

# Effects of *d*-Amphetamine and Ethosuximide on Responding Under Delayed-Matching-to-Sample Procedures With Differential and Nondifferential Outcomes

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POLING, A., K. ALLING, M. MAKHAY, M. NICKEL, E. BLAKELY, M. ROMAN AND H. SCHLINGER. *Effects of d-amphetamine and ethosuximide on responding under delayed-matching-to-sample procedures with differential and nondifferential outcomes.* PHARMACOL BIOCHEM BEHAV 42(4) 871-877, 1992. — Pigeons were exposed to delayed-matching-to-sample (DMTS) procedures in which food or a flash of the feeder light followed correct responses. When these consequences were correlated with a particular stimulus (e.g., food followed matching responses to red and a flash of the feeder light followed matching responses to green), accuracy was higher (i.e., stimulus control was greater) than when discriminative stimuli and consequences were not correlated. Although stimulus control in the absence of drug appeared to be weaker under the uncorrelated procedure, neither *d*-amphetamine (0.5–3.0 mg/kg) in Experiment 1 nor ethosuximide (40–160 mg/kg) in Experiment 2 disrupted accuracy to a greater extent under that procedure. These results, like those of a prior investigation, suggest that drug effects are similar under DMTS procedures regardless of whether correlated or uncorrelated outcomes are arranged.

*d*-Amphetamine    Ethosuximide    Delayed-matching-to-sample    Pigeons    Stimulus control  
Differential outcomes effect

MANY studies, reviewed elsewhere (11), demonstrated that performance in discrimination tasks is enhanced if different outcomes are presented for correct responses to different stimuli. This phenomenon, generally termed the differential outcomes effect (DOE), can be readily demonstrated under delayed-matching-to-sample (DMTS) procedures (1,3,5,8,17–21,29,31,33). A study by Alling et al. (1) provides a simple example of the DOE under a DMTS procedure. Those researchers gave pigeons a DMTS task in which the sample and comparison stimuli were red and green key lights and the outcomes were 4-s food deliveries or 0.5-s flashes of a hopper light. When these consequences were correlated with particular stimuli (e.g., food followed matching responses to red and a flash of the feeder light followed matching responses to green), accuracy was significantly higher than when consequences were not correlated with sample stimuli. The sample

stimulus correlated with food also engendered a much higher rate of responding than the stimulus correlated with the light flash.

In most cases, drug effects are smaller under conditions where behavior is strongly controlled by a discriminative stimulus than under conditions where stimulus control is weaker (12,13,28). Given this, Alling et al. (2) hypothesized that phenobarbital would disrupt behavior to a greater extent under the version of the DMTS procedure with uncorrelated outcomes. When administered acutely, 30 and 40 mg/kg doses of phenobarbital reduced accuracy under both variations of the DMTS procedure and lower doses did not significantly affect accuracy under either. At the dose range tested (10–40 mg/kg), rate of responding was not significantly affected under either version of the DMTS procedure. These results suggest that degree of stimulus control in the absence of drug did

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not modulate the effects of phenobarbital. Whether similar results would be obtained with two other drugs, *d*-amphetamine and ethosuximide, was examined in the present study.

Ethosuximide is a succinimide used clinically to manage absence and other seizures (23,25). There is little information about the drug's mechanism of action (25). The effects of ethosuximide on the operant behavior of nonhumans have been examined in some detail (24). Data are available concerning effects of the drug in pigeons responding under a DMTS procedure with uncorrelated outcomes (22), but not under such a procedure with correlated outcomes. The behavioral effects of *d*-amphetamine, a prototypical stimulant (23), also have been studied extensively (6). Prior studies have examined the effects of *d*-amphetamine under DMTS procedures with uncorrelated outcomes (9,10,14,26,27,34), but no reports of the effects of the drug under the correlated version of the DMTS procedure have appeared.

## EXPERIMENT 1: EFFECTS OF *d*-AMPHETAMINE

### METHOD

#### Subjects

Eight experimentally naive White Carneau pigeons, maintained at 80% of their free-feeding weights and individually housed with unlimited access to water and grit, served as subjects.

