued training upon removal of the dopamine antagonist results in an immediate, but temporary, leftward shift in peak time, which has been called a *rebound effect* (Maricq & Church, 1983; Meck, 1983, 1996).

Our results with MK-801 differ from those reported with dopamine antagonists in a few important respects. First, the shift we observed in peak times with MK-801 did not completely return to predrug values with continued training, although the trend was in that direction. Second, no obvious rebound effect (an abrupt and transient shift in peak times in the opposite direction) was observed following the cessation of MK-801 injections, as has been observed with dopamine antagonists (Meck, 1983, 1986, 1996; Meck & Church, 1987).

It is possible that the lack of a rebound effect is because of state-dependent learning (Beninger & Hahn, 1983; Ohyama et al., 2000; Siegel, 1988). In the present study, rats were first trained without any injection (saline or MK-801), which may be considered one state. A new state may have accompanied the initiation of injections either from the sensation of the injections or from the sensations produced by the MK-801. Perhaps following the cessation of injections, rats returned immediately to the state formed without injections; thus, no rebound in peak time was observed. One method to address this possibility is to continue injections during the postdrug sessions by substituting saline for MK-801.

Experiment 2

We addressed in Experiment 2 several issues raised in Experiment 1. First, a critical test of whether MK-801 mediates clock function is that changes in peak time completely return to the criterion time with continued training. In Experiment 1, 2 weeks of training under the influence of MK-801 may have been insufficient for complete return of the peak time to 12 s, although the trend was in the right direction. We thus added a third week of training in Experiment 2 with MK-801 to determine whether further testing with drugs would produce a more complete renormalization of peak times. Second, another characteristic of an alteration of the clock stage of SET is a rebound effect following cessation of the drug. However, a rebound effect was not observed in Experiment 1. To investigate the possibility that the lack of a rebound effect may have been because of state-dependent learning, saline injections were administered during postdrug sessions in Experiment 2. Third, all rats in Experiment 2 were experimentally naïve, unlike in Experiment 1 in which some rats were tested in both saline and drug conditions. Fourth, only the highest dose of MK-801 (0.2 mg/kg) was examined in Experiment 2 because this dose produced the most dramatic effects on peak time, response rate, and variability. Finally, PI-gap sessions were removed from the testing procedures because the reset pattern observed for all rats (saline and MK-801) in the preceding experiment precluded the use of the PI-gap procedure to test the role of hippocampal NMDA receptors in timing behavior.

Method

Rats

Fifteen male adult Fisher 344 rats similar to those used in Experiment 1 were subjects for the study. Housing, food restriction, and training were the same as in Experiment 1. Rats were divided into two groups: saline (n = 8) and 0.2 mg/kg MK-801 (n = 7). All rats were experimentally naïve at the start of testing. Testing sessions were conducted once each day, 5 days

per week (Monday–Friday). All procedures followed NIH guidelines for handling and caring of animals and were approved by the Bowling Green State University Institutional Animal Care & Use Committee.

Apparatus

This experiment used the same operant boxes as those used in Experiment 1.

Drug

Thirty minutes prior to the beginning of testing, rats were injected intraperitoneally with saline or 0.20 mg/kg MK-801.

Procedure

The training procedures for Experiment 2 were identical to those for Experiment 1. After reaching the training criterion (peak time within 2 s of the target 12-s duration), rats were tested for five sessions to establish a baseline measure of performance. For the next 15 sessions, rats were tested with either saline or 0.2 mg/kg MK-801. Following the 15 sessions, all rats were tested for an additional five sessions with saline.

Data Analysis

For the purpose of analysis, data were divided into five blocks of sessions: Sessions 1–5 (baseline), Sessions 6–10 (Drug 1), Sessions 11–15 (Drug 2), Sessions 16–20 (Drug 3), and Sessions 21–25 (postdrug). Data collection and the fitting procedure for estimating peak time, peak rate, and variability were identical to Experiment 1.

