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NMDA Receptor Channel Antagonism by Dizocilpine (MK-801) Impairs Performance of Rats in Aversively Motivated Complex Maze Tasks

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SPANGLER, E. L., E. L. BRESNAHAN, P. GAROFALO, N. J. MUTH, B. HELLER AND D. K. INGRAM. *NMDA receptor channel antagonism by dizocilpine (MK-801) impairs performance of rats in aversively motivated complex maze tasks.* PHARMACOL BIOCHEM BEHAV **40**(4) 949–958, 1991.—To determine the involvement of the N-methyl-D-aspartate (NMDA) receptor in shock-motivated complex maze performance, the drug dizocilpine (DIZO; a.k.a. MK-801) was administered a) to naive, 3-month-old male F-344 rats prior to acquisition (AQ) in the 14-unit T-maze (Experiment 1), and b) to well-trained 11-month-old male F-344 rats prior to testing in a delayed-matching-to-sample (DMTS) task in the detour maze (Experiment 2). For Experiment 1, rats first were pretrained in a straight runway on one-way active avoidance (13/15 correct avoidances) for a maximum of 30 trials. On the following day, either DIZO 0.025 (n=8), 0.05 (n=8), 0.1 (n=8), mg/kg, or saline (SAL; n=15) was administered subcutaneously (SC) 20 min prior to 15 AQ trials in the shock-motivated 14-unit T-maze. The highest dose disrupted all measures of maze performance including errors, alternation errors, runtime, shock duration and frequency, but also produced marked motor ataxia. The 0.05-mg/kg group displayed significant impairment in AQ of this task but only on the cognitive measures, errors and alternation errors, and the 0.025-mg/kg group was impaired on the alternation measure only. One week later, the 15 SAL rats were divided into 2 groups and tested on retention with either SAL or 0.05 mg/kg DIZO. No effects on maze performance were observed. For Experiment 2, after receiving extensive pretraining in the shock-motivated detour maze, 7 rats were exposed to a novel sequence of 4 problems (P) during each of 7 daily sessions. Performance was evaluated 20 min after SC injection of either DIZO—0.025, 0.05, 0.125 mg/kg, or SAL. The 0.125-mg/kg dose caused extreme motor ataxia which precluded testing during that session. The 0.05-mg/kg but not the 0.025-mg/kg dose significantly disrupted performance on both error and trials to criterion measures. Both problem and interaction effects were significant. Disruption was most evident on two specific problems, those involving a side change from the first to second detour. Also, rats had more difficulty switching sides from problem to problem (few errors on P-1 and most on P-4), suggesting proactive interference effects. In sum, DIZO was observed to significantly disrupt performance in both mazes in a dose-related manner similar to effects observed in previous studies following administration of the anticholinergic drug scopolamine. For the 14-unit T-maze, the present results simulate age-related deficits previously found in acquisition of that task.

MK-801 Glutamate receptor Calcium channels Excitatory amino acids Aging Learning and memory

THE N-methyl-D-aspartate (NMDA) receptor has been implicated in development, learning and memory, and neuropathology in humans and other mammalian species [for reviews, (7,14)]. Studies designed to evaluate NMDA receptor involvement in learning and memory in mammals have implicated this neuroexcitatory receptor in the induction, but not maintenance, of hippocampal long-term potentiation (23,39). Long-term potentiation (LTP) refers to a long-lasting electrophysiological change observed in hippocampal and certain other cell types after brief stimulation that may last for weeks in an intact animal (9,39), and it has been implicated in the storage of experience-derived information (1). Involvement of this receptor in the neuropathology of stroke also has been suggested [for review (21)].

Age-related losses of NMDA receptors in a variety of mammalian species including rat brain have been reported (8, 22, 35); however, receptor loss may be dependent on the region surveyed (24). Further, hippocampal NMDA receptor loss has been correlated with age-related impairments in acquisition of a Mor-

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ris water maze task (26). NMDA receptor antagonism with drugs such as ketamine or dizocilpine (DIZO, a.k.a. MK-801), (+)-5-methyl-10,11-dihydro-5H-dibenzo-[a,d]-cyclohepten-5,10 imine hydrogen maleate, disrupts not only LTP, but learning and memory as well (1). Behaviors that are particularly sensitive to hippocampal disruption such as spatial memory (1) also appear to be sensitive to NMDA receptor blockade. For example, DIZO which is a noncompetitive, ion channel-blocking drug, disrupted place (i.e., spatial) learning in the Morris water maze and taste potentiation of an acquired odor aversion (27). The drug, however, had no effect on cue (i.e., nonspatial) learning in the Morris water maze or on the association of odor or taste with an unconditioned stimulus in the conditioned aversion task. In the radial arm maze, DIZO administration impaired acquisition (5,29), and memory for the arms entered following an interposed delay (4,29). Using various glutamatergic antagonists, Flood et al. (12) observed that both NMDA and non-NMDA glutamate receptor blockade disrupted retention of T-maze avoidance behavior in mice. However, strong arguments have been made that better control over sensorimotor effects of NMDA antagonists is needed to support the hypothesis of NMDA receptor involvement in memory processing and LTP (18). Thus a specific role for NMDA receptors in learning and memory requires further clarification in other behavioral paradigms.

Through a systematic series of investigations, cholinergic system involvement in the acquisition of a complex shock-avoidance 14-unit T-maze task has been established in young rats. The deficits found from cholinergic manipulation were similar to the age-related impairments observed during acquisition of this task (15,16). Specifically, in young rats, muscarinic receptor blockade with scopolamine disrupted acquisition (30,31) but did not affect retention (31); similarly, in young rats, lesions of the fimbria-fornix (2) disrupted learning in this maze. However, in contrast to our expectations, treatment of aged rats with cholinomimetics had little or no beneficial effect on maze acquisition (17), and thus involvement of other systems alone or in conjunction with cholinergic systems appeared plausible. Evaluation of the noradrenergic system alone (by depletion with DSP4) and in combination with cholinergic blockade (scopolamine treatment) was undertaken in young rats. Whereas cholinergic systems were further implicated by disruption in a scopolamine control group, no effect of noradrenergic depletion alone or interactively was observed in this maze (32). Thus the previous findings prompted further studies to evaluate involvement of other neurotransmitters. NMDA receptors were considered as an excellent candidate due to their implication in acquisition (27,29) and retention (12) of a number of behavioral tasks, and in several neurodegenerative disorders (8,21) that result in memory deficits.

Similarly, cholinergic system involvement was implicated in complex maze-avoidance performance by Bresnahan et al. (3), who used a novel delayed-matching-to-sample (DMTS) paradigm in a new 3-section detour maze. Unlike the 14-unit T-maze that requires the rat to acquire and retrieve a fixed pattern of 14 position discriminations to move without error through the maze, the detour maze task involves retrieving a memory for a correct pathway on choice trials following two sample trials. After choice trial criterion is attained on a given problem, the correct pathway is changed for each following problem in a given problem sequence. The detour maze, like the 14-unit T-maze, was sensitive to muscarinic cholinergic disruption by scopolamine administration and by fimbria-fornix lesions in young rats (3).