#### Apparatus

Experimental sessions were conducted in four test chambers (Lehigh Valley Electronics, Lehigh Valley, PA) measuring 36 cm high, 36 cm wide, and 30 cm long. A 6 × 6 cm aperture centered on the front wall permitted eating from a grain feeder. When raised, the feeder was illuminated with a 7-W white bulb. Three response keys, which could be illuminated in red or green, were mounted in a horizontal row on the front wall. The right key was 9.5 cm from the right wall and the three keys were spaced 8.9 cm apart. Each key could be operated by a force of 0.2 N. Ambient illumination was provided by a 7-W white light (houselight) centrally located on the ceiling of the chamber. Masking noise was supplied by a white-noise generator through a speaker mounted on the lower right corner of the front wall. A PDP8/A minicomputer (Digital Equipment Corporation, Maynard, MA), equipped with SUPERSKED software (State Systems, Kalamazoo, MI), arranged experimental conditions and collected data.

#### Procedure

Complete details of training are identical to those described by Alling et al. (1). In brief, all birds were first exposed to a variable-time 1-min schedule of access to grain until each reliably ate from the feeder. Birds were then exposed to an autoshaping procedure in which the center key was illuminated (either red or green) on the average of once each minute. After 5 s or one peck on the center key, whichever occurred first, the center key light was darkened and one of the side keys was illuminated with the color previously presented on the center key. The side key was illuminated until a key-peck occurred on that key or until 5 s elapsed, after which grain was presented for 6 s. Red and green illuminations were presented in a random sequence. When a bird pecked both center and side keys on at least 80% of the trials for three consecutive sessions, it was exposed to DMTS procedures.

Two variations of the DMTS procedure, equivalent except for the consequences of correct responses, were employed in the experiment proper. Four birds were exposed to each variation. Under one, the uncorrelated DMTS procedure, trials were separated by 7-s intertrial intervals (ITIs). Each trial began with a 0.25-s darkening of all lights, after which the houselight was illuminated and the center keylight was lighted in either red or green (i.e., the sample stimulus was presented). After 5 key-pecks, the center keylight was darkened and a delay of 0.01 s (hereafter referred to as 0 s) or 8 s ensued. In each session, the delay value selected for a given trial was determined by random selection without replacement from blocks of 10 delays, 5 of each value. This ensured that a similar number of 0- and 8-s delays were arranged. After the delay ended, both side keys were illuminated, one in red and one in green (i.e., the comparison stimuli were presented). A peck to the side key that matched the color previously on the center key, designated a correct response, produced either 4-s access to grain or a 0.5-s flash of the feeder light. During each session, the outcome on a given trial was determined by random selection without replacement from blocks of 10 outcomes, comprising 5 flashes of the hopper light and 5 food deliveries. This ensured that a similar number of food deliveries and hopper flashes were arranged. A peck to the other side key, termed an incorrect response, produced a 2-s blackout followed by the ITI. The same trial was then repeated until a correct response occurred. Trials were aborted if the response requirement on either the center or the side key was not completed within 30 s. These trials were not considered incorrect. Red and green sample stimuli, and the key locations on which red and green comparison stimuli occurred, were arranged at random with the exception that red and green illuminations were presented equally often as the sample stimulus in each session. Sessions ended after 70 trials or 50 min elapsed, whichever occurred first. Nearly all sessions ended after 70 trials. Exceptions occurred when *d*-amphetamine produced sustained periods without responding to the sample stimulus, which occurred infrequently.

Under the second variation, the correlated DMTS procedure, the outcome for a given correct response depended upon whether the trial involved a red or green sample stimulus. For two subjects, food was presented after correct responses on red trials and a flash of the feeder light was presented after correct responses on green trials; for two other subjects, food was delivered on correct green trials and a flash of the feeder light on correct red trials.

Subjects were exposed to the DMTS procedures of the experiment proper for a) at least 10 sessions and b) until there was no visually evident trend in percent correct responses for each delay across 5 consecutive sessions. When both criteria were met, all birds were given acute *d*-amphetamine injections under a BBBCD design wherein B represents baseline (no injection), C vehicle control sessions (0.9% sodium chloride solution), and D drug sessions. Two series of *d*-amphetamine injections were given; each series comprised four dosages (0.5, 1, 2, and 3 mg/kg, expressed as the salt) selected on the basis of prior studies (14,26,27). Within each series, the four doses were given in random order for each bird. All injections were administered IM at a 1 ml/kg volume 30 min before the session. The *d*-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.9% sodium chloride solution.

