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Scopolamine Impairs Spatial Working Memory in the Radial Maze: An Analysis by Error Type and Arm Choice[1]

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PILCHER, J. J., G. R. SESSIONS AND S. A. MCBRIDE. *Scopolamine impairs spatial working memory in the radial maze: An analysis by error type and choice.* PHARMACOL BIOCHEM BEHAV **58**(2) 449–459, 1997.—The effects of scopolamine hydrobromide on performance in uninterrupted and delayed radial maze trials were studied in the rat. In addition to defining errors as incorrect arm entries, errors were defined by incorrect nose pokes in a food trough and were summed across the number of correct choices remaining. The average time elapsed from arm entry to nose poke was also calculated as a new measure of motivation and mobility. Working memory errors increased significantly following scopolamine injection in the uninterrupted trials and occurred significantly more often before the last correct choice. Errors in nonbaited arms during the last portion of a 3-h delay task increased significantly following scopolamine injection both before and after the first portion of the task and occurred more often before the last correct choice. However, nonbaited errors occurred more readily and at lower doses when scopolamine was injected 20 min before the onset of the task than when scopolamine was injected immediately after the completion of the first portion of the task. These data indicate that scopolamine affects current working memory and specifically affects acquisition more than consolidation of working memory. © 1997 Elsevier Science Inc.

Scopolamine Anticholinergic drugs Working memory Spatial memory Memory consolidation Memory acquisition Memory retrieval Radial maze Rat

IMPAIRMENT of central cholinergic systems negatively affects learning and memory in a variety of paradigms [e.g., (2,9,23,24,27)]. More specifically, using a centrally active anticholinergic such as scopolamine hydrobromide disrupts acquisition of new tasks and performance on previously learned tasks [e.g., (1,13)]. The radial maze testing paradigm has been used by a number of investigators specifically to test the effects of scopolamine on spatial working memory [see (5,15)]. One radial arm maze procedure that tests for general deficits in current spatial working memory is the uninterrupted radial maze task in which all arms of the maze are baited. Scopolamine administration, 20–30 min prior to testing in the uninterrupted radial maze task, has a detrimental effect on current spatial working memory [e.g., (10,14,16)]. In these studies, investigators usually recorded working memory errors when an animal reentered (usually defined as four paws past the arm threshold) a previously entered arm and then reported the total number of errors committed.

One limitation of the uninterrupted radial arm maze task is that decreases in performance cannot be attributed to specific types of memory difficulties. For example, the uninterrupted radial arm maze task with all arms baited does not provide a means to test for specific deficits in memory acquisition vs. consolidation, because only the current component of memory (i.e., working memory) is utilized while completing the task. One manner of using the radial arm maze specifically to test acquisition and consolidation of working memory is to impose a delay in the task after the animal has successfully completed a portion of the maze. If the delay is long enough to allow scopolamine to be sufficiently metabolized, errors committed during the second portion of the maze task can indicate difficulties in memory acquisition or consolidation instead of memory retrieval because scopolamine would have little, if any, effect after the delay. Similar to the paradigm used in the uninterrupted radial maze procedure, errors under delay conditions were usually defined as reentries into previ-

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ously entered arms, which were then summed and reported as the total number of errors committed while completing the task. In studies using a radial arm maze delay procedure, a dose-dependent decrease in performance has been found when scopolamine is injected before the animal is allowed to complete the first half of the radial maze but not if scopolamine is injected immediately after completing the first half of the maze (3,7,12). These data suggest that scopolamine affects acquisition but not consolidation of working memory.

To date, the majority of studies using the radial maze procedure have limited the manner in which they report their outcomes by reporting only the total number of errors made during the completion of the task. However, there is some evidence that the manner in which errors are recorded can have an effect on error rate and thus the conclusions drawn about the effects of scopolamine on performance and memory. One study (10) defined specific types of errors: nose over plane of arm entrance, two paws over plane of arm entrance, four paws over plane of arm entrance and head over food cup. Error rates following scopolamine administration were greater when using the nose entry vs. four-paws entry as arm entry criteria. Their results suggest that error definition influences the interpretation of the effect of scopolamine on memory.

An additional means of more closely examining the effects of scopolamine on memory is to examine error rate as the task becomes more difficult and thus increases the likelihood of error occurrence. For example, in the radial arm maze task, the probability of reentering a previously entered arm increases with each successive correct choice; consequently, the difficulty of the task may be conceived as increasing with each correct choice. Therefore, an increase in error rate as the difficulty level of the task increases would be indicative of a deficit in working memory. One means of examining the pattern of errors as difficulty level increases in the radial arm maze is to analyze the number of errors committed prior to each correct arm choice. Eckerman et al. (10) tracked errors in a similar manner by analyzing their data for each arm choice. They reported that choice accuracy did not change when animals were completing the first four choices but gradually decreased during choices 5–8. An alternative method of examining errors as difficulty level increases in the radial maze is to sum errors committed for each correct choice. This method allows a more precise interpretation of the pattern of errors committed while completing the maze than simply reporting errors made in the first eight choices.

To document better the effects of scopolamine on working memory in the radial arm maze, the present study used a computer-monitored maze to quantify more precisely the types and pattern of errors. Animals were tested in both uninterrupted and delay trial procedures. However, unlike previous studies, errors were separated into specific categories of arm entry errors (defined by breaking a vertical plane 15 cm inside the arm entrance) and nose poke errors (defined as breaking a vertical plane inside the food trough positioned at the end of the arm). It was expected that arm entry errors would be committed more frequently than nose poke errors because nose poke errors required the animal to traverse the length of the arm. In addition, all errors were summed across each correct choice, permitting us to examine the pattern of errors across correct choices made. Because scopolamine impairs working memory, it was expected that the number of arm entry and nose poke errors would increase as the number of remaining correct choices decreased. As measures of motivation and mobility, we recorded time to maze completion, total number of food pellets retrieved and total arm entries. In addition, our ability to record arm entries separately from nose pokes allowed us to develop a new measure of motivation and physical mobility by calculating the average time from arm entry to nose poke in a food trough.

STUDY 1

This study examined the effects of scopolamine on memory and performance in uninterrupted radial arm maze trials with all arms baited. Three types of errors were defined and cumulated across the number of correct choices remaining. In addition, as indicators of motivation and mobility, total number of pellets retrieved, total time in maze, total number of arm entries and time from arm entry to nose poke in food trough were recorded and analyzed.