The objective of the two experiments reported here was to determine NMDA receptor involvement in performance of these two maze tasks by young rats. Such demonstration could provide further information pertinent to the age-related performance deficits previously observed in the 14-unit T-maze (17). To accomplish this goal, we injected rats with different doses of DIZO prior to: a) acquisition in the 14-unit T-maze; b) retention in the 14-unit T-maze; and c) DMTS performance in the detour maze.

EXPERIMENT 1: 14-UNIT T-MAZE

METHOD

Subjects

Two weeks prior to testing, 39 3-month-old male Fischer-344 rats obtained from Harlan Sprague-Dawley were delivered to the Gerontology Research Center, where they were housed two per cage in plastic cages in a vivarium maintained at 22°C with a 12-h light/12-h dark photocycle (lights on 6 a.m. EST). Food (NIH-07 formula) and water were provided ad lib.

Apparatus

A previously described *straight runway* (30) was used for pretraining in one-way active avoidance. The runway (2 m long) was constructed of clear Plexiglas with a diagonally oriented, stainless steel grid floor wired to receive a constant-current scrambled electric shock (Model E13-08; Coulbourn Instruments, Lehigh Valley, PA). A hand-held mechanical switch was wired to one clock for initiating a shock contingency and to a second clock for recording shock duration. Interchangeable black, Plexiglas boxes, each having a movable rear panel with a rod attached, served as start and goal boxes that could be placed over the grid floor at each end of the straight runway. A tall gray wall (74 cm) on either side of the runway prohibited external visual cues other than the overhead fluorescent lights.

As described previously (30), the *14-unit T-maze* (see Fig. 1) had a diagonally oriented stainless steel grid floor wired to a shock source (Model E13-08, Coulbourn Instruments, Lehigh Valley, PA). This large maze (2 × 2 m) was divided into 5 segments by guillotine doors that could be lowered as the rat crossed into each subsequent segment. Thus backtracking into the prior segment was prevented. Infrared photocells located throughout the maze were wired to a microprocessor for electronic recording of runtimes and number of entrances into the 14 cul-de-sacs located throughout the maze. As in the straight runway, identical black Plexiglas boxes were interchangeable for start and goal boxes. Four gray walls surrounded the maze, and four fluorescent overhead lights provided ambient light without casting shadows over the maze. The entire maze could be raised by means of an automatic hoist and pulley system to permit cleaning between trials. Four audio speakers mounted below the maze provided 20-dB white noise for masking extraneous sound.

Procedure

Pretraining (day 1). At least 30 min prior to straight runway avoidance training, all rats were brought to the test room and allowed to adapt to 20-dB white noise. For the initial trial, a rat was removed from its home cage; placed into an interchangeable start/goal box; and gently pushed from the start box into the runway. Once the rat was in the runway, a guillotine door was lowered to prevent start box reentry. The rat had 10 s to run down the straight runway into the goal box to avoid footshock or to escape footshock (0.8 mA) if its runtime exceeded the 10-s criterion. Upon goal box entry, a guillotine door was lowered, and the rat remained in the goal area for 30 s. It was then moved to a holding area for an additional 90 s, i.e., a 2-min

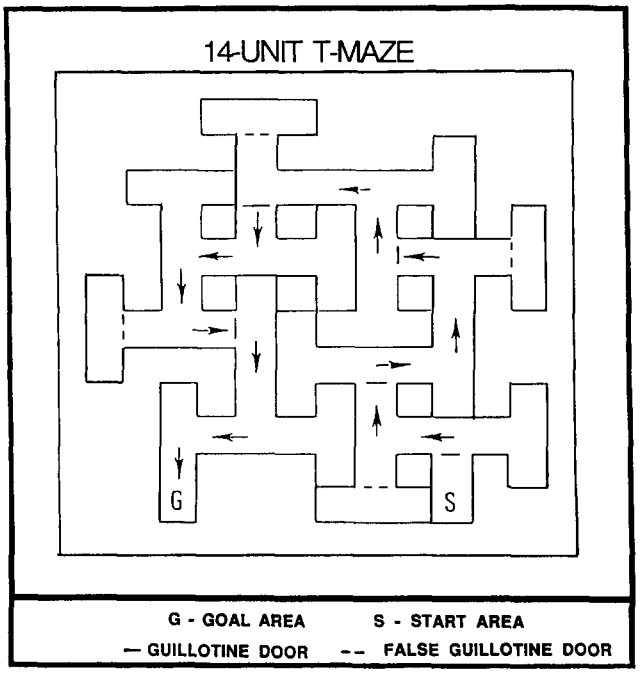

FIG. 1. Configuration of the 14-unit T-maze (2×2 m).

intertrial interval (ITI) occurred before the next trial. Criterion for completion of straight runway pretraining was 13 correct (no shock) trials out of 15 with a 30-trial maximum.

Maze acquisition (day 2). Before 14-unit T-maze training began, rats were brought to the test room in their home cages for a minimum 30-min adaptation period to white noise. Each rat then was removed from its home cage and placed in the start box. After the start box was placed over the grid floor in the start area, the rat was gently pushed into the maze. The start box door was lowered, and the shock avoidance contingency was set mechanically. To avoid footshock in each of 5 maze segments, the rat was required to move through a segment beyond the guillotine door within 10 s. If the 10-s time limit was exceeded, shock was automatically initiated and continued until the rat passed beneath the guillotine door. This guillotine door was then lowered, and the shock avoidance contingency for the new segment was reset. A trial was completed when the rat entered the goal box located in the final maze segment. After remaining in the goal area for 30 s, the goal box containing the rat was moved to a holding area for an additional 90 s awaiting the next trial (i.e., a 2-min ITI). During each ITI, the maze was hoisted, and the grid floor was cleaned with a 95 percent ethanol solution to mask possible odor cues. Each rat received 15 acquisition trials in this 14-unit T-maze. All training was conducted between 9:00 a.m. and 5:00 p.m.

Drug treatment. Rats were assigned randomly to one of the following treatment groups: saline—SAL (n=15); DIZO—0.025 mg/kg (n=8); DIZO—0.05 mg/kg (n=8); or DIZO—0.1 mg/kg (n=8). DIZO was mixed fresh daily and delivered as subcutaneous injections (volume=0.5 cc/kg) 20 min prior to maze learning. The experimenter performing maze testing was naive as to drug treatment.

Retention testing. One week after acquisition testing, the group of SAL rats from acquisition were given 10 successive retention trials. The 15 rats were randomly assigned to one of two groups, SAL (n=7) or DIZO—0.05 mg/kg (n=8). Procedures for adaptation to the white noise and the test room were identical to those during acquisition.