Separate mixed model ANOVAs were conducted to examine effects of drug group (saline and 0.2 mg/kg MK-801) and test block (baseline, Drug 1, Drug 2, Drug 3, and postdrug) on peak time, normalized peak rate, and variability. Greenhouse–Geisser corrections were used in any case in which the assumption of sphericity was violated; for consistency, the degrees of freedom reported in these instances are uncorrected. Post hoc tests for the between-subjects factors were conducted, when necessary, using Tukey's HSD, with alpha set at .05. As in Experiment 1, data for peak rate were normalized relative to the baseline performance prior to conducting statistical analyses, and the baseline values were omitted from analysis.

Results

During baseline sessions, temporal response functions for saline and 0.2 mg/kg MK-801 groups peaked near the FI target, indicating that the rats learned to accurately produce responses that were centered on the target interval (see Figure 3A and 3B). As in Experiment 1, peak times remained stable across all test session blocks for the saline group, whereas the 0.2 mg/kg MK-801 group displayed a dramatic lengthening of peak time upon initiation of drug injections (Drug 1; see Figure 4A). With continued testing on MK-801 (Drug 2 and Drug 3), peak times migrated toward the target time. Even with additional testing on MK-801, peak times remained longer than those observed during baseline (see Drug 3 in Figure 4A). Peak times for the final block of saline (postdrug) were slightly shorter than those observed during baseline sessions (mean difference = 0.38 s), $t(17) = 2.20$, $p < .05$. Greenhouse–Geisser corrections were used on the ANOVA on peak time, which confirmed a significant main effect of session block, $F(4, 52) = 13.61$, $p < .001$; a main effect of drug group, $F(1, 13) = 11.76$, $p < .01$; and a significant Session Block × Drug Group interaction, $F(4, 52) = 13.13$, $p < .001$.

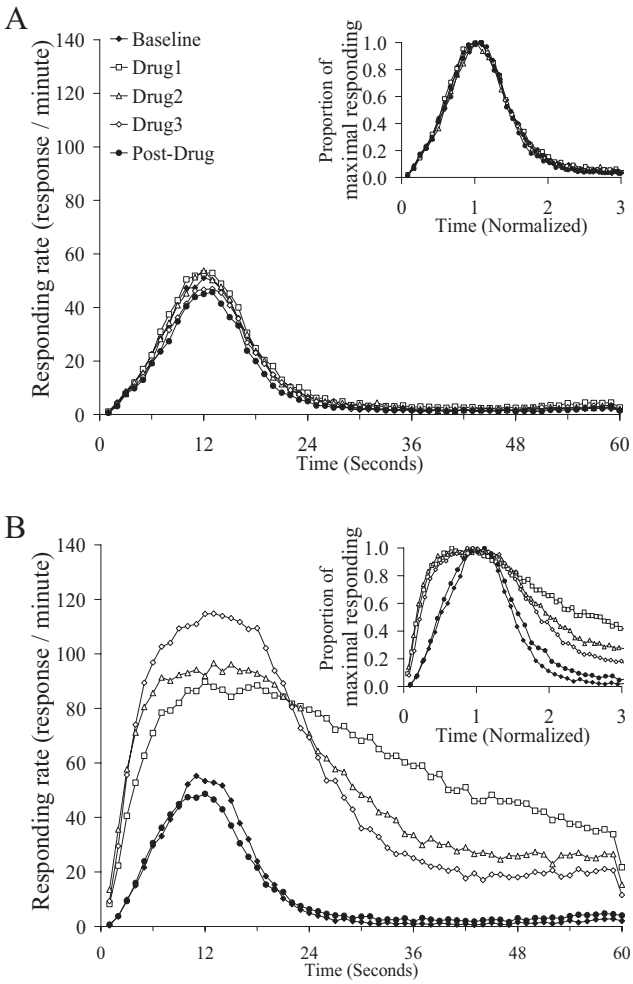

Figure 3. Temporal response profiles for each drug condition across testing blocks. Inset figures are response profiles normalized by both peak rate and peak time. A: saline. B: 0.2 mg/kg MK-801.