METHOD

Subjects

The subjects were 10 male Sprague–Dawley rats (Zivic Miller Laboratories, Allison Park, PA) approximately 4 months old at the onset of training. The animals were housed individually in an air-conditioned colony room in acrylic rack-mounted cages with pine sawdust bedding. The room was illuminated with overhead fluorescent lights maintained under a 12-h light–dark cycle, with light onset at 6 AM. The animals were allowed ad libitum access to water and Purina Rat Chow until they reached body weights of approximately 450 g. Food was then gradually restricted over a 4-week period until the body weights were reduced to approximately 80% of the initial free-feeding level. Thereafter, food was given in an amount sufficient to maintain body weight at the 80% level and water was freely available.

Apparatus

A symmetrical, totally enclosed, eight-arm radial maze was used. The maze was constructed from 6.25-mm polycarbonate plastic and was mounted on stainless steel legs 75 cm above the floor. The arms extended from an octagonal center compartment 51.5 cm in diameter and 12.7 cm high. Each arm was 19.7 cm wide, 61 cm long and 12.7 cm high. Each arm was equipped with a photocell sensor 15 cm inside the entrance. The center of the maze could be isolated from the arms by guillotine gates that were operated manually by an experimenter, who was approximately 3 m from the radial maze, via strings suspended from the ceiling. A photocell-equipped recessed food trough was mounted on the end wall of each arm connected to a food dispenser (Coulbourn Instruments, Allentown, PA). The food dispenser delivered one 45-mg food pellet (Dustless Purified Diet Precision Pellets, BioServ, Frenchtown, PA) when the food-trough photocell beam was interrupted. Also mounted on the end wall of each arm was a 1.27 cm miniature stimulus light. Additional details on the construction of the maze have been described in a previous publication (11).

The maze was housed in an air-conditioned room and surrounded on all sides by walls, equipment racks or office separator panels. The separator panels were made visually distinguishable by a 24.13 cm high plus sign or triangle attached to the panels. A laboratory computer (PDP 11/73, Digital Equipment Corporation, Nashau, NH) running SKED-11 software (25) was interfaced with each photocell in the maze via Lablink interface modules (Coulbourn Instruments) and was

used to detect arm entries, arm exits and nose pokes into the food troughs and to deliver pellets.

Procedures

Standard eight-arm paradigm. The animals performed the maze task 5 days a week (Monday through Friday) between 12:00 and 4:00 PM. The laboratory computer was programmed to record interruptions in the photocell receptors inside the arm entrances, indicating an arm entry or exit (beam breaks) or interruptions in the food trough photocell receptors (nose pokes), and to deliver one pellet following the first nose poke in each arm.

Each animal was placed in the center of the maze with the doors to all arms closed at the onset of each trial. Approximately 30 s later, the stimulus lights at the end of each arm were turned on by the computer, indicating the beginning of the trial. The experimenter then raised all doors and allowed the animal free access to all arms. After the animal entered an arm, all arm doors were closed except the door for the arm entered. When the animal exited the arm, that arm door was closed and all arm doors remained closed for 5 s, thus containing the animal in the center of the maze and discouraging patterning behavior. After 5 s, all doors were raised. This pattern was repeated until the animal had retrieved a pellet from each arm or until 10 min had elapsed, thus ending the trial.

Baseline performance stabilization. Following a week of adaptation to the radial maze and shaping to obtain food from the food troughs, the animals performed the eight-arm maze procedure for approximately 6 weeks before the onset of the study. At the conclusion of the 6-week period, all animals were successfully retrieving a pellet in each arm of the maze in 3 min or less, usually without error. Furthermore, the animals did not display an obvious decrease in errors or time in maze during the last 2 weeks of the 6-week baseline period, indicating a stable response pattern.

Drug sessions. Following response stabilization and before the onset of drug testing, the animals were given intraperitoneal (IP) injections of saline (1 ml/kg of body weight) for 2 days prior to completing the maze task as acclimation to the injection process. Drug tests consisted of a drug or vehicle (0.9% NaCl) IP injection (1 ml/kg of body weight) 20 min prior to testing on Tuesday and Friday of each week. Scopolamine hydrobromide (Sigma Chemical Company, St. Louis, MO) was dissolved in saline and injected at doses of 0.0, 0.125, 0.25 and 0.5 mg/kg. The standard eight-arm procedure was used for testing on drug and nondrug days (Monday, Wednesday, Thursday). Because the animals were naive to the drug, each rat received an injection of 0.5 mg/kg of scopolamine 20 min prior to completing the maze on the Friday before beginning the drug testing sessions to be used in the data analysis. Drug administration was completed in a randomized block fashion, resulting in each animal receiving each drug condition and the vehicle condition once.

A second replication using the same animals and same procedure was completed approximately 5 months after the conclusion of the initial training and testing. Between the first and second replications, the animals received injections of benzodiazepine-related drugs (zolpidem and triazolam). During the second replication, the animals again received injections of 0.0, 0.125, 0.25 and 0.5 mg/kg of scopolamine. To ensure that we used a scopolamine dose low enough to result in no major performance effect, we added a fourth scopolamine dose of 0.0625 mg/kg during the second replication. As a means of better stabilizing the results, we administered the 0.0625-mg/kg dose twice during the second replication. As in the first replication, to control for order effects and effects of drug repetition, drug administration was completed in a randomized block fashion, resulting in each animal receiving each drug and vehicle condition once except the 0.0625-mg/kg dose, which each animal received twice during the second replication.

Behavioral measures. All behavioral measures were categorized by data reduction programs that accessed the SKED-11 data produced from the laboratory computer. Working memory errors were divided into three categories: initial arm entry (INTA) errors, arm entry (ARM) errors and nose poke