Statistical Analysis

Acquisition. The 14-unit T-maze acquisition data comprised five measures: errors, alternation errors, runtime, shock frequency, and shock duration. Alternation errors as previously defined (30) refer to errors committed during forward movement that result from the pursuit of an alternation strategy (i.e., an inaccurate sequence of LRL or RLR turns).

The mean for each block of 3 trials was computed (5 trial blocks for each measure), and then these trial block means were subjected to a square root transformation to reduce the marked heterogeneity of variance observed in the DIZO—0.1-mg/kg group. Transformed data were submitted to 4 (drug treatment) × 5 (trial block) analyses of variance (ANOVAs) with repeated measures on the latter factor. Dunnett's tests (10) were conducted to compare each DIZO treatment group with the SAL control group.

Retention. As with acquisition, retention data were collected for the five measures. Because heterogeneity of variance was not observed with the two retention groups (SAL and DIZO—0.05 mg/kg), these data were not transformed. For the 10 trials, means for two blocks of 5 trials each were computed and analyzed by 2 (drug treatments) × 2 (trial blocks) ANOVAs with repeated measures on the latter factor.

RESULTS

Compared to the SAL controls, treatment with DIZO differentially impaired maze acquisition for the three treatment groups (Fig. 2). First, treatment with the 0.1-mg/kg dose significantly increased errors, alternation errors, runtime, shock duration, and shock frequency. Further, all rats within this high-dose group exhibited motor ataxia when rearing but not when running to avoid shock. Thus the ability to run was not completely impaired. Second, treatment with the 0.05-mg/kg dose impaired performance on the error and alternation error measures only. Runtimes and shock avoidance were not affected at this dosage. Third, the lowest dose of DIZO, 0.025 mg/kg, affected only the alternation error measure. Thus runtimes and shock avoidance measures were not affected by the two lower levels of the drug, whereas errors and/or alternation errors were affected at all three dosages. In contrast to the increase in errors and alternation errors for the DIZO—0.05-mg/kg group during acquisition, retention performance (Table 1) was not impaired for previously trained SAL control rats given DIZO (0.05 mg/kg) prior to retention. Statistical confirmation of these findings is presented below.

Acquisition

Errors. As shown in Fig. 2A and revealed by the main effect of drug treatment, $F(3,35)=32.03$, $p<0.001$, DIZO impaired error performance in a dose-related manner. Further, a significant main effect of trial block was evident to indicate that learning occurred, $F(4,32)=52.65$, $p<0.001$; and significant learning differences occurred among the four groups, as shown by the significant drug treatment by trial-block interaction, $F(12,85)=2.34$, $p<0.05$. By the last block of trials, both the SAL and 0.025 groups' mean error scores were less than 4, whereas those of remaining groups were higher. For all groups, the greatest decline in errors occurred between blocks 1 and 2.

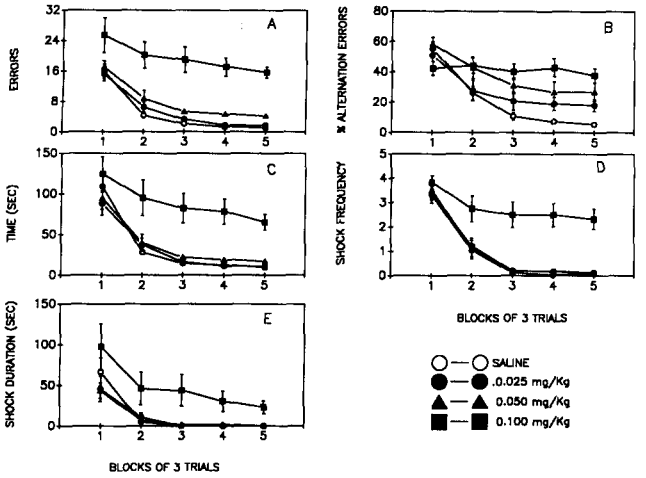

FIG. 2. (A) Mean ERRORS and SE's per trial made on 5 trial blocks for each of 4 groups: SAL (n=15); DIZO—0.025 mg/kg (n=8); DIZO—0.05 mg/kg (n=8); and DIZO—0.10 mg/kg (n=8). (B) Mean % ALTERNATION ERRORS and SE's on each trial block for all SAL- and DIZO-treated rats. (C) Mean RUNTIME in s and SE's on each trial block for the SAL- and DIZO-treated rats. (D) Mean SHOCK FREQUENCY and SE's on each trial block for all SAL- and DIZO-treated rats. (E) Mean SHOCK DURATION and SE's on each trial block for all SAL- and DIZO-treated rats.

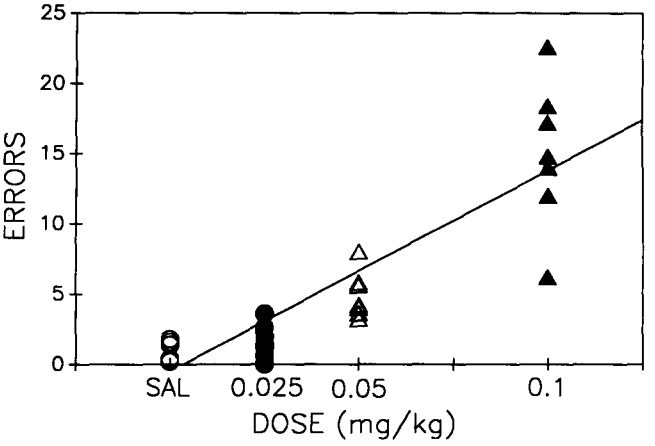

FIG. 3. Scatterplot showing the dose-response effect of mean errors per trial on the final trial block for individual subjects.

However, mean errors for the 0.1-mg/kg group never dropped below 15; thus learning occurred by the last trial block for all except this 0.1-mg/kg group. Dunnett comparisons at each block of trials confirmed the dose-related error differences (p's<0.05). Relative to SAL controls, the 0.1-mg/kg group was impaired at all 5 trial blocks, whereas the 0.05-mg/kg group was impaired at blocks 2–5 only. In contrast, no impairment was observed in the 0.025-mg/kg group. This dose-dependent error increase is particularly clear as shown by the scatterplot of individual data for the final trial block (see Fig. 3).