Similar to Experiment 1, MK-801 produced an overall increase in responding (cf. Figure 4B with Figure 2B). For the saline group, peak rate was stable across all test session blocks. In contrast, the MK-801 group displayed an immediate increase in response rate upon receiving the drug (Drug 1). Response rate continued to increase over the next two testing blocks (Drug 2 and Drug 3). Upon switching from MK-801 to saline injections, response rate returned back to levels similar to baseline sessions (postdrug). Overall, the ANOVA on normalized peak rate indicated a significant main effect of session block, $F(3, 39) = 20.52$, $p < .001$; a significant main effect of drug group, $F(1, 13) = 9.39$, $p < .01$; and a significant Session Block × Drug Group interaction, $F(3, 39) = 18.60$, $p < .001$.

Variability was increased by MK-801 (see Figure 4C). Variability remained stable across test session blocks for the saline group. However, the MK-801 group displayed a dramatic and immediate increase in variability following drug injections (Drug 1). During Drug 2 and Drug 3 sessions, variability decreased, although it remained larger than baseline sessions. Variability for this group returned to predrug levels upon termination of the injections (post-

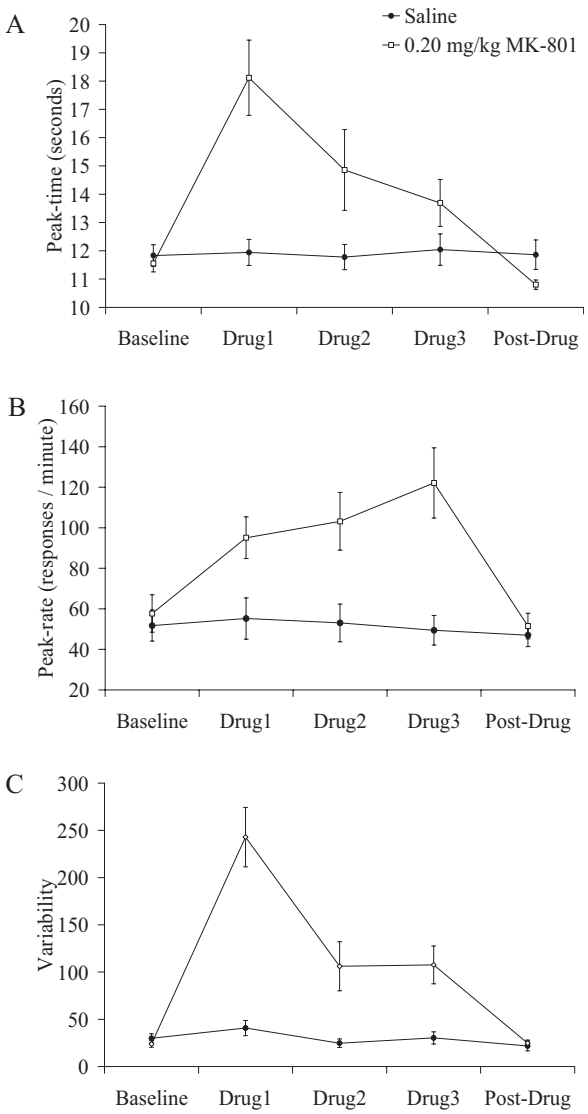

Figure 4. Peak time (A), peak rate (B), and variability (C) plotted by drug group (saline and 0.2 mg/kg MK-801) and by test block (baseline, Drug 1, Drug 2, Drug 3, and postdrug). Error bars express standard error of the mean.

drug). Consistent with these observations, the ANOVA on variability (with Greenhouse–Geisser corrections applied) revealed a significant main effect of session block, $F(4, 52) = 43.85$, $p < .001$; a main effect of drug group, $F(1, 13) = 42.14$, $p < .001$; and a significant Session Block × Drug Group interaction, $F(4, 52) = 33.59$, $p < .001$.