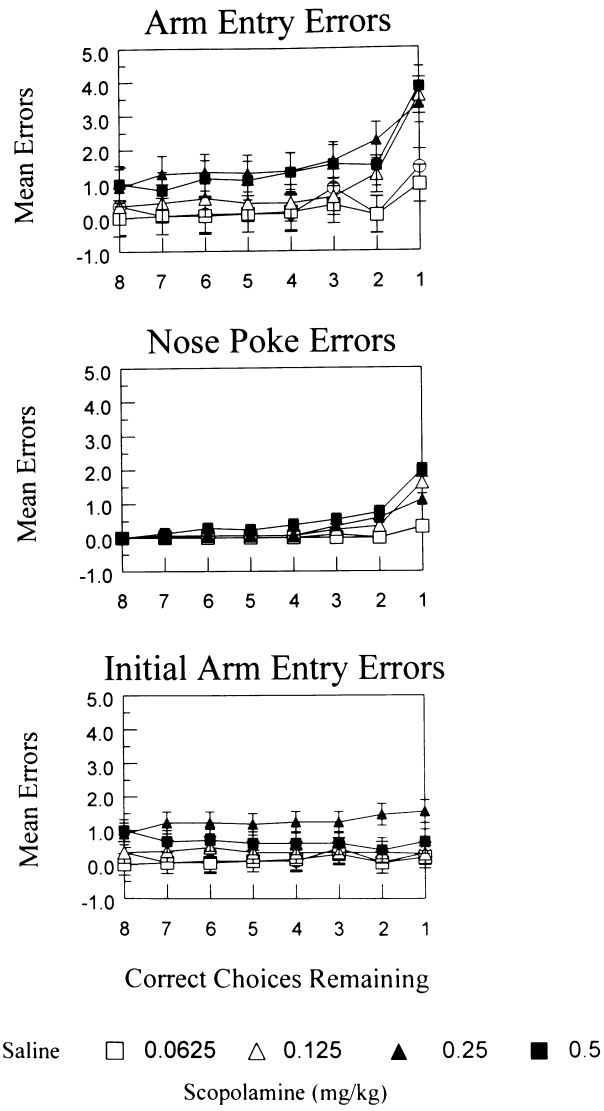

FIG. 1. Study 1: Cumulative arm entry (ARM, INTA) and nose poke (POKE) working memory errors (±SE) from uninterrupted trials as a function of the number of correct choices remaining. The artifact in the cumulative plots of apparent decreases in errors in the grouped data occurred because some animals committed a number of errors early in the eight possible correct choices but did not complete the maze. When this occurred, there were no data entered for that animal's remaining correct choices, thus resulting in a decrease in the total number of errors committed across all animals.

(POKE) errors. INTA errors were assigned when an entry beam break occurred in a baited arm that was followed by an entry beam break in a different arm (i.e., when the animal entered and then exited an arm where a pellet delivery had not yet occurred) without making a nose poke. ARM errors were defined as INTA errors plus any entry beam break in a previously baited arm (an arm where a pellet delivery had already occurred) followed by an entry beam break in a different arm without an intervening nose poke in the first arm. POKE errors were classified as any nose poke following a beam break in a previously baited arm. This criterion precluded counting repeated nose pokes as errors during a single arm entry without movement sufficient to break the entry photocell. All errors were cumulated across the number of correct choices remaining.

As measures of physical mobility and motivation, total number of pellets retrieved, total time (in seconds) in the maze and total number of arm entries were recorded for each session. In addition, mean time (in seconds) from beam break to nose poke was averaged across all arm choices during each trial and recorded for each testing session.

Data analyses. All data analyses were completed on SAS (SAS Institute Inc., Cary, NC). The error variables were averaged across the two repetitions and then analyzed using a two-factor repeated measures multivariate analysis of variance (MANOVA) with drug and the number of correct choices remaining as factors. The replications were not used as a factor because time was not an issue in this study and the time between replications was not held constant. Therefore, replication was used as a means to stabilize variability in the data. All remaining variables, total pellets retrieved, total time in maze, total number of entries and time from beam break to nose poke, were averaged across replications and analyzed in a one-factor repeated measures MANOVA with drug as the factor. Post hoc analyses to identify the source of significant main effects were completed using Tukey's Studentized range statistic. An alpha level of 0.05 was used for all post hoc analyses.

RESULTS

Scopolamine produced a dose-related increase in arm entry and nose poke errors in the radial arm maze task as compared with saline. Furthermore, scopolamine administration resulted in a greater increase in the number of arm entry errors than nose poke errors. The animals committed approximately twice the number of ARM errors as POKE errors (Fig. 1). Examination of the breakdown of errors across the number of correct choices remaining revealed that the number of ARM and POKE errors remained relatively stable until the last correct choice when a clear increase in errors occurred. In contrast, INTA errors showed an initial increase in error rate with few errors occurring across the remaining correct choices.

When analyzed by a two-factor MANOVA, ARM, POKE and INTA errors were significant as a function of drug condition. Specifically, the animals committed significantly more ARM errors [$F(4, 343) = 10.73$, $p < 0.0001$], POKE errors [$F(4, 343) = 10.83$, $p < 0.0001$] and INTA errors [$F(4, 343) = 13.88$, $p < 0.0001$] in the higher dose conditions. Post hoc analysis revealed that 0.5 and 0.25 mg/kg scopolamine resulted in significantly more ARM and INTA errors than saline and 0.0625 mg/kg scopolamine. Only the 0.5 mg/kg scopolamine resulted in significantly more POKE errors than saline and 0.0625 mg/kg scopolamine.

When analyzed by correct choices remaining, ARM errors [$F(7, 343) = 7.13$, $p < 0.0001$] and POKE errors [$F(7, 343) = 19.40$, $p < 0.0001$] differed significantly. Post hoc analyses revealed that the last correct choice resulted in significantly more ARM and POKE errors than all other correct choices. In addition, a significant interaction between drug condition and correct choices remaining was found for POKE errors [$F(28, 343) = 1.96$, $p < 0.01$], indicating that the effect of scopolamine on POKE errors depended on the number of correct choices remaining.

The means and standard deviations for total number of pellets retrieved, total time in maze, total number of entries and time from beam break to nose poke are shown in Table 1. The one-factor repeated measures MANOVA revealed that scopolamine significantly decreased total number of pellets retrieved [$F(4, 36) = 4.74$, $p < 0.01$] and increased total time in maze [$F(4, 36) = 7.08$, $p < 0.001$]. Post hoc analysis indicated that 0.5 mg/kg scopolamine resulted in significantly fewer total number of pellets retrieved and more total time in maze than did saline and 0.0625 mg/kg. Neither total number of entries nor time from beam break to nose poke changed significantly with scopolamine administration.

STUDY 2

In Study 1, scopolamine had a greater effect on ARM errors than POKE errors in a dose-dependent fashion. In addition, the number of errors generally increased as the number of correct choices decreased. However, because an uninterrupted maze trial was used, the results only allow us to inter-

TABLE 1

STUDY 1*: MEANS (±SD) OVER EIGHT CORRECT CHOICES**

	Drug Condition				
Variables	Saline	0.0625†	0.125†	0.25†	0.5†
TOTPEL	7.35 ± 1.87	7.80 ± 0.70	6.70 ± 2.68	6.70 ± 2.68	5.10 ± 3.61
TOTTIM‡	238.40 ± 189.70	213.00 ± 138.79	335.15 ± 206.18	339.65 ± 198.94	439.10 ± 199.60
TOTENT	9.70 ± 4.68	9.00 ± 3.60	10.15 ± 5.85	9.85 ± 5.32	8.85 ± 5.06
ARMTIM‡	0.74 ± 0.33	0.72 ± 0.29	0.86 ± 0.60	0.94 ± 0.61	1.08 ± 1.54

Note: TOTPEL = total pellets retrieved, TOTTIM = total time to maze completion, TOTENT = total number of arm entries, ARMTIM = time from arm entry beam break to nose poke in food trough.

