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Short-Term Memory in the Rhesus Monkey: Disruption from the Anti-Cholinergic Scopolamine[1]

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BARTUS, R. T. AND H. R. JOHNSON. *Short-term memory in the rhesus monkey: disruption from the anti-cholinergic scopolamine.* PHARMAC. BIOCHEM. BEHAV. 5(1) 39–46, 1976. – Two separate experiments were conducted to evaluate the effects of the anti-cholinergic scopolamine on primate visual discrimination and short-term memory (STM). In the first experiment it was shown that relatively mild doses of scopolamine severely impaired visual discrimination performance, even though the test procedure provided strong stimulus control. This deficit in visual discrimination suggested that previous research which used the delayed matching to sample procedure (DMS) to evaluate the role of cholinergics in primate STM may have confounded an accurate measure of specific STM effects because the DMS is inherently dependent on accurate visual discrimination. Therefore, the second experiment evaluated the effects of scopolamine on STM, using an automated apparatus and test procedure designed to minimize the discrimination component and other confounding variables present in the earlier research. In this second experiment, an indirect delayed response (DR) procedure was used, measuring the monkeys' ability to recall simple stimulus events over retention intervals of 0, 2.5, 5, and 10 sec. The monkeys were tested under 2 doses of the anti-cholinergic scopolamine and their performance was compared to that obtained on several nondrug control days. Contrary to earlier reports using the DMS, a clear interaction of drug and retention interval occurred in this situation. Under scopolamine, greatest impairments occurred on the longest delays, with little or no effect with zero second retention. Furthermore, the impairments observed on the longer delays were even greater with the highest dose of scopolamine. These data, therefore, support the notion that cholinergic mechanisms play an important role in the expression of STM in primates.

Memory Visual discrimination Anti-cholinergics Primate behavior

DURING the last decade considerable interest in defining the biochemical mechanisms of learning and memory has developed. Although consistent posttraining amnesic effects have led to a growing acceptance of the idea that cholinergic mechanisms actively participate in learning and subsequent long-term retrieval, [10] a controversey still exists over whether cholinergic mechanisms are critically important in short-term memory (STM). Conceptually, STM differs from long-term memory in that new learning is not necessarily involved in STM, and the information from a particular trial need be only temporarily retained for a short period of time before it is used, and can then be disregarded. Despite the existence of some evidence for a cholinergic involvement in short-term memory in rodents and man, [1, 11, 25] little conclusive support has been generated. A major criticism of the available data is that although cholinergic and anti-cholinergic agents have significantly altered performance on tasks purported to measure short-term memory, controls for more general, nonmemory effects have been inadequate.

One important requirement for demonstrating a specific cholinergic role in STM is evidence that as the retention intervals get longer, the effects of particular cholinergic drugs become even greater. The underlying assumption of such a test is simply that the longer retention intervals require greater involvement of STM mechanisms because the information stored must be maintained for longer periods of time. Thus, if acetylcholine plays an important role in STM, performance at the longer retention intervals should suffer more from the effects of anti-cholinergics than does performance at the shorter intervals.

This idea was in fact tested by Jarvik and his colleagues, using monkeys and a delayed-matching-to-sample (DMS) procedure. [8,29] Although the anti-cholinergic agent scopolamine impaired performance, the monkeys performed as poorly at the minimal control intervals as they did at the longer retention intervals, where use and vulnerability of STM mechanisms were presumed to be greater. The lack of a significant interaction between the effects of scopolamine and the length of the retention

[1] A summary of the data reported in this paper was previewed at the 5th Annual meeting of the Neuroscience Society, November 3, 1975, New York, New York, [3].

interval led Jarvik and colleagues [29] to conclude that cholinergic mechanisms are not directly involved in STM. Furthermore, because their monkeys were impaired on a control condition that simply required normal visual discrimination -- by continuing to present the sample stimulus during the time the 2 choice stimuli were on -- they suggested that the debilitating effects of scopolamine were probably due to an interference with perceptual mechanisms. More recently, it has been reported that scopolamine impaired primate performance on tasks specifically designed to measure discriminatory abilities. [12] It therefore seems quite probable that much of the scopolamine-related deficit on the DMS task may in fact be due to a disruption of visual discrimination.

On the other hand, evidence that supports a cholinergic involvement in discriminatory processes does not in itself refute the notion that cholinergic mechanisms also may be involved in short-term memory. In fact, since the DMS task requires that the monkey be able to perform visual discrimination problems as a prerequisite to demonstrating even minimal short-term retention, significant impairment of these discrimination abilities could sufficiently obscure an accurate measurement of specific STM effects. In other words, because of its inherent dependence on discrimination abilities, the DMS task may not provide an accurate assessment of the effects of anti-cholinergics on primate STM, and a definitive interpretation of the existent data therefore may not be possible.