Alternation errors. Figure 2B portrays the dose-dependent characteristic for the percentage of alternation errors in response to DIZO treatment, with the 0.1-mg/kg group maintaining this alternation strategy throughout the 15 trials. This variable represents a derived estimate of the proportion of errors made using an alternation strategy involving at least 3 choice-point responses (LRL or RLR). Alternation errors were significantly higher for drug-treated groups, $F(3,35)=9.94$, $p<0.001$, indicating that DIZO-treated rats showed a greater tendency to use an alternation strategy for problem solution. The significant effect of trial blocks, $F(4,32)=30.01$, $p<0.001$, combined with decreases in alternation errors for all groups except the 0.1-mg/kg group indicates learning across the 15 trials for these 3 groups. A significant treatment by trial-block interaction, $F(12,85)=3.71$, $p<0.001$, indicated that the learning slopes across trial blocks were different for the four groups. Dunnett comparisons at each trial block revealed no significant group differences at block 1. However, relative to the saline control group, the 0.05- and 0.1-mg/kg groups each made significantly more alternation errors at blocks 2–5, whereas the 0.025 group made significantly more alternation errors at blocks 4–5 only (p's<0.05). Although the percentage of alternation errors for the SAL control group continued to decrease across all 5 trial blocks, little decrease was observed after trial block 3 for the 0.025 and 0.05 groups, and no decrease was observed for the 0.1-mg/kg group. In the 14-unit T-maze, this alternation error measure appears most sensitive to the dose-dependent effects of DIZO.

TABLE 1

RETENTION TEST PERFORMANCE ON FIVE MEASURES FOR A SALINE (SAL) GROUP (n=7) AND A DIZO, 0.05 mg/kg GROUP (n=8)

Behavior Measure	Saline Control	DIZO 0.05 mg/kg
Errors	1.44 (0.54)	2.10 (0.39)
Alternation Errors	0.09 (0.03)	0.14 (0.03)
Runtime	11.09 (2.26)	10.96 (1.47)
Shock Frequency	0.19 (0.12)	0.21 (0.08)
Shock Duration	1.03 (0.71)	1.11 (0.59)

Means (standard errors) per trial are shown.

Runtimes. As shown in Fig. 2C and as indicated by the significant drug treatment effect, $F(3,35)=15.14$, $p<0.001$, runtime differences occurred among groups. Dunnett tests comparing the mean runtime per trial collapsed across all trials indicated only one significant group difference. Compared to controls, the 0.1-mg/kg group took significantly more time to traverse the maze. Additionally, as learning progressed, runtimes decreased significantly across the 5 trial blocks, $F(4,32)=34.57$, $p<0.001$; there was no significant interaction on this measure.

Shock frequency. Mean shock frequency for each group is portrayed in Fig. 2D. Significant effects among drug treatment groups, $F(3,35)=22.34$, $p<0.001$, and trial blocks, $F(4,32)=151.17$, $p<0.001$, were found. As learning progressed across trial blocks, there was a rapid decrease in the number of shocks received. A significant drug treatment by trial-block interaction, $F(12,85)=4.66$, $p<0.001$, revealed differences in the group slopes across trials. That is, shock frequency decreased to almost zero at block 3 for all groups except the 0.1-mg/kg drug group. This group continued to receive shock for section runtimes longer than 10 s. Dunnett comparisons revealed that relative to the control group, only the 0.1-mg/kg group received a significantly greater number of shocks on trial blocks 2–5. There were no group differences at the first trial block.

Shock duration. Mean shock duration (amount of shock) for each group is portrayed at each trial block (see Fig. 2E). The

ANOVA indicated significant group differences, $F(3,35)=9.96$, $p<0.001$, and a significant effect of trial block, $F(4,32)=21.5$, $p<0.001$. The interaction, however, was not significant ($p>0.05$). Dunnett tests comparing the mean shock duration per trial collapsed across all trials indicated only one significant group difference ($p<0.05$); compared to controls, the 0.1-mg/kg group received significantly more shock.

Retention

Table 1 shows the retention test means and standard errors for SAL and DIZO (0.05 mg/kg) treated rats on all performance measures. No significant drug treatment effect was observed. However, a significant effect of trial block on each measure emerged to indicate that relearning occurred rapidly within the 10 trials, $F's(1,13)=12.96$, $p<0.002$, for error; 7.96, $p<0.01$, for alternation error; 14.61, $p<0.002$, for runtime; 11.04, $p<0.005$, for shock frequency; and 6.32, $p<0.03$, for shock duration. No significant drug treatment by trial-block interaction was evident, i.e., decreases in these measures from the first to second trial blocks were not different for the SAL and DIZO–0.05-mg/kg treated groups.

EXPERIMENT 2: DETOUR MAZE

METHOD

Subjects

Seven male Fischer-344 rats were born and reared for 6–7 months as a cohort in a large clear Plexiglas cage (60 × 60 × 37 cm) in a vivarium at Essex Community College, Baltimore, MD. Before the beginning of detour maze training, rats were placed (2 per cage) in large stainless steel suspended cages (Wahmann) and remained in these cages throughout 17 weeks of DMTS pretraining and subsequent behavioral test sessions. The DMTS test sessions began when the seven rats were approximately 11 months old. Throughout rearing, training, and behavioral testing, both food (Purina Lab Chow) and water were available ad lib; temperature in the room was maintained at 22°C, and overhead lights were on from 7:00 a.m. to 7:00 p.m.

Apparatus

As previously described (3), the shock-avoidance detour maze had 3 pairs of detours extending bilaterally from the inner straight runway portion, one pair in each of 3 maze sections (S1, S2, S3). This maze (see Fig. 4) was constructed of white and black Plexiglas with walls 20 cm high. The straight runway portion was white, and the detours were black. The entire maze (278 × 83 cm) rested on a rectangular stainless steel grid floor. The grid floor was wired to receive constant, scrambled shock current from a Coulbourn Instruments Grid Floor Shocker (Model 13-08). The entire apparatus was supported on a stand, elevated 49 cm from the floor, with four speakers located beneath each corner to provide white noise. Onset and offset of shock were initiated manually by a hand-held momentary switch connected to the grid floor shock unit.

Identical start and goal boxes constructed of black Plexiglas with white strips on the interior sides and a movable back panel could be used interchangeably by placement over the grid floor at opposite ends of the center runway (222 cm long). Two removable guillotine doors, positioned in the straight runway portion between the 3 maze sections, could be lowered to prevent backtracking during early stages of pretraining. A 100-watt light bulb, suspended beneath a white shade, hung directly above the goal area. In each maze section, white inserts (entrance and exit doors of a detour) could be removed for detour use or replaced for runway use as required by any particular problem. One or more clear Plexiglas squares could be inserted in the center runway portion immediately past the detour entrance(s) to block the runway, thereby forcing the rat to enter a detour. A black Plexiglas removable panel could be inserted in the distal portion of any detour to form a cul-de-sac (detour block). Thus, as constructed with multiple removable inserts, this maze afforded 26 possible problems of varying complexity by using different detour pair combinations from the 3 maze sections with either a left or right side option for a detour block (cul-de-sac).