### RESULTS

During each session, rate of responding to the sample stimulus and percent correct responses (accuracy) were recorded

for all subjects. Figure 1 presents mean rate and accuracy data for subjects exposed to the uncorrelated and correlated DMTS procedures. In the absence of drug, mean percent correct responses at both the 0- and 8-s delay was higher under the correlated DMTS procedure than under the uncorrelated DMTS procedure (99 vs. 97% and 94 vs. 75%).

Accuracy data provide no evidence that *d*-amphetamine produced greater effects under the uncorrelated procedure. Statistical analysis of variance (ANOVA) for the uncorrelated condition revealed significant overall drug effects at both the 0-s delay,  $F(4, 12) = 11.3, p < 0.01$ , and 8-s delay,  $F(4, 12) = 7.5, p < 0.01$ . Tukey's test revealed that accuracy was significantly below the control level only at 3 mg/kg for both the 0-s delay,  $q = 5.9, p < 0.01$ , and 8-s delay,  $q = 4.9, p <$

0.01. Equivalent analysis of accuracy data for the correlated procedure revealed a significant overall drug effect at both the 0-s,  $F(4, 12) = 6.7, p < 0.01$ , and 8-s delay,  $F(4, 12) = 9.0, p < 0.01$ . Accuracy was significantly below the control level only at 3 mg/kg for both the 0-s delay,  $q = 4.4, p < 0.01$ , and 8-s delay,  $q = 5.2, p < 0.01$ .

Under the uncorrelated procedure, trial outcomes and response rates were not systematically related. In the absence of drug under the correlated procedure, response rates were much lower in the presence of the sample stimulus correlated with the hopper light flash than in the presence of the sample stimulus correlated with access to grain. For both trials that ended with food and those that ended with a flash of the feeder light, response rates under the uncorrelated procedure generally decreased with drug dose under the uncorrelated