For this reason, two separate experiments were undertaken to reevaluate the role of acetylcholine in primate visual discrimination and short-term memory (STM). Recent evidence indicates that scopolamine produces significantly greater impairments in situations of poor stimulus control. Therefore, in the first experiment an automated testing procedure, proven to provide excellent stimulus control, was used to provide a more rigorous test of the effects of scopolamine on discrimination performance. Doses studied were comparable to those used by Jarvik and colleagues [8,29] in their evaluation of the effects of scopolamine in the DMS.

EXPERIMENT 1: EFFECTS ON DISCRIMINATION PERFORMANCE

METHOD

Animals

Eight male adolescent monkeys (M. mulatta) were used in this experiment. All monkeys were test-sophisticated, having been used in numerous behavioral and pharmacological studies during the past year. Each monkey was food deprived for 23 hr before testing, while water was available ad lib in the home cage. Each monkey's daily ration of food and fruit was given in the home cage immediately after each test session was completed.

Apparatus

Testing was conducted in sound-attenuated chambers, using modified versions of the Automated Primate Discrimination Apparatus. [17] This version of the apparatus was fitted to a Plas-Labs primate restraining chair, allowing free movement of the monkey's hands and head while restricting him to the front of the apparatus (Fig. 1).

The stimuli were derived from 2 sets of 100 light-emitting diodes (LEDs) (Hewlett-Packard No. 5082–4494) sorted for equal intensity and light-direction via a photo-transistor circuit. Each set of LEDs was arranged in a 10 x 10 matrix approximately 5 cm square. Discriminative stimuli were produced by lighting selective LEDs to form patterns resembling letters of the alphabet. Each discrimination problem used a novel pair of patterns produced in this manner.

Procedure

The entire procedure was automatically controlled by solid state programming logic located outside the test chambers.

Each monkey was trained to place his face into an observation window through which the 2 stimulus displays could be seen. The displays were located approximately 13 cm beyond the window and were arranged side by side, 8 cm apart, center to center. Each time the monkey placed his face in the window, a photocell beam was broken which initiated a trial by turning on the stimuli. The monkey was required to maintain this observing period, after which time the response levers were unlocked and a discriminative response could be executed. These procedures have been shown to produce excellent stimulus control, both in situations of dynamically presented stimuli (for review, see Bartus and LeVere [7]) as well as tachistiscopically presented stimuli. [2,5]

The discriminative response was made by pulling 1 of 2 levers associated with the 2 discriminative stimuli. These levers were located below the observation window and were slightly recessed so that they were not visible to the monkey when his face was in the observation window. The levers were locked with electromechanical solenoids during the observation period, and again as soon as a discriminative response was made.

Correct discriminative responses were reinforced with 190-mg whole-diet Noyes monkey pellets delivered via 1 of 2 dispensers located behind and slightly above the 2 stimulus displays. When a correct response was made, the dispensed pellet dropped onto the projection screen that had displayed the S^D and then rolled into a cup located directly below the correct response lever.

Incorrect responses were immediately followed by a 750 msec, 100 HZ buzzer. When the monkey removed his face from the observation window following an incorrect response, a 7 sec time-out period began. During the time-out, the house light in the test chamber was extinguished and the next trial could not be initiated.

The spatial position of the S^D for each trial was randomly determined via a 10,000 HZ solid-state oscillator. A correctional procedure was used so that following an incorrect response, the S^D remained on the same side until the monkey made the correct response. Thus, a new trial was considered to begin only following a correct response. An intertrial interval of 2 sec separated trials and began as soon as the monkey removed his face from the observation window following a correct response.

The monkeys were given a maximum of three 50-trial test-blocks each day (i.e., 150 trials), or until 90% or better first-choice correct responses were obtained on a single test-block. The day after criterion was reached, each monkey was dosed according to a randomized block design. The randomization was restricted, however, so that no monkey could receive the same drug on two successive treatments, and every monkey received at least one saline control injection. Several doses of scopolamine were ad-