*Study 1 used the eight-arm maze paradigm.

**Average of 20 data points per drug condition.

†Scopolamine Hydrobromide (in mg/kg).

‡Time in seconds.

pret the performance decrements as an impairment in current spatial working memory and not a more specific interpretation concerning the mechanisms contributing to the memory deficit. To address this issue, we examined the effects of scopolamine on the acquisition and consolidation of working memory in a radial arm maze task in which a delay was imposed between the completion of the first and second halves of the eight-arm maze task. Six types of errors were defined and cumulated across correct choices remaining. In addition, total number of pellets retrieved, total time in maze, total number of arm entries and time from arm entry to nose poke in food trough were analyzed as indicators of motivation and mobility.

METHOD

Subjects

Twelve additional Sprague–Dawley rats approximately 12 months old were used for Study 2. All animals were maintained in a manner comparable to that described in Study 1. At the onset of this experiment, the rats were well trained in the standard eight-arm maze paradigm and had been performing the maze task for approximately 10 months. In addition, all animals were experienced with the drug and had received injections of triazolam, zolpidem and diazepam.

Apparatus

Study 2 was conducted in the eight-arm radial maze used in Study 1.

Procedures

The 3-h delay paradigm. In the current study, a 3-h delay paradigm was implemented on drug-injection days. All animals completed the eight-arm maze task using the procedure described in Study 1 but with a 3-h delay imposed immediately after the animals had retrieved the first four pellets. When the animal retrieved the fourth pellet, it was immediately removed from the arm and returned to its home cage for the 3-h delay period. At the conclusion of the 3-h delay, each animal was allowed to retrieve the last four pellets from the maze. The animal was removed from the maze after successfully retrieving the four remaining pellets or when 10 min had elapsed. All animals had completed the 3-h delay condition periodically during the 4 months preceding the onset of this study. To utilize the delay procedure as a memory probe test under the drug condition, the animal's maze running behavior was maintained using the eight-arm maze procedure described in Study 1 on nondrug-injection days.

Drug sessions. Drug tests consisted of a drug or vehicle (0.9% NaCl) IP injection at 1 ml/kg of body weight 20 min before the animal was placed in the maze to retrieve the first four pellets. Scopolamine hydrobromide was prepared as described in Study 1 and injected at doses of 0.0, 0.25, 0.5 and 1.0 mg/kg. The 1.0-mg/kg dose was used to ensure a dose response when using a delay procedure. Drugs were administered each Tuesday and Friday using the 3-h delay paradigm. The standard eight-arm testing sessions were continued on Monday, Wednesday and Thursday of each week. Drug administration was completed in a randomized block fashion, resulting in each animal receiving each drug and vehicle condition once.

Behavioral measures. The three working memory errors defined in Study 1 (ARM, POKE, INTA) were categorized separately for the first four pellets retrieved and for the last four pellets retrieved. In addition, total number of pellets retrieved, total time in maze, total number of entries and time from beam break to nose poke were calculated separately for the first four pellets retrieved and the last four pellets retrieved.

The data also were analyzed for errors specific to the 3-h delay condition. After the 3-h delay, the animals had the opportunity to commit errors that involved entering the arms from which they had retrieved pellets before the 3-h delay (nonbaited arm errors). Specifically, three nonbaited ARM entry and POKE errors were categorized. A nonbaited initial arm entry (NBINTA) error was classified as an entry beam break in a nonbaited arm followed by an entry beam break in a different arm without an intervening nose poke. A nonbaited arm entry (NBE) error was specified as an entry beam break in a nonbaited arm with or without a subsequent nose poke. A nonbaited arm entry followed by a POKE (NBPOKE) error was defined as only those entry beam breaks in a nonbaited arm followed by a nose poke in the same arm without an intervening entry beam break in a different arm. NBE errors were redefined as working memory errors (i.e., arm entry errors in arms previously entered while retrieving the last four pellets) after the animals made a beam break in a nonbaited arm and then exited that arm. As in Study 1, all errors were cumulated across the number of correct choices remaining.

Data analysis. The data recorded while the animals retrieved the first four pellets were summarized by drug condition but not by the number of correct choices remaining because almost no errors were committed. Similarly, a repeated measures MANOVA was not performed on the error data. However, because meaningful data were gathered for total number of pellets retrieved, total time in maze, total number of entries and time from beam break to nose poke while the animals retrieved the first four pellets, the data on these variables were analyzed by drug condition using a one-factor repeated measures MANOVA. The data recorded while the animals retrieved the last four pellets were analyzed as described in Study 1.

RESULTS

The data recorded during the first half of the maze are summarized by drug condition in the top portion of Table 2. The animals committed only seven errors, two POKE errors and five INTA errors, across the 48 maze task completions. The one-factor repeated measures MANOVA revealed that total number of pellets retrieved, total time in maze, total number of entries and time from beam break to nose poke were not significantly different by drug condition.

Scopolamine administration generally caused little increase in the number of working memory errors committed while retrieving the last four pellets. Animals committed only slightly more ARM and INTA errors and almost no POKE errors when making the last correct choice (Fig. 2). The two-factor repeated measures MANOVA indicated that none of the working memory errors were significant by drug condition. Only ARM errors increased significantly [$F(3, 165) = 268$, $p < 0.05$] as correct choices decreased; however, the post hoc analysis did not result a significant difference by choice. None of the working memory errors resulted in a significant interaction between drug condition and correct choices remaining.

In contrast to working memory errors, NBE and NBPOKE errors committed while retrieving the last four pellets increased in a dose-dependent fashion and as a function of correct choices remaining (Fig. 2). Scopolamine-treated ani-

mals committed NBPOKE and NBE errors beginning with their first choice, and they continued to make errors as the number of correct choices remaining decreased. Virtually no NBINTA errors were committed while completing the last half of the maze. A two-factor repeated measures MANOVA revealed that NBPOKE errors [$F(3, 165) = 20.15, p < 0.0001$] and NBE errors [$F(3, 165) = 8.84, p < 0.0001$] were significantly increased when analyzed by drug condition. Post hoc analysis indicated that 1.0 and 0.5 mg/kg scopolamine produced more NBE and NBPOKE errors than either 0.25 mg/kg or saline.