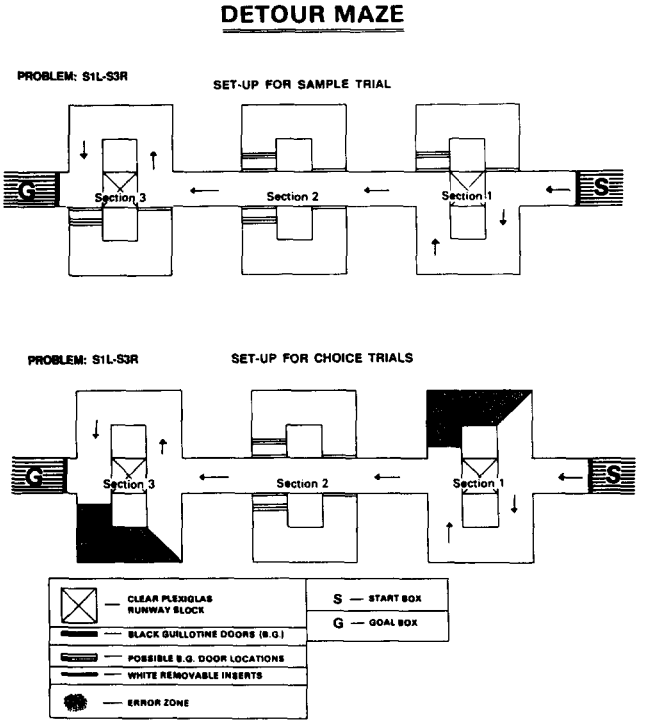

FIG. 4. A diagram of the detour maze showing an example of the maze configuration used for one specific 2-detour problem on sample and choice trials.

Problem Construction

For any given problem, one detour from a pair (right or left) was unblocked (correct detour), and the opposing detour of that pair was blocked (incorrect detour). Each possible problem could involve either one detour pair in one maze section, two detour pairs in two maze sections, or three detour pairs in three maze sections. On sample trials for any given problem, the incorrect/blocked detour entrance(s) was closed, and the animal was "forced" to travel through the correct detour(s) to reach the goal box. On choice trials, the entrance to the blocked detour(s) was opened permitting a side choice at the choice-point(s). Figure 4 shows the maze configuration on sample and choice trials for one specific 2-detour (2-D) problem, i.e., a problem requiring two correct choices on each choice trial for errorless performance. Problems could either be presented singly (one per day), or as a sequence of problems presented each day (e.g., 3 problems per day). Whereas rats were trained first with 24,

1-detour (1D), 2-detour (2D), and 3-detour (3D) problems, all testing for the present experiment occurred with only one chosen problem sequence composed of four 2-detour problems. As shown in Fig. 4, errors were defined as full entry into the blocked detour and were punished by a brief shock pulse (0.5 mA for 0.12 s duration).

Pretraining Procedures

Straight runway avoidance and DMTS pretraining. Each rat was first trained for 3 consecutive days (14 trials per day) to avoid pulsed footshock (0.5 mA) in the long straight runway portion of the maze. Ten weeks of detour training followed with one of 24 problems presented each day in a DMTS paradigm. For each problem, 14 trials occurred as follows: 2 sample trials—5 choice trials; 2 sample trials—5 choice trials. The time interval between sample trials was 12 s, whereas that between subsequent choice trials was 30 s (a delayed condition). During the early weeks of this detour pretraining, both rearing and hesitation tended to drop out as these behaviors were punished with a brief shock pulse(s). As training progressed, rats ran to the goal box with little hesitation, seldom receiving footshock except for errors in the blocked detour. At the end of the 10-week period, all 7 rats were performing at better than 85 percent correct choices.

Multiple problem DMTS pretraining. During the following 6 weeks, DMTS training was modified to a 3 problem per day procedure with a 30-min interval occurring between successive problems. Time intervals between successive trials remained unchanged. The problems were combined into varied daily sequences with a different combination of 3 problems for each day of the week. From these varied sequences, a chosen set of 10 different 3-problem sequences was repeated 3 times over the 6 weeks (5 sequences per week). That is, 30 changing problems occurred every 2 weeks. With each individual problem, a criterion of 2 correct trials from 3 consecutive choice trials was imposed. Once the rat met this problem criterion, it was returned to its home cage to await the next problem in the sequence. Thus, on any given problem, the minimum number of choice trials was 2 and the maximum number of choice trials was set at 10. During the 6th week of this DMTS training with the varied 3-problem sequences, each rat achieved criterion by the second choice trial on most problems and by the third choice trial if an error was made. Performance was close to perfect and was deemed sufficiently accurate for subsequent drug testing.

Test Procedures

Problems. For seven daily sessions, the single sequence of four 2-detour problems was chosen for testing under both drug and control conditions (see Table 2). These same four problems were repeated on each saline or drug session. This new and moderately difficult sequence afforded reasonably accurate baseline performance for comparison with that under drug conditions.

General. Following a simple 1-detour warm-up problem to denote the start of each test session, the rat received a subcutaneous injection of either saline (SAL) or DIZO. Testing on the first problem of the sequence began 20 min after injection. A 25-min interval separated the 4 test problems. For each problem, the above-described multiple problem DMTS procedure was in effect. That is, on both sample and choice trials, the rat was required to run from start to goal without stopping; a full entrance into the blocked detour was punished; and the performance criterion for each problem was 2 correct from 3 consecutive choice trials. Because these rats were well trained, only one adaptation session was necessary for familiarization with the 4-problem sequence.

TABLE 2

DESCRIPTION OF TEST PROBLEMS (P) PRESENTED IN THE DETOUR MAZE DURING EXPERIMENT 2

Four 2-Detour Problems — One Sequence Only	
P-1	S1L-S2L
P-2	S1R-S3L
P-3	S1R-S2R
P-4	S1L-S3R

Note: Each P involves 2 detours, i.e., 2 choices per problem. Each P involves a side change from the previous problem. Two P's are same side problems and two opposing side problems. Each rat makes 4 turns to enter, run through, and exit each detour (see Fig. 2).

Three pairs of detour sections (S1, S2, S3) and two opposing sides in each section, left (L) and right (R) were combined into four 2-Detour problems. S1 is adjacent to the start box; S3 is adjacent to the goal box; and S2 occurs between S1 and S3.

Drug treatment. Each rat received a subcutaneous injection of SAL on sessions 1, 2, and 5. For sessions 3 and 4, DIZO, mixed fresh and provided at doses of either 0.025 or 0.05 mg/kg, was administered in a counterbalanced order 20 min prior to maze testing. On session 6, no saline (NO-SAL) was administered but the rat was handled as though it were receiving an injection. On session 7, the 0.125-mg/kg dose of DIZO was administered 20 min prior to maze testing. Because severe motor ataxia precluded further behavioral testing following this higher dose of DIZO, test session analyses ended with session 6.

Statistical Measures

Individual subject data were collected on four behavioral measures for each problem: number of errors (ERRORS), number of trials to criterion (TC), mean sample runtime (SRT), and mean choice runtime (CRT). These data were used in four 2-factor repeated-measures ANOVAs over six test sessions (control or drug) and test problems (1 through 4). Wherever appropriate, separate ANOVA comparisons over each pair of treatment sessions were conducted to determine specific drug, problem, and interaction effects.