In order to determine whether the increase in variability observed in the MK-801 group was scalar, the data were plotted on a normalized time scale. For the saline group, the normalized response functions (see Figure 3A) superimposed, supporting scalar timing. However, as in Experiment 1, the MK-801 group (see Figure 3B) revealed a different scenario; the normalized temporal functions for baseline and postdrug sessions superimposed, and the normalized temporal functions for Drug 1, Drug 2, and Drug 3 sessions superimposed, but the three drug blocks did not superimpose with the two nondrug blocks, suggesting that, as in Experiment 1, the effect of MK-801 at the highest dose (0.2 mg/kg MK-801) was nonscalar.

Discussion

Overall, the three primary findings of Experiment 1 were replicated in Experiment 2. First, the 0.2 mg/kg dose of MK-801 produced an overestimation of the criterion time that was reduced with continued training, as measured by peak time. Second, MK-801 increased response rate, as measured by peak rate. Third, MK-801 produced a nonscalar increase in variability. Additionally, two questions were addressed in Experiment 2 that tested the possibility that MK-801 mediates timing function in a manner similar to dopamine antagonists.

The first question addressed in Experiment 2 was whether peak times would completely return to the criterion time with further training. However, even with the additional week of MK-801, we found that produced peak times did not return to the criterion time. In terms of SET, rapid shifts in peak times have typically been attributed to a change in the speed of an internal pacemaker or clock, with the renormalization of peak times attributed to an updating of memory on the basis of the new clock speed (Meck, 1983, 1996). One possible reason for the failure of peak times to completely renormalize with additional training is that MK-801 may have also interfered with the updating of memory processes after a change in clock speed.

The second question addressed in Experiment 2 was whether the lack of a rebound of peak time following the cessation of MK-801 may be because of rats learning different criterion times for two states, noninjected and injected. To test this possibility, saline injections were administered during the postdrug test block. Although no clear rebound was found, peak times did reliably overshoot the criterion time following cessation of the drug, but only by a small degree. This result suggests that the absence of a rebound in Experiment 1 was not solely because of change in behavioral states caused by the experience of injections. We cannot discount the possibility, however, that state-dependent learning contingent to the subjective experiences of MK-801 may be important. Matell, King, and Meck (2004) also failed to find an expected rebound in peak times following long-term daily cocaine injections. They hypothesized that the clock speed itself may have been readjusted instead of the temporal memories, a process that may change depending on subtle differences in administration schedules of drugs. It is possible that a similar phenomenon occurred in the present study. Taken as a whole, the results from Experiment 2 suggest that effects of MK-801 on PI performance are at least partially consistent with a change in clock speed.

General Discussion

Effects of the NMDA antagonist MK-801 on short-interval timing in Fisher 344 rats were examined in two experiments. There were four main findings. First, for the PI procedure, the highest tested dose of MK-801 (0.2 mg/kg) produced a rightward shift in the distribution of peak times (overestimation of time) that attenuated with continued testing but did not completely return to the criterion time (see Experiments 1 and 2). Second, MK-801 in-

creased peak rate of responding (see Experiments 1 and 2). Third, the highest tested dose of MK-801 (0.2 mg/kg) produced a nonscalar increase in variability (see Experiments 1 and 2). Finally, a reset pattern was observed during the PI-gap procedure for all rats (see Experiment 1).

The rightward shift in the distribution of peak times (overestimation of time) produced by MK-801 stands in contrast to the effects of MK-801 and other NMDA receptor antagonists on DRL performance. Both chronic and acute administration of NMDA antagonists result in leftward shifts of IRTs (Sanger, 1992; Stephens & Cole, 1996; Tonkiss et al., 1988; Welzl et al., 1991). The leftward shift in IRTs has been interpreted as an underestimation of time, possibly because of speeding up the clock used for short-interval timing or shortening of the remembered time of reinforcement (Tonkiss et al., 1988; Welzl et al., 1991). Alternatively, the leftward shift in IRTs could be because of a drug-induced increase in response rate or impairment in the ability to withhold lever responses for the length of the target duration. The PI procedure was used in the present study to try to distinguish between these two interpretations.