When analyzing by the number of correct choices remaining, NBPOKE errors [$F(3, 165) = 5.50, p < 0.001$] and NBE errors [$F(3, 165) = 8.51, p < 0.0001$] were significantly increased. Post hoc analysis revealed that the animals committed more NBPOKE errors with one correct choice remaining than with four correct choices remaining. In addition, the animals committed more NBE errors with one correct choice remaining than when making either of their first two correct choices. None of the interactions between drug condition and correct choices remaining were significant for NBPOKE, NBE and NBINTA.

The means and standard deviations for total number of pellets retrieved, total time in maze, total number of arm entries and time from beam break to nose poke are shown in the bottom portion of Table 2. The one-factor repeated measures MANOVA by drug indicated that scopolamine given before the first four pellets were retrieved did not significantly alter these measures when the last four pellets were retrieved.

STUDY 3

Because scopolamine was injected 20 min prior to the first half of the trial in Study 2 and it took the rats approximately 2 min to retrieve four pellets, the decrement in performance observed during the second portion of the task could be attributed to difficulties in either the acquisition or consolidation of working memory from the first portion of the task. To differentiate the effects of scopolamine on consolidation vs. acquisition of working memory, we conducted an additional series of delayed radial arm maze trials with scopolamine injections immediately after the animals completed the first half of the maze. The same performance and motivation measures as those described in Study 2 were used.

METHOD

Subjects

The subjects were the Sprague–Dawley rats used in Study 1. They were housed and fed as previously described. All animals were drug experienced at the start of the present study.

Apparatus

Study 3 was conducted in the eight-arm radial maze used in Study 1.

Procedures

The 3-h delay paradigm. In this experiment, the animals completed the 3-h delay procedure as described in Study 2. All animals had performed the maze task with the 3-h delay condition before the onset of this study.

Drug sessions. As in Study 2, the animal's maze running behavior was maintained using the eight-arm procedure described in Study 1. Drug tests consisted of a drug or vehicle (0.9% NaCl) IP injection at 1 ml/kg of body weight immediately after each animal had retrieved the first four pellets in

TABLE 2

STUDY 2*: MEANS (± SD)**

Variables	Drug Condition			
	Saline	0.25†	0.5†	1.0†
FIRST FOUR CORRECT CHOICES				
TOTARM‡	0.00 ± 0.00	0.08 ± 0.29	0.17 ± 039	0.33 ± 1.15
TOTPOKE§	0.00 ± 0.00	0.00 ± 0.00	0.08 ± 0.29	0.08 ± 0.29
TOTINTA¶	0.00 ± 0.00	0.08 ± 0.29	0.08 ± 0.29	0.25 ± 0.87
TOTPEL	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
TOTTIM+	114.00 ± 113.78	99.50 ± 41.87	101.92 ± 54.91	107.67 ± 50.69
TOTENT	4.00 ± 0.00	4.08 ± 0.29	4.17 ± 0.39	4.33 ± 1.15
ARMTIM+	1.06 ± 0.52	1.30 ± 0.58	1.08 ± 0.52	1.36 ± 0.83
LAST FOUR CORRECT CHOICES				
TOTPEL	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
TOTTIM+	102.25 ± 51.84	105.83 ± 42.15	125.75 ± 70.02	152.67 ± 93.87
TOTENT	5.08 ± 0.67	5.25 ± 0.96	6.92 ± 3.37	6.33 ± 1.61
ARMTIM+	0.91 ± 0.31	0.88 ± 0.36	0.91 ± 0.34	1.52 ± 1.44

Note: TOTPEL = total pellets retrieved, TOTTIM = total time to maze completion, TOTENT = total number of arm entries, ARMTIM = time from arm entry beam break to nose poke in food trough.

*Study 2 used a 3-h delay after the fourth pellet retrieval, with drug injection 20 min before the animals were placed in the maze to retrieve the first four pellets.

**Average of 12 data points per vehicle or drug condition.

†Scopolamine Hydrobromide (in mg/kg).

‡Total number of ARM errors.

§Total number of arm entry followed by nose poke errors.

¶Total number of INTA errors.

+Time in seconds.

the maze and before being placed in its home cage for the 3-h delay. Scopolamine hydrobromide was prepared as described in Study 1 and was injected at doses of 0.0, 0.125 and 0.5 mg/kg. Drug tests were conducted on each Tuesday and Friday using the 3-h delay paradigm. The standard eight-arm testing sessions were continued on Monday, Wednesday and Thursday of each week. Drug administration was completed in a randomized block fashion, resulting in each animal receiving each drug and vehicle condition once.

A second replication using the same animals and 3-h delay procedure was conducted approximately 3 months later. As in the first replication, the animals were injected with 0.0, 0.125 and 0.5 mg/kg of scopolamine immediately after retrieving four pellets. However, in the second replication, the animals performed the maze task 7 days a week. The 3-h delay drug sessions were conducted on Monday, Wednesday and Friday, and the standard eight-arm testing procedure was continued on Tuesday, Thursday, Saturday and Sunday of each week. Drug administration was completed in a randomized block fashion, resulting in each animal receiving each drug and vehicle condition once.

To ensure that a dose response would occur, immediately after the second replication of the 0.125 and 0.5 mg/kg scopolamine doses, a single drug session using 1.0 mg/kg scopolamine in the 3-h delay condition was completed. The same 10 rats and 7-day maze running schedule used during the second replication were implemented. Animals were injected with either saline or 1.0 mg/kg of scopolamine immediately after they retrieved four pellets in the maze. Drug administration was completed in a randomized block fashion, resulting in 8 of the 10 animals receiving saline and 7 of the 10 animals receiving 1.0 mg/kg scopolamine, with no animal receiving the same drug condition or the vehicle condition more than once.

Behavioral measures. The working memory errors described in Study 1 (ARM, POKE, INTA) and the nonbaited arm errors described in Study 2 (NBE, NBPOKE, NBINTA) were cumulated across correct choices remaining. In addition, total number of pellets retrieved, total time in maze, total number of entries and time from beam break to nose poke were calculated across the four correct choices. As in Study 2, all variables were categorized separately for the data recorded before the 3-h delay and the data recorded after the 3-h delay.