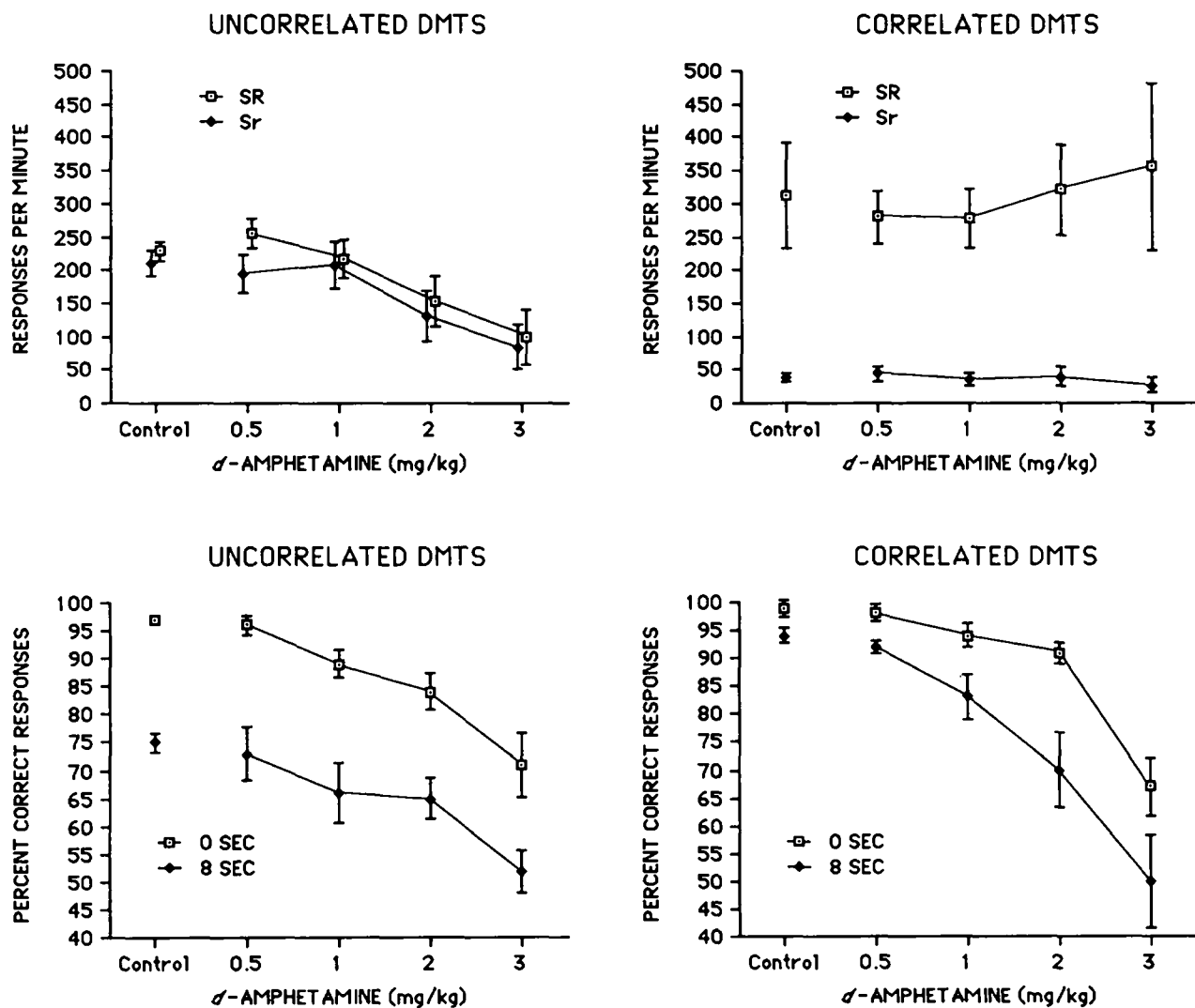


FIG. 1. Data for all conditions of Experiment 1. The upper frames depict mean responses per minute in the presence of sample stimuli when food (SR) or a flash of the feeder light (Sr) followed correct responses. Under the correlated procedure, each outcome was specifically paired with a particular stimulus color (e.g., food followed matching responses to red and a flash of the feeder light followed matching responses to green). Stimulus colors and outcomes were not paired under the uncorrelated procedure. The lower frames depict the percentage of correct responses to the comparison stimuli at 0- and 8-s delays under the correlated and uncorrelated DMTS procedures. Control data points represent the mean of all control sessions for four birds; *d*-amphetamine data points are the mean of both series of administrations for those birds. Vertical lines are standard errors.

procedure, but not under the correlated procedure. Statistical analysis revealed, however, that the drug did not significantly affect response rate relative to control values under either procedure, regardless of trial outcome ( $p > 0.05$ ).

#### DISCUSSION

In the absence of drug, accuracy at both the 0- and 8-s delays was higher under the correlated procedure than under the uncorrelated procedure. This finding, indicative of the DOE, accords with the results of many other studies (1,3,5,8,17-21,29,31,33).

Response rate data for the present study are consistent with those reported by Alling et al. (1). Under the correlated procedure, the stimulus correlated with a flash of the hopper light consistently engendered a much lower rate of responding than the stimulus correlated with food. Prior studies have shown that sample-specific response patterns, including dissimilar rates of responding to different sample stimuli, enhance accuracy under DMTS procedures [e.g., (4,7,16,29,30,35)]. Therefore, as explained in detail elsewhere (1,11), it is certainly plausible that the difference in response rates associated with food- and light-paired sample stimuli contributed to the improved accuracy observed under the correlated DMTS procedure in the present study.

Given that *d*-amphetamine often produces rate-dependent effects, increasing low-rate behaviors at doses that decrease high-rate behaviors (6), we speculated that the drug might produce rate convergence under the correlated DMTS procedure. But this did not occur, perhaps because local response rates were relatively high under all conditions, and the obtained results failed to clarify the role that sample-specific responding plays in producing the DOE. The present findings perhaps are noteworthy in indicating that a drug can alter accuracy in a DMTS task without simultaneously affecting response rate. Similar results were recently reported with phenobarbital (15).