RESULTS

The highest DIZO dosage (0.125 mg/kg) resulted in severe motor ataxia. Rats could neither stand nor run in the maze until the drug began to dissipate, approximately 2 h postinjection. Thus performance was analyzed for 6 sessions only. DIZO at the 0.05-mg/kg dose had a significant effect on memory for a preceding sample event in this detour maze ($p<0.001$). ERRORS and TC (see Fig. 5) were significantly higher during this drug session than during each remaining session (all p's<0.05). As compared to all SAL control sessions, the lower dose of the drug, 0.025 mg/kg, did not significantly impair DMTS choice accuracy. However, relative to the NO-SAL session wherein choice accuracy was close to perfect, choice performance was moderately disrupted by the 0.025-mg/kg dose of DIZO ($p<0.05$). Further, the increase in errors during the 0.05-mg/kg test session was most pronounced on the more difficult problems from the sequence (P2 and P4), those requiring a side change between

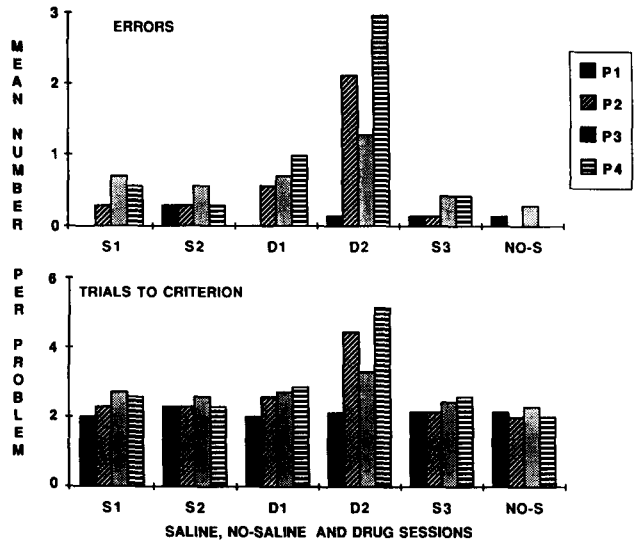

FIG. 5. Experiment 2: S = saline; D1 = 0.025 mg/kg and D2 = 0.05 mg/kg. Mean errors and trials to criterion for 7 rats on choice trials for each of 4 problems during control and DIZO sessions. On the 4 problems, the SE's for all control sessions ranged from 0.0 to 0.32; for the 0.025-mg/kg session, SE's ranged from 0.0 to 0.32; and for the 0.05-mg/kg session, from 0.16 to 1.31. Note that the same four problems, each separated by 30 min, occur during each session. All control sessions are compared to the drug session in a within-subjects design.

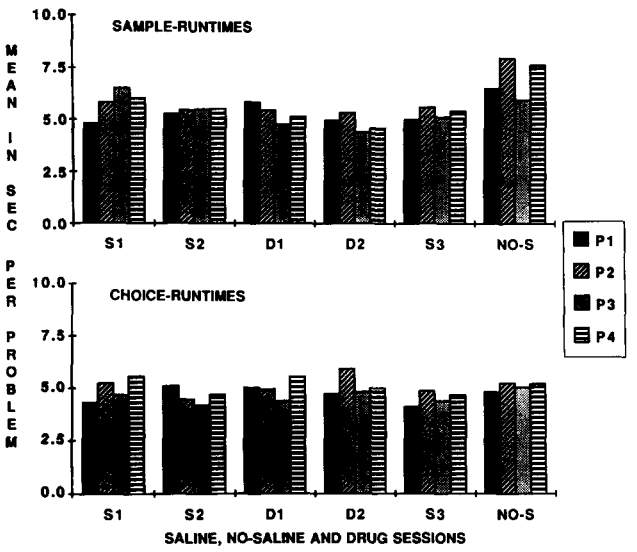

FIG. 6. Experiment 2: S = saline; D1 = 0.025 mg/kg and D2 = 0.05 mg/kg. Mean sample and choice runtimes for 7 rats on each of 4 problems during control and DIZO sessions. On the 4 problems, the SE's for all control sessions ranged from 0.26 to 1.40; for the 0.025-mg/kg session, SE's ranged from 0.31 to 0.56; and for the 0.05-mg/kg session, SE's ranged from 0.33 to 0.78.

the two detours (LR or RL). Few errors occurred on the first problem in the sequence, whereas most errors occurred on the fourth problem. These different drug effects across problems suggested that proactive interference was affecting response accuracy in this detour maze, as noted previously (3). Although choice runtimes (CRTs) were not affected by the drug (see Fig. 6), sample runtimes (SRTs) were significantly faster under the influence of the 0.05-mg/kg dose, which may have contributed to the significant increase in errors, i.e., less time for attending to and processing relevant information on sample trials.

Test Session Effect

Significant main effects on both ERROR and TC measures were indicated by the 2-factor repeated-measures ANOVAs [ERROR, $F(5,30) = 9.0$; and TC, $F(5,30) = 10.3$; p's<0.001]. As shown by ANOVA comparisons, ERRORS and TC were significantly greater during the 0.05-mg/kg DIZO session than during each remaining session including the 0.025-mg/kg session (all p's<0.05). Also, ERRORS AND TC were significantly higher ($p = 0.01$) during the 0.025-mg/kg DIZO session than during the NO-SAL control session only. Choice accuracy was close to perfect during this last control session. Although there were no significant choice runtime differences among the six test sessions, the ANOVA over SRT data did show significant test session effects, $F(5,30) = 10.4$, $p<0.001$. The ANOVA comparisons for SRT revealed significantly faster sample runtimes during the 0.05-mg/kg session than those during all five remaining test sessions (all p's<0.05) and SRTs during the NO-SAL session were longer than those during both the 0.05- and 0.025-mg/kg sessions only. Thus, during the 0.05-mg/kg DIZO test session, SRTs were considerably faster and errors were higher as compared to all control sessions, whereas, during the 0.025-mg/kg session, SRTs were faster and errors were higher only when compared to the near-perfect NO-SAL session.

Problem Effect

The repeated-measures ANOVAs indicated significant problem effects for ERROR, TC and CRT measures [ERROR, $F(3,18) = 4.8$, $p<0.05$; TC, $F(3,18) = 4.7$, $p = 0.01$; and CRT, $F(3,18) = 3.3$, $p<0.05$]. Combined across all test sessions, less ERRORS and TC occurred on problem 1 than on the three remaining problems, a possible indication of proactive interference effects. Error means for the four problems were: P1, 0.12; P2, 0.57; P3, 0.67; P4, 0.88; errors tended to increase with successive problems. Also, choice runtimes collapsed across sessions were shortest on problems 1 and 3. Mean CRTs in s for each problem were: P1, 4.71; P2, 5.15; P3, 4.61 and P4, 5.14.