Data analysis. Because the drug and vehicle injections occurred following the retrieval of the first four pellets, the animals were not expected to make many errors while retrieving the first four pellets. Thus, the data recorded while the animals retrieved the first four pellets were described with means and standard deviations and were not analyzed in terms of drug condition or number of correct choices remaining. The remainder of the data for Study 3 were averaged across replications and were analyzed as described in Studies 1 and 2.

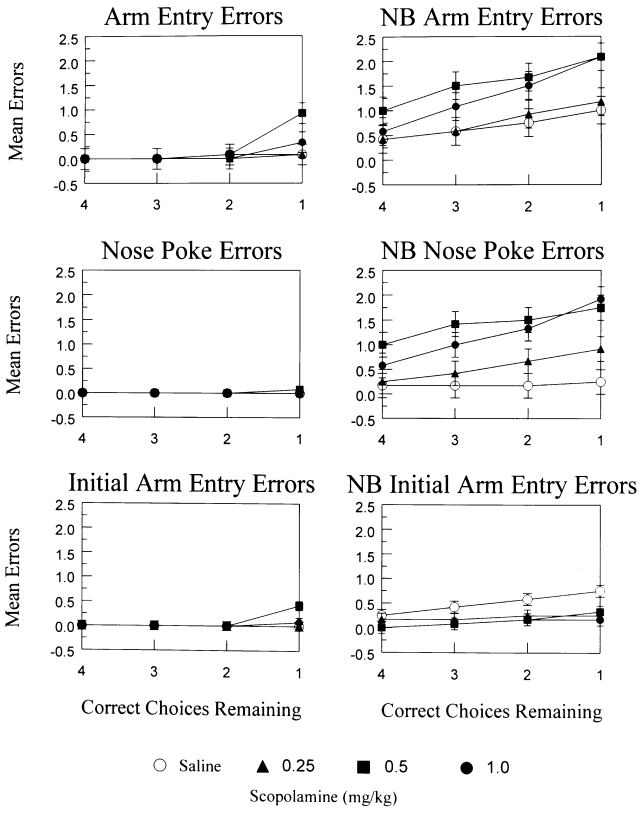

FIG. 2. Study 2: Cumulative errors (±SE) committed while completing the last half of the delayed radial maze task as a function of correct choices remaining. Left column: Cumulative arm entry (ARM, INTA) and nose poke (POKE) working memory errors. Right column: Cumulative nonbaited arm entry (NBE, NBINTA) and nose poke (NBPOKE) errors. Scopolamine was injected 20 min before the onset of the first half of the radial maze task.

RESULTS

As expected the animals committed almost no working memory errors when retrieving the first four pellets prior to drug injections. No POKE errors and only four INTA errors were committed across the 75 maze task completions. All animals retrieved four pellets in each of the 75 maze task completions in an average of 67.25 ± 28.34 s and made an average of 4.07 ± 0.30 arm entries. The average time from beam break to nose poke was 0.86 ± 0.42 s.

Scopolamine administration followed by a 3-h delay generally caused little increase in the number of working memory errors (errors committed in arms initially baited after the delay) while the animals were retrieving the last four pellets. Marginally more ARM errors than POKE and INTA errors were committed across the four correct choices (Fig. 3). The two-factor repeated measures MANOVA indicated that none of the working memory errors were significant when analyzed as a function of drug condition or correct choices remaining. In addition, none of the working memory errors resulted in a significant interaction between drug condition and correct choices remaining.

In contrast to the working memory errors, the NBE errors were more readily affected by drug condition and by correct choices remaining. NBPOKE, NBE, and NBINTA errors increased in a dose-dependent fashion and increased as a function of the number of correct choices (Fig. 3). Specifically, when analyzing by drug condition, NBPOKE errors [$F(3, 123) = 2.63$, $p < 0.05$] and NBINTA errors [$F(3, 123) = 2.84$, $p < 0.05$] increased significantly. Although the increase in NBE errors was not significant, it did approach significance [$F(3, 123) = 2.27$, $p < 0.08$]. Post hoc analysis revealed that 1.0 mg/kg scopolamine resulted in significantly more NBPOKE and NBE errors than saline; however, there was no significant difference between any specific scopolamine condition and saline for NBINTA errors.

When analyzing by correct choices remaining, NBPOKE errors [$F(3, 123) = 15.25$, $p < 0.0001$], NBE errors [$F(3, 123) =$

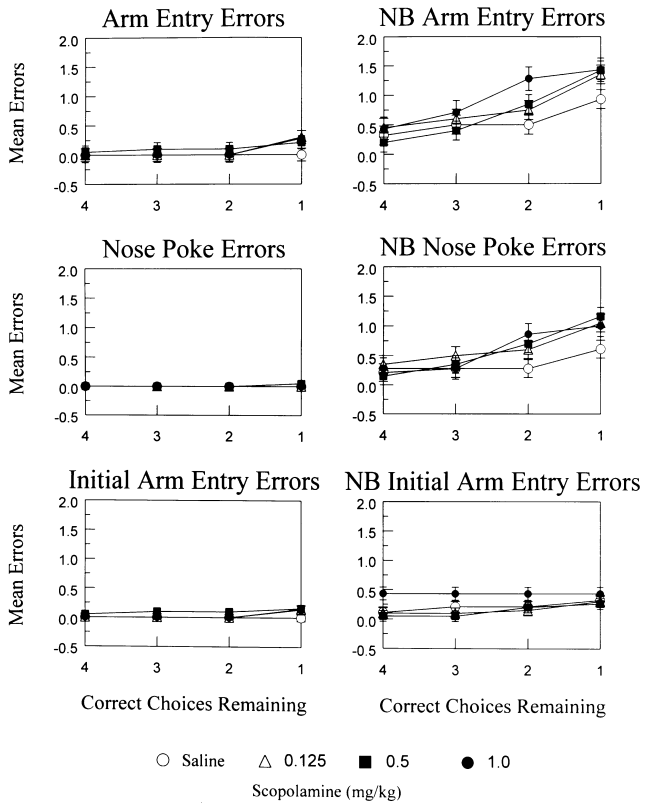

FIG. 3. Study 3: Cumulative errors (±SE) committed while completing the last half of the delayed radial maze task as a function of correct choices remaining. Left column: Cumulative arm entry (ARM, INTA) and nose poke (POKE) working memory errors. Right column: Cumulative nonbaited arm entry (NBE, NBINTA) and nose poke (NBPOKE) errors. Scopolamine was injected immediately following completion of the first half of the maze.