The DMTS procedure has been used often and effectively to analyze drug effects on stimulus-controlled responding (28), but to our knowledge there is only one published study of drug effects under the correlated version of the DMTS procedure (2). In many cases, behavior that is strongly controlled by a discriminative stimulus is less affected by drugs than similar behavior that is stimulus controlled to a lesser degree (12,13,28). Given this, it is tenable that a given drug and dose would disrupt accuracy to a lesser degree under the correlated version of the DMTS procedure than under the uncorrelated version. This did not occur with *d*-amphetamine in the present study, nor with phenobarbital in an earlier investigation (2). Although stimulus control was weaker (i.e., accuracy was lower) under the uncorrelated version of the DMTS procedure, neither drug produced greater reductions in accuracy under that procedure.

In previous studies, Glick and Jarvik (9,10) reported that high doses of *d*-amphetamine reduced accuracy in monkeys exposed to a conventional (i.e., uncorrelated) DMTS procedure. Similarly, Spetch and Treit (26) reported that a 2 mg/kg dose disrupted accuracy in pigeons responding under a DMTS procedure with 0- and 20-s delays. In contrast to these results and those of the present study, McMillan (14) and Teal and Evans (27) found that *d*-amphetamine did not reduce the accuracy of pigeons responding under a DMTS procedure. The highest dose administered in those studies was 1 mg/kg, which may account for the absence of behavioral disruption. Pilot data reported by Spetch and Treit (26) are consistent

with this suggestion. They found that doses of 1.0 mg/kg or lower did not produce robust effects. Similarly, in a study examining the effects of *d*-amphetamine in pigeons responding under a titrating DMTS procedure, Wenger and Wright (34) found that the drug disrupted matching only at doses that also reduced rates, 3.0 mg/kg in most cases.

Neither pentobarbital nor *d*-amphetamine differentially affected accuracy under correlated and uncorrelated versions of DMTS. Experiment 2 examined whether ethosuximide would produce like results.

#### EXPERIMENT 2: EFFECTS OF ETHOSUXIMIDE

##### METHOD

##### *Subjects and Apparatus*

Eight White Carneau pigeons, maintained at 80% of their free-feeding weights, served as subjects. Subjects were maintained as in Experiment 1 and were tested in the apparatus used in that study. All subjects had previously received *d*-amphetamine or phenobarbital under DMTS procedures.

##### *Procedure*

Experimental procedures were similar to those employed in Experiment 1 except a crossover design, not a simple two-groups design, was used in this study. Because all birds had a history of exposure to DMTS procedures, no initial training was necessary. Uncorrelated and correlated DMTS procedures were employed in the experiment proper. Four subjects (Group 1) initially were exposed to the correlated procedure as described in Experiment 1; four others (Group 2) initially were exposed to the uncorrelated procedure as described in Experiment 1.

Subjects were exposed to the assigned procedure for a) at least 10 sessions and b) until there was no visually evident trend in percent correct responses for each delay across 5 consecutive sessions. When both criteria were met, all birds were given acute ethosuximide injections under a BBCD design wherein B represents baseline (no injection), C vehicle (distilled water) control injection sessions, and D drug sessions. Two series of ethosuximide injections were given; each series comprised four doses (40, 80, 120, and 160 mg/kg) selected on the basis of prior studies (22,24). Within each series, the four doses were given in random order for each bird. All injections were administered IM at a 1 ml/kg volume 30 min before the session. The ethosuximide (Warner-Lambert, Ann Arbor, MI) was dissolved in distilled water.

After subjects completed two series of ethosuximide injections under the conditions described above, conditions were reversed so that Group 1 was exposed to the uncorrelated DMTS procedure and Group 2 to the correlated DMTS procedure. These procedures were arranged as described above. After performance stabilized, the effects of ethosuximide were again examined. This was done in the same fashion as the first drug evaluation (i.e., each bird received each of four doses twice in random order under a BBCD design).