Interaction Effects

In addition to the above-described main test session effects, the repeated-measures ANOVAs indicated significant test session by problem interactions for the ERROR, TC and SRT measures [ERROR, $F(15,90) = 1.96$; TC, $F(15,90) = 2.05$; and SRT, $F(15,90) = 2.07$; all p's<0.05]. These significant interactions reflect differences in the slopes of the scores from problem to problem that exist on the six test sessions. For the ERROR measure, the 2-factor ANOVA comparisons over pairs of test sessions indicated only two significant interactions: those between the NO-SAL session and each DIZO session (both p's<0.05). For these two DIZO sessions, errors tended to increase across the 4 problems, whereas, during the NO-SAL control session, the slope across problems was flat with only 1, 0, 2, and 0 total errors occurring on P1 through 4, respectively. For the 0.025-mg/kg DIZO session, total errors were 0, 4, 5, and 7, respectively, whereas those for the 0.05 DIZO session

were 1, 15, 9, and 21, respectively. Significantly more errors were made on problems 2, 3 and 4 during both the 0.025- and the 0.05-mg/kg DIZO sessions compared to the NO-SAL session, wherein performance was close to perfect. ANOVA comparisons for the TC measure indicated similar effects (all p's<0.05). For the SRT measure, the significant interaction between test sessions and problems reflects the differences among test sessions in runtimes from problem to problem. As shown by the ANOVA comparisons, the major portion of this effect was due to an increase in SRTs across the four problems during the first SAL test session compared to the decrease in SRTs across the four problems during both DIZO sessions.

Although a selective but significant effect of ERROR occurred among the four problems for both DIZO sessions, the major effect on errors from 0.05 mg/kg DIZO was a general enhancement across problems, as shown by the significant main effect of test session. That is, error scores were significantly higher under the influence of this 0.05-mg/kg dose than were those during all remaining sessions. Further, chi-square analyses of equal error frequency distributions across the 4 different problems were completed for each individual test session revealing an unequal distribution of errors for the 0.05-mg/kg DIZO session only ($\chi^2 = 19.04$, $p<0.001$). Additionally, for each behavioral measure, an ANOVA over all four control sessions indicated no significant differences among the four control sessions for ERROR, TC, and CRT measures. For the SRT measure, however, a significant difference was indicated among controls sessions ($p<0.01$). The ANOVA comparisons revealed that the effect was due to mean differences in overall SRTs between the third SAL session (mean SRT = 5.31) and the NO-SAL session (mean SRT = 7.04; $p<0.01$). Although errors were least on this last test session (NO-SAL), sample runtimes were longer. This finding is directly opposite to that shown during the 0.05-mg/kg DIZO session, wherein errors were higher and sample runtimes were faster.

GENERAL DISCUSSION

Learning and memory performance in two aversively motivated complex maze tasks was disrupted following NMDA receptor antagonism with dizocilpine. Naive, young rats in the 14-unit T-maze and well-trained adult rats in the detour maze were disrupted in all aspects of maze performance at the higher doses of DIZO (0.1 mg/kg in the 14-unit T-maze; 0.125 mg/kg in the detour maze). An adverse reaction to these higher doses occurred in both mazes, i.e., motor ataxia was observed in all rats. In the 14-unit T-maze, although rats from the DIZO—0.1-mg/kg group made swaying head and body movements, they were able to run to avoid shock. In the detour maze, the 0.125-mg/kg dose resulted in similar movements, but more significantly, rats fell and were unable to right themselves. This effect did not dissipate for almost 2 h. As a result, data from this session were not included in analyses. These ataxic effects are similar to those reported by Robinson et al. (27) and further confirm that high doses of this compound can have severe effects on sensorimotor function. Additionally, these dose-related effects of DIZO could be due to blockade of NMDA receptors in vestibulomotor areas, as suggested by a previous investigation of NMDA and vestibular compensation in the guinea pig (28).

At the DIZO dose of 0.05 mg/kg, disruption was observed in error and alternation error measures in the 14-unit T-maze with no effects on noncognitive performance measures of runtime and shock avoidance. In the detour maze, the same dose affected error and trials to criterion measures as well as producing faster sample runtimes, suggesting that the drug may have had an effect on sensorimotor performance. In the 14-unit T-maze, the lowest dose (0.025 mg/kg) did result in a tendency for rats to maintain an alternation strategy during the final blocks of training; in the detour maze, this lowest dose resulted in a small but significant increase in errors and trials to criterion when compared to the last NO-SAL session, a session with near-perfect choice accuracy. Otherwise, the lowest dose of DIZO had little impact on performance in either maze. These data agree with those of Robinson et al. (26), who found impaired acquisition of the Morris water maze following a 0.05-mg/kg dose of DIZO; with those of Shapiro and Caramanos (29), who used a slightly higher dose (0.06125 mg/kg) to demonstrate a deficit in the Morris water maze without sensorimotor effects; and with those of McLamb et al. (19), who also found a deficit without sensorimotor impairment in this water maze following a 0.05-mg/kg dose of DIZO. Although cognitive deficits did occur in the 14-unit T-maze with both the 0.05- and 0.025-mg/kg doses, these two DIZO groups were nearly identical to the SAL group on runtime and shock measures, indicating that neither the neurotoxic effects observed at the highest dose (0.10 mg/kg) nor other sensorimotor effects were evident at these lower dosages. In addition, the 0.05-mg/kg dose produced no performance effects in this maze when administered prior to a retention test. Thus, in accordance with others, a 0.05-mg/kg dose of DIZO appears to be effective for impairing learning of the 14-unit T-maze by naive young rats with little effect on sensorimotor performance.

The alternation error results in the 14-unit T-maze further confirm that this cognitive measure is particularly sensitive (17,32). As previously stated, this alternation strategy is probably adaptive for initial learning trials. However, it should drop out as learning progresses, and does so with young control rats. Whereas use of this alternation strategy declined from trial blocks 1 to 3 in the 0.05-mg/kg DIZO group, indicating that some learning occurred, these rats continued to make alternation errors throughout training (see Fig. 2B). Similarly, the 0.025-mg/kg group tended to continue this strategy through the final trial blocks. That is, slightly less than 20 percent of the 0.025-mg/kg group's opportunity for errors during these blocks reflected alternation errors, and this group was not deficient on other performance measures. In contrast, only 5–6 percent of such errors made by the SAL group during the final two blocks of trials were alternation errors. Thus the DIZO-treated rats tended to perseverate in the use of this strategy, a finding similar to that seen in previous studies of 14-unit T-maze acquisition with aged rats and rats with cholinergic blockade (16).