21.84, $p < 0.0001$] and NBINTA errors [$F(3, 123) = 4.02$, $p < 0.01$] increased significantly. Post hoc analysis indicated that more NBPOKE and NBE errors were committed during the last correct choice than any of the other correct choices. The post hoc analysis indicated that the animals made more NBINTA errors when making their last correct choice but only in comparison with the first correct choice. None of the interactions between drug condition and correct choices remaining were significant for NBPOKE, NBE and NBINTA.

The means and standard deviations for total pellets retrieved, total time in maze, total number of arm entries and time from beam break to nose poke are presented in Table 3. The repeated measures MANOVA × Drug interaction indicated that scopolamine administration did not significantly affect any of these variables after a 3-h delay.

DISCUSSION

The results of the present investigation indicate that scopolamine administration significantly decreases performance levels in uninterrupted and delayed trials in the radial arm maze. The number of errors committed generally increased in a dose-dependent manner and as a function of the number of correct choices remaining. Furthermore, errors associated with an arm entry were more likely to be committed than POKE errors in both uninterrupted and delayed trials.

The data from Study 1, which examined the effects of scopolamine on memory and performance in uninterrupted trials, confirm the general conclusions seen in the literature [see (5,15)], namely that scopolamine caused an increase in the number of errors committed and did so in a dose-dependent manner. However, the current data extend the findings of previous investigations by differentiating working memory errors into three distinct categories—ARM errors, INTA errors and POKE errors—and by tracking the pattern of errors across the number of correct choices made.

Our finding that error rate increased specifically during the last two correct choices differs with that of Eckerman et al. (10). After reporting a relatively stable decrease in accuracy of the 5th through 8th arm choice, they concluded that scopolamine affects discriminative control and not specific memory processes. In contrast, our data support the conclusion that scopolamine directly affects memory instead of only producing a deficit in discriminative control because one would expect memory deficits to increase as the level of task difficulty increases. A possible explanation for the difference in results and interpretation between the study by Eckerman et al. and the present study is the manner in which the data were gath-

TABLE 3

STUDY 3*: MEANS (±SD) OVER THE LAST FOUR CORRECT CHOICES

	Drug Condition			
Variables	Saline**	0.125†‡	0.5†‡	1.0†§
TOTPEL	4.00 ± 0.00	3.95 ± 0.22	3.90 ± 0.45	4.00 ± 0.00
TOTTIM¶	77.61 ± 23.95	108.60 ± 121.04	134.70 ± 134.55	75.57 ± 22.26
TOTENT	4.93 ± 0.81	5.60 ± 1.96	5.60 ± 1.76	5.57 ± 0.98
ARMTIM¶	0.75 ± 0.25	0.75 ± 0.31	0.89 ± 0.32	0.80 ± 0.19

Note: TOTPEL = total pellets retrieved, TOTTIM = total time to maze completion, TOTENT = total number of arm entries, ARMTIM = time from arm entry beam break to nose poke in food trough.

*Study 3 used a 3-h delay after the fourth pellet retrieval, with drug injection immediately after the fourth pellet retrieval.

**Average of 28 data points.

†Scopolamine Hydrobromide (in mg/kg).

‡Average of 20 data points.

§Average of 7 data points.

¶Time in seconds.

ered. Eckerman et al. only reported the number of errors across the first eight choices. Because our animals made an average of nine arm entries to complete the task successfully, they usually made at least eight consecutive choices before reaching the last correct choice. Therefore, it is possible that the increase in errors made and, thus, decrease in selection accuracy, would not have been reported in the study by Eckerman et al.

Unlike ARM and POKE working memory errors, INTA errors did not increase as the correct number of choices decreased. INTA errors were often committed before the first correct choice was made followed by almost no additional INTA errors for the remainder of the task. These data indicate that INTA errors are not the result of a specific memory deficit because with a memory deficit one would expect the error rate to increase as the number of possible correct choices decrease. A possible explanation for these data are that scopolamine may inhibit the ability of the animal to complete the task in the most efficient manner. It is feasible that scopolamine decreases the ability of the animal to inhibit unnecessary behavior, i.e., scopolamine may cause a decrease in motor inhibition.

A related point is the general effect of scopolamine on muscle control and motivation. Previous studies often have addressed this issue by recording the time to maze completion [e.g., (14,16,18–21,26)]. In addition to using time to maze completion as a measure of motor control and motivation, we recorded the number of pellets retrieved, the number of arm entries and a new measure, the time from an arm entry beam break to a nose poke in the food trough. The dose-dependent increase in time in maze found in the current study is consistent with the results reported from previous uninterrupted trial studies (14,16,20). However, because we also recorded time from beam break to nose poke, we can better interpret the activity of the animal during this increase in time to task completion. Because there was no significant change in time from beam break to nose poke, the animals must have spent the additional time either in the center of the maze or at the end of the arms around the food troughs. Experimenter observation indicated that the animals did not remain immobile in the center of the maze but moved from arm to arm, often without actually entering an arm. These data support the conclusion that scopolamine inhibits the ability of the animal to complete the maze in the most efficient manner. In addition, scopolamine administration may lead to greater difficulty in making arm entry choices as seen by the animals moving from arm entrance to arm entrance without entering the arms. These data suggest that the animals had sufficient motivation and motor control to complete the task in that they did not remain motionless in the center of the maze and that once they entered an arm, their run time down the arm was not significantly decreased under scopolamine conditions.

Seemingly in contrast to the conclusion that the animals were motivated and maintained motor control is the dose-dependent decrease seen in total number of pellets retrieved. One possible explanation for the decrease in number of pellets retrieved is that the animals may not have been sufficiently motivated to retrieve the pellets due to a dry mouth. Drying of the mucosa in the mouth is a peripheral effect of scopolamine, which may result in dry food pellets being unpalatable to the animals (22). However, more recent studies have found that liquid food does not improve performance levels over those observed with dry food (4). In addition, the animals in the current study were offered the opportunity to consume only eight pellets, and investigator observation confirmed that the animals consumed all pellets retrieved. Another explanation for the dose-dependent decrease in the number of pellets retrieved could be a decrease in motor control. However, total number of arm entries were not significantly decreased in animals injected with scopolamine, demonstrating that the animals maintained sufficient motor control to make the necessary arm entries to complete the task. Therefore, the inability of the animals to retrieve all available pellets was most likely due to impairments in working memory resulting in an inability to choose the remaining baited arms instead of motivational or motor control issues. These data support a conclusion consistent with that drawn in previous studies [e.g., (10,14,15,17)], namely that the effect of scopolamine on working memory is not confounded by lack of motivation or mobility.