Our results demonstrate that MK-801 produces at least two effects: an impairment of short-interval timing and a disruption of the motor action system (lack of response inhibition). With regard to the effect of short-interval timing, MK-801 produced an overestimation of time rather than an underestimation, as suggested by the DRL studies. This pattern of responding on the PI procedure under the influence of MK-801 is different from that observed after hippocampal lesions. On the one hand, in the PI procedure, rats with lesions of the hippocampus show a gradual and sustained *underestimation* of time (Meck, 1988; Meck et al., 1984, 1987; Olton et al., 1988). On the other hand, rats in the present study given systemic injections of MK-801 showed an immediate and partially transient *overestimation* of time. Thus, neither direction nor pattern of change caused by systemic NMDA antagonist and hippocampal lesions was similar in the PI procedure. These results suggest that the predominate effects of MK-801 on short-interval timing is unlikely to be occurring in the hippocampus, even though the hippocampus itself can influence timing, as demonstrated by the lesion studies.

With regard to the effects of MK-801 in disrupting motor inhibition, we found that MK-801 increased response rate. Further analysis of our data showed that rats under the influence of MK-801 had lever responses that started earlier, as well as a greater number, than those treated with saline. The earlier onset of responding is consistent with the pattern of results observed in DRL studies and would lead to a leftward shift in IRTs. On the basis of the results of the present study, our interpretation is that the leftward shift in IRTs in DRL studies is not because of an underestimation of time but rather because of the enhanced responding. This effect on responding may involve the hippocampus, as direct administration of MK-801 into the hippocampus has the same effect on DRL performance as systemic administration (Sanger, 1992; Sanger & Jackson, 1989; Tonkiss et al., 1988; Welzl et al., 1991). Previous studies have suggested a link between hippocampus and response inhibition (Jarrard, 1973; Tracy, Jarrard, & Davidson, 2001). In the present study, effects of MK-801 in the hippocampus may manifest as an increase in the rate of responding.

In regard to the MK-801-induced impairments on short-interval timing, it is important to comment here that the shift in peak time and increase in variability was observed only at the highest dose of MK-801 (0.2 mg/kg). It is possible that the initial, very large rightward shift in peak times may have been partly because of the dramatic increase in response rate and variability produced by the highest drug dose in the first drug block. Note, however, that in the second drug block, response rate and variability decreased, but peak times remained significantly longer than the criterion time of 12 s, and the effects seen on this second drug block may be more representative of the initial magnitude of overestimation than the first drug block. The fact that alterations in peak time were only observed at 0.2 mg/kg suggests a cautious interpretation is necessary. This dose is in the range in which MK-801 has been reported to cause disruption of performance on select timing tasks (Berz, Battig, & Welzl, 1992; Sanger & Jackson, 1989), although other studies using DRL have been successful in testing rats at 0.2 mg/kg (Sanger, 1992; Welzl et al., 1991). In DRL studies, it is typical to see a high dose of MK-801 causing a rapid drop in responding and an associated reduction in reinforcement (Sanger & Jackson, 1989; Welzl et al., 1991). For the present study, we did not observe uncoordinated movements, disorientation, or a drop in lever responding at 0.2 mg/kg of MK-801. In fact, our rats responded more than controls, and the response profiles showed peaks, suggesting that the stimulus still had some control over the behavior of the rats at this dose. Therefore, although it would be more convincing if the effects on peak time and variability were observed at more than one dose, preferably a lower dose, our rats did not display any signs of nonspecific effects typically associated with high doses of MK-801. One reason that we may not have observed the nonspecific effects of MK-801 at doses that others have is that the function of glutamatergic receptors can be dependent on strain (Manahan-Vaughan & Braunewell, 2005).