In the detour maze, the observation of faster sample runtimes during the 0.05-mg/kg DIZO session is suggestive of a general sensorimotor change, e.g., hyperlocomotion, a reported characteristic of DIZO, PCP and PCP-like drugs (27). Such effects could create problems for a strict cognitive interpretation (18). In their review, Keith and Rudy (18) noted that higher doses of DIZO (>1.0 mg/kg) are required to effectively block LTP, and these same doses have been observed to induce sensorimotor impairments. However, before discounting a cognitive interpretation of the data in the detour maze, it is important to note that only sample runtimes, not choice runtimes, differed during testing with the 0.05-mg/kg dose. Thus, during 0.05-mg/kg DIZO session, rats ran faster only when the incorrect detour entrance was blocked, i.e., on sample (forced) runs. The fact that no differences were observed during choice runs indicates that if hyperlocomotion were involved, it was not severe and may have affected the encoding of, or the attention to, the correct pathway during sample runs, rather than affecting retrieval of that information on subsequent choice trials. Also, if sensorimotor effects were responsible for the cognitive effects observed in this task, the disruption in error and trials to criterion measures should be more evenly distributed across problems. But this is not the case,

as revealed by problem interaction analyses.

Further explanation for the results obtained in this detour maze refers to the 4-problem sequence used in the present DMTS task. That is, increased sensitivity to proactive interference after DIZO treatment may be responsible for increased errors and trials to criterion during drug sessions. Proactive interference in this task refers to disruption of present problem performance created by the stimuli from, and responses to, the previous problem. The present data fit well with Winocur's interference model (37). In a recent report using a DMTS operant task with rats, Dunnett and Martel (11) demonstrated that bar pressing on the side opposite to that from the previous trial resulted in increased errors, which was due to proactive interference. Similarly, in the detour maze, more errors were made during the 0.05-mg/kg session when problems changed from same-side problems (Ps 1 and 3) to opposite-side problems (Ps 2 and 4). Also, the fact that minimal errors occurred on P1 for all six test sessions (only 5 total errors for 7 rats) strongly suggests a role for proactive interference in this sequence (3). Also, the fact that choice accuracy was significantly disrupted under the influence of DIZO (0.05 mg/kg) further suggests that the DIZO may increase sensitivity to such proactive interference effects.

Although the DMTS task in the detour maze was well learned, DIZO significantly disrupted performance. These results are not in agreement with Wozniak et al. (38), who observed that DIZO disrupted retention of new information (reversal of a position habit could be learned but not remembered the following day), whereas DIZO did not disrupt tasks that were well learned prior to drug administration (spatial alternation and radial arm maze performance). The detour maze results are also not in total agreement with the hypothesis presented by Cotman and Monaghan (8). These authors suggested that because NMDA receptors are responsible for the induction, but not the maintenance of LTP, blockade of NMDA receptors should disrupt new learning but not retention or performance on tasks in which the animal has been well trained. In the detour maze, all rats were well trained after having 16 weeks experience on the DMTS task with all possible problems, and yet disruption occurred during DIZO treatment. However, the 4 test problems did occur in a new sequential arrangement, i.e., this specific 4-problem sequence was never in effect during pretraining, a fact that could support the hypothesis of disruption for new learning only. But the sequential nature of the problem set as well as the specific problems chosen were major factors in the presently observed deficits. That is, these opposite-side problems previously were found to be significantly more difficult than same-side problems (3). The present sequence contains two such difficult problems, as well as the imposition of a side change for correct detours that occur from each problem to the next. Thus the present task appears to be especially difficult and sensitive to proactive interference. DMTS performance on the difficult problem sequence as presented in the present study may be more susceptible to proactive interference than was performance in those tasks used by Wozniak et al. (38). In complex and demanding tasks, then the above issue raised by Cotman and Monaghan (8) remains equivocal.

Similar to the 14-unit T-maze, the detour maze is an egocentric task dependent upon internal movement cues. For entry into the correct detours on choice trials, the rat must acquire space and response attributes related to the correct detour(s) during sample trials and retain this information during choice trials. Part of the "to-be-remembered" information includes movement-related excitation, i.e., movement coming from the multiple right angle turns required to reach the goal (34). In large mazes such as the 14-unit T-maze and the detour maze, this type of movement may be an important aspect of learning and memory (3, 13, 17, 34). Although similar in many other respects (avoidance-motivated; large and complex mazes), these two tasks are different with respect to the type of memory required for successful performance. Whereas performance in the detour maze (a DMTS task) is dependent upon working (25) or representational (33) memory for a different and changing goal path, the 14-unit T-maze requires the rat on repeated trials to learn only one complex path to the goal. Thus performance in the 14-unit T-maze is more dependent upon reference (24) or dispositional (33) memory than that in the detour maze. Another important difference in these two mazes involves the use of a within-subjects design in the detour maze. Once subjects are well trained on the multiple-problem DMTS task, they can be repeatedly tested over time with changing problems and sequences. This flexibility is similar to that in operant tasks and is equally economical with respect to numbers of subjects. For example, difficulty level can be manipulated further by increasing or decreasing the length of the problem sequence or by varying the delay between sample and choice trials. Additionally and importantly, after the initial weeks of pretraining, subjects require and receive little shock; thus a high performance level can easily be maintained. This detour maze with its many differences, especially that of working memory dependence for performance accuracy, adds to our analyses of performance in complex avoidance-motivated maze tasks.

To further understand results of our past studies showing maze performance disruption from septo-hippocampal cholinergic system interventions (2, 30, 31) in comparison to our present finding of disruption with the NMDA receptor antagonist DIZO, we must incorporate additional information on the hippocampal system. For example, the densest concentrations of central NMDA receptors in rats and in humans have been observed in the CA1 region of the hippocampus, a region that also contains high levels of muscarinic cholinergic receptors (7). Further, acetylcholine has been observed to potentiate responses of iontophoretically applied NMDA in hippocampal slice (19); and double-labeling studies have indicated that at least in some regions of the brain, muscarinic cholinergic and glutaminergic cells are colocalized on the same neurons (6). Thus a study to evaluate a possible interaction between these two systems and their impact on performance in the 14-unit T-maze and in the detour maze is in progress.

Further, the robust age-related acquisition deficits often observed in the 14-unit T-maze (15,17) that are similar to those found in young rats following scopolamine (0.5 mg/kg) treatment (30,31) also are similar to the present acquisition impairment following NMDA receptor channel blockade with DIZO treatment. Although some reports have found little age-related alteration in excitatory amino acid neurotransmission in rat brain (24), other reports of marked declines in NMDA receptors are emerging (22,35). Thus loss of these receptors also may be responsible, at least in part, for the previously observed declines in cognitive performance observed during 14-unit T-maze acquisition by aged rats. However, it is curious that in a previous report, hippocampal NMDA receptor concentration was found to correlate directly with maze errors made during retention testing in the 14-unit T-maze, i.e., rats that made the most errors during retention had the highest concentration of NMDA receptors (36). To further explore this relationship, we have initiated studies to evaluate possible age-related changes in sensitivity to DIZO and its effects on performance in these two mazes. These new avenues of research may lead to more productive outcomes than have been possible thus far under the cholinergic hypothesis of geriatric memory dysfunction.

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