The present results following injections of scopolamine prior to the first half of a delayed maze task (Study 2) agree with much of that reported in the literature (3,6–8). As expected, almost no working memory errors (ARM, POKE, INTA) were committed while completing the first half of the task. This result is in agreement with the data collected in Study 1, which indicated that working memory errors generally occur while making the last two correct choices of the eight correct choices available. In the first half of the delayed radial maze task, the animals can choose any four of eight baited arms and thus are not forced to make a choice with only one or two correct choices remaining. The present results also agree with data reported by Beatty and Bierley (3). Although they did not actually present their data from the first half of the maze task, they did state that almost no errors were committed.

Because we imposed a 3-h delay between the first and second portions of the maze task, it is unlikely that the dose-dependent increase in NBE errors and NBPOKE errors was due to an effect of scopolamine on memory retrieval mechanisms. In addition, the significant increase in NBE and NBPOKE errors as the number of correct choices decreased supports the conclusion that scopolamine administration had a differential effect on memory acquisition and possibly memory consolidation. The lack of an increase in working memory errors (ARM, POKE, INTA) indicates that scopolamine had no effect on current working memory and on working memory 3 h after administration. Virtually no NBINTA errors were committed, suggesting that scopolamine had little, if any, effect on motor inhibition during the completion of the last half of the maze task. Scopolamine also did not appear to have an effect on motivation or motor control 3 h after administration because total time in maze, total number of pellets retrieved, total number of arm entries and time from beam break to nose poke did not significantly change during the last half of the maze task, and all animals ate all pellets retrieved. Therefore, given the lack of an effect on the motivation and motoric variables and the increase in NBE errors, the results from Study 2 suggest that the detrimental effect of scopolamine is due to a direct effect on working memory, which is independent of a more general effect on motivation and motor control. Further evidence for this conclusion is found in previous studies that implemented different delay lengths and found that animals commit more errors following longer delays than following shorter delays when under scopolamine conditions (8), thus indicating that the detrimental effects of scopolamine on performance are most likely due to disturbances in memory. However, because scopolamine was injected prior to the onset of the delay task in the present study, it is difficult to separate the effects that scopolamine may have on the acquisition vs. consolidation of memory.

When we injected scopolamine immediately after the completion of the first half of a delayed radial maze task (Study 3), the animals committed more nonbaited arm errors (NBE, NBPOKE) while completing the second half of the maze but only after the administration of 1.0 mg/kg scopolamine. In addition, all nonbaited errors increased across the number of correct possible choices; however, NBE and NBPOKE errors showed a much greater increase than NBINTA errors. The lack of working memory errors (ARM, POKE, INTA) suggest that 3 h after administration, scopolamine did not have a direct effect on working memory or memory retrieval processes and only a slight effect on motor inhibition. In addition, scopolamine did not appear to have an effect on motivation or mobility during the second half of the task because total time to maze completion, total number of pellets retrieved, total number of arm entries and time from beam break to nose poke were not altered by scopolamine administration. Therefore, the observed increase in NBPOKE and NBE errors can be most easily explained by 1.0 mg/kg scopolamine but not by lower doses of scopolamine specifically affecting the consolidation of working memory.

This conclusion is in agreement with a number of other studies. Most investigations using scopolamine doses of less than 1.0 mg/kg [e.g., (3,7)] have concluded that scopolamine has no effect on consolidation of working memory. Bolhuis et al. (6) found an increase in the number of errors made in nonbaited arms following scopolamine injection immediately after completing the first half of the maze. However, because they tested the animals after only a 20-min delay, they were incapable of differentiating the effects of scopolamine on memory consolidation vs. memory retrieval, and in fact they concluded that scopolamine affected retrieval of working memory. However, our results contradict those reported by Godding et al. (12). They reported no increase in errors during the second portion of the task when scopolamine (1.0–5.0 mg/kg) was administered immediately after completing the first portion of the task. Levin (15) concluded that high doses of scopolamine may be differentially disrupting performance functions such as attention instead of directly affecting working memory consolidation. However, the present data suggest that the animals are attending to the task at hand because there was no change in total time to maze completion, number of pellets retrieved, number of arm entries and time from beam break to nose poke. These objective measures should have reflected a disassociation from the task. Therefore, the most likely reason for the difference between the present and previous findings is our ability to differentiate between types of errors and the analysis of cumulative errors across correct choices.

The present results show a differential effect of scopolamine depending on time of injection. Scopolamine injected prior to the onset of the first half of the delayed maze procedure had a greater detrimental effect on performance than scopolamine administered immediately after completing the first half of the maze task. More specifically, scopolamine injected prior to the first half of the maze task (possibly affecting both working memory acquisition and working memory consolidation) significantly increased both nonbaited arm entry and NBE/POKE errors at 1.0 and 0.5 mg/kg. However, scopolamine injected immediately after the first half of the maze task (possibly affecting working memory consolidation) significantly increased nonbaited arm entry and NBE/POKE errors only at 1.0 mg/kg. Thus, the present data indicate that although scopolamine has some effect on working memory consolidation, it has a much larger effect on working memory acquisition.

The present results have emphasized a methodology that allowed us to separate errors into different types such as POKE errors vs. ARM errors. Although we have classified them as separate types (i.e., ARM, INTA, POKE, NBARM, NBINTA, NBPOKE), there is an overlap between the variables. For example, a POKE error cannot occur unless an ARM error first occurs. However, the differentiation of the errors into different categories allows us to examine more precisely the exact manner in which scopolamine affects performance levels. In the present studies, we have shown that scopolamine negatively affects the arm entry decision more than the nose poke response.

A consideration with the methodology of the present set of studies involves the use of the totally enclosed radial maze, which differed from the open maze construction used in many studies, and the potential for this variable to introduce unique findings. However, this concern would appear to be unlikely because the results obtained in the present studies, particularly with respect to variables such as the total number of errors committed and total time to maze completion, were very similar to those from studies using a nonenclosed radial maze (3,6–8,14,16).

In conclusion, the present studies demonstrate that scopolamine administration more easily affects ARM errors than POKE errors and that these errors occur more frequently when fewer correct choices remain both in uninterrupted and delayed radial arm maze trials. In addition, the separation of INTA errors from other potential errors provides evidence that scopolamine may cause a loss of motor inhibition in addition to impairing current working memory in the uninterrupted maze task. Furthermore, the data from the delay trial studies indicate that scopolamine significantly influences the acquisition of working memory more than the consolidation of working memory. Therefore, the data from the present set of studies support the involvement of cholinergic mechanisms in current spatial working memory and the acquisition and, to a lesser extent, the consolidation of working memory.

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