##### RESULTS

During each session, rate of responding to the sample stimulus and percent correct responses (accuracy) were recorded for all subjects. Figure 2 presents mean rate and accuracy data for subjects exposed to the uncorrelated and correlated DMTS procedures. In the absence of drug, mean percent correct re-

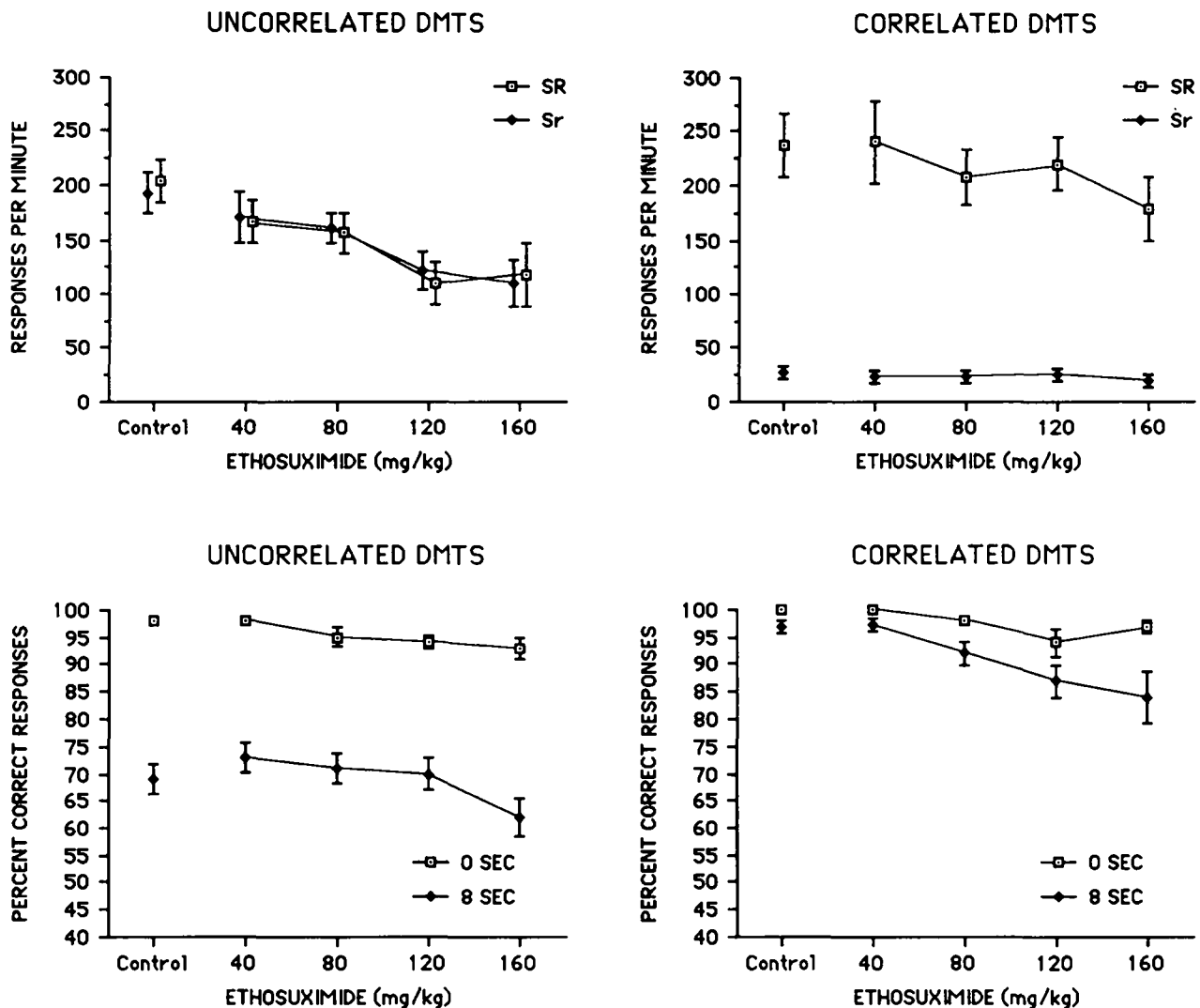


FIG. 2. Data for all conditions of Experiment 2. Details are as in Fig. 1 except control and drug data represent the performance of eight birds, four initially exposed to the uncorrelated DMTS procedure and four initially exposed to the correlated DMTS procedure, after which conditions were reversed.

sponses at both the 0- and 8-s delays was higher under the correlated DMTS procedure than under the uncorrelated DMTS procedure (100 vs. 98% and 97 vs. 69%).