The observed effects of MK-801 are partly consistent with those observed with drugs that interfere with the dopamine system (Hinton & Meck, 1997; Maricq & Church, 1983; Maricq et al., 1981; Meck, 1983, 1986). Dopamine antagonists produce similar immediate overestimates of time (rightward shifts in peak time) that renormalize with continued training (Maricq et al., 1981; Meck, 1996). Upon removal of such antagonists, an immediate underestimate of time (leftward shift in peak time) occurs, which also renormalizes with additional training. Dopamine agonists have been shown to produce the opposite pattern (Maricq & Church, 1983; Meck, 1986, 1996). On the basis of these results, the dopamine system has been hypothesized to have an effect on the speed of the internal pacemaker, or clock (Meck, 1983, 1986, 1996; Meck & Church, 1987).

The notion that MK-801 may be interacting with the dopamine system to produce the effects observed here is consistent with other reports of interactions between NMDA receptor antagonists and the dopamine systems on behavior (Jeziorski, White, & Wolf, 1994; Marek, Beneliyahu, Gold, & Liebeskind, 1991; Trujillo & Akil, 1994) and memory processes (Castellano, Cestari, Ciamei, & Pavone, 1999; Castellano, Pavone, & Allegra, 1984; Cestari & Castellano, 1997; Quevedo, Moretto, Colvero, Roesler, & Ferreira, 1997). In fact, Meck (1996) hypothesized a role for interactions between glutamate and dopamine in temporal processing; however, he predicted that peak time under the influence of NMDA

antagonists would shift in the opposite direction of what was observed in the present study.

Our results differ from the effect of dopamine antagonists in a few respects. First, peak time shifts under MK-801 did not fully renormalize to the criterion time even with the addition of an extra test block in Experiment 2. Second, there was no meaningful rebound (abrupt opposite shift in peak times during postdrug blocks) following removal of MK-801 injections, as is typically the case with dopamine antagonists (Meck, 1983, 1986, 1996; Meck & Church, 1987). However, if, in the present work, there was interference from the initial dramatic increase in response rate during the first drug block, then (a) the first drug block may not have accurately measured the magnitude of overestimation, and (b) the magnitude of the expected rebound effect should be smaller than what we anticipated. Moreover, there is some precedent that drug manipulations known to affect the dopamine system do not always produce rebounds in peak times (Matell et al., 2004).

With regard to interactions between glutamatergic and dopaminergic systems in timing, future studies should examine the effects of NMDA antagonists on multiple durations. It would be important to know whether shifts in peak time caused by NMDA antagonists are scaled to the duration being timed, as with manipulations of the dopaminergic systems (Meck, 1996). A scalar shift in peak time would be consistent with an interaction of NMDA antagonist with the clock component of SET. Nonscalar changes to peak time may indicate a drug effect on latency to start/stop timing or alterations in the memory for the criterion time, but unlike that proposed for hippocampal or frontal cortex lesions (Meck et al., 1987; Olton, 1989).

In summary, we conclude that MK-801 has at least two effects. First, MK-801 interferes with short-interval timing by producing an overestimation of time and a nonscalar increase in variability. Overall, the lengthening observed in the present study is most consistent with a slowing in the speed of the "clock," suggesting that the primary effects of MK-801, on timing in tasks like the PI procedure, lies in nonhippocampal brain systems or at least include other brain systems in addition to hippocampus (Church, 2003; Meck, 1996; Meck et al., 1987). Second, MK-801 increases response rate, suggesting a decrease in response inhibition. This latter result is consistent with the pattern of results observed in DRL studies, and this effect on responding may involve the hippocampus (Jarrard, 1973; Tracy et al., 2001). These results extend our previous knowledge of the role of the NMDA receptor on learning, memory, and synaptic plasticity to that of short-interval timing (Morris, 2003; Morris et al., 1986; Shapiro & Caramanos, 1990; Shapiro & O'Connor, 1992). Evidence from this study suggests that NMDA receptors may interact with the dopaminergic system to influence short-interval timing.

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