Accuracy data do not indicate that ethosuximide produced greater effects under the uncorrelated procedure. One-way repeated-measures ANOVA of accuracy data for the uncorrelated procedure revealed significant overall drug effects at both the 0-s delay,  $F(4, 28) = 4.6, p < 0.01$ , and 8-s delay,  $F(4, 28) = 3.2, p < 0.05$ . Tukey's test indicated that accuracy at all ethosuximide doses did not differ significantly from the control level. One-way repeated-measures ANOVA of accuracy data for the correlated procedure revealed significant overall drug effects at both the 0-s delay,  $F(4, 28) = 10.9, p < 0.01$ , and 8-s delay,  $F(4, 28) = 11.3, p < 0.01$ . Tukey's test showed that accuracy at the 0-s delay was significantly below the control level when 120 mg/kg ethosuximide was administered,  $q = 8.2, p < 0.01$ . Accuracy at the 8-s delay

was significantly below the control level at ethosuximide doses of 120,  $q = 5.3, p < 0.05$ , and 160 mg/kg,  $q = 7.4, p < 0.01$ .

Trial outcomes and response rates were not systematically related under the uncorrelated procedure. In contrast, under the correlated procedure response rates were much lower in the presence of the sample stimulus correlated with the feeder light flash than in the presence of the sample stimulus correlated with access to grain. One-way repeated-measures ANOVA performed on rate data collected under the uncorrelated DMTS revealed a significant overall effect for both trials that ended with food,  $F(4, 28) = 4.5, p < 0.01$ , and trials that ended with a flash of the hopper light,  $F(4, 28) = 5.2, p < 0.01$ . Tukey's test revealed that response rates were significantly below control levels at ethosuximide doses of 120 and 160 mg/kg for trials followed by food,  $q = 5.0, p < 0.05$ ,  $q = 4.9, p < 0.05$ , and at the 160 mg/kg ethosuximide dose,

$q = 5.4$ ,  $p < 0.05$ , for trials followed by a flash of the hopper light. No significant effects were evident in rate data collected under the correlated procedure ( $p > 0.05$ ).

#### DISCUSSION

In Experiment 2, as in Experiment 1 and several prior investigations (1,3,5,8,17-21,29,31,33), accuracy (i.e., percent correct responses) in the absence of drug was greater under the correlated DMTS procedure than under the uncorrelated procedure. Drug effects often are weaker when behavior is strongly controlled by a discriminative stimulus than when it is stimulus controlled to a lesser degree (7,8,17). Consequently, it is reasonable to posit that drugs might disrupt behavior to a greater extent under the uncorrelated version of the DMTS procedure, where accuracy in the absence of drug is substantially lower (i.e., stimulus control is weaker). This did not occur with phenobarbital in a prior study (2), with *d*-amphetamine in Experiment 1, or with ethosuximide in this experiment. In fact, no dose of ethosuximide significantly impaired accuracy under the uncorrelated version, which is consistent with prior findings (22). Under the correlated version,

however, accuracy was significantly below the mean control value at certain ethosuximide doses. There is no obvious mechanism of drug action that accounts for this apparent difference in the effects of ethosuximide under the two versions of DMTS.

In the present study, as in Experiment 1 and earlier investigations employing similar procedures (1,2), the sample stimulus correlated with food delivery controlled a much higher rate of responding than the stimulus correlated with a flash of the food hopper. As discussed previously, it is possible that the difference in response rates associated with food- and light-paired sample stimuli contribute to the improved accuracy observed under the correlated DMTS procedure. In principle, pharmacological manipulations could help to clarify the role of sample-specific response rates in producing the DOE: If rates converge at doses that also disrupt accuracy, this would suggest that rate differences contribute to the DOE. This did not occur with ethosuximide in the present study, with *d*-amphetamine in Experiment 1, or with phenobarbital in an earlier investigation (2). To date, pharmacological manipulations have not proven valuable in isolating the behavioral mechanism responsible for the DOE.

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