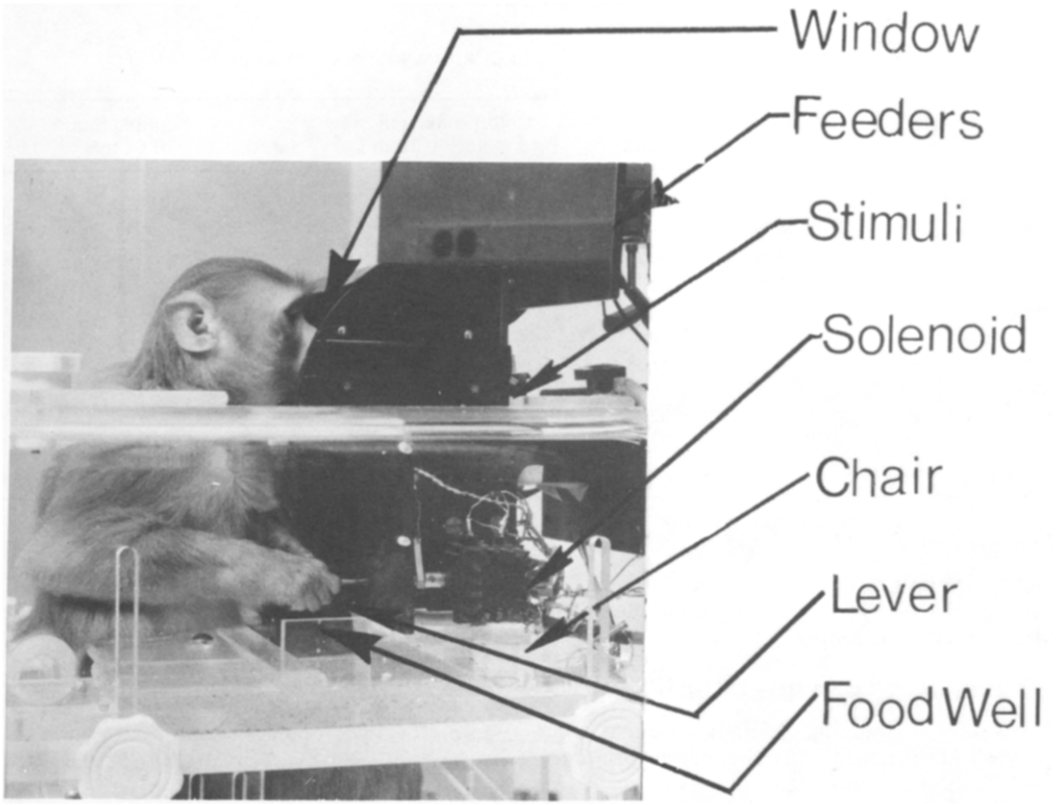

FIG. 1. Photograph of monkey working in the Automated Primate Discrimination Apparatus, used to measure the effects of scopolamine on primate discrimination learning. The location of the more important features of the apparatus are labeled and discussed in the text.

ministered in addition to 2 doses each of chlorpromazine and sodium pentobarbital for additional control comparisons. Table 1 indicates the injections that each monkey received.

The dose range for each drug was empirically established, defining the highest dose under which each monkey would continue to work in the apparatus for food reinforcement. This was done to help equalize potentially confounding effects of each drug on non-discriminatory variables such as motivation, psychomotor coordination, etc. The doses of scopolamine were well within the range tested by Jarvik and colleagues. [29] All injections were given intramuscularly 30 min prior to the intitiation of behavioral testing. The effects of these drugs on discrimination ability were evaluated by measuring the monkeys' ability to maintain criterion performance on the previously learned problem during 50 test trials. A minimum of 3 days was interspersed between each drug iniection in all cases.

RESULTS AND DISCUSSION

The results of Experiment 1 are illustrated in Fig. 2 (individual test scores are shown in Table 1). These data indicate that scopolamine severely disrupts discrimination performance in nonhuman primates, even at extremely low doses, where few if any, overt effects (such as pupil dilation, ptosis, etc.) were observed. Most of the test scores obtained with scopolamine are at, or near, chance levels and in no case were they as high as those occurring with injections of saline.

By comparison, the effects of chlorpromazine and sodium pentobarbital were not nearly as disruptive. Chlorpromazine showed little or no direct effect on discrimination ability; the scores obtained at the low dose were all in the range of the saline controls, while the scores at the high dose indicated little effect, except in the 2 cases where the monkeys actually stopped working during the test session.

Sodium pentobarbital impaired discrimination performance more then chlorpromazine, but this effect was substantially less than what occurred following scopolamine. The low dose of sodium pentobarbital was ineffective, while performance even under the high dose remained consistently above chance. Attempts to produce greater impairments by increasing the dose of sodium pentobarbital resulted in the monkeys becoming too sedated to even work in the apparatus.

In summary, the results of Experiment 1 confirm that relatively mild doses of scopolamine profoundly impair visual discrimination performance. This severe impairment, at doses producing few overt effects, suggests a direct effect on discrimination mechanisms. Therefore, tests designed to evaluate the role of acetylcholine in other behavioral processes, such as STM, should control for this confounding, debilitating influence on visual discrimination when anti-cholinergic agents are used. If such effects are

TABLE 1

PERCENT CORRECT ON 50 TRIAL TEST BLOCK/DISCRIMINATION PERFORMANCE

Drug	Saline	Sodium Pentobarbitol		Chlorpromazine		Scopolamine		
Dose	0.3 m/k	5 m/k	10 m/k	0.15 m/k	0.30 m/k	0.03 m/k	0.04 m/k	0.05 m/k
Monkey:								
Captain	100	100	—	98		—	†	50*
Bo Jangles	96	94	80	96		22	—	60*
Maxwell	94	100	66	—	77.5*	58	—	30
Bimbo	98	—	—	—		60	61	60*
Atilla	98	96	—	—	96	64	66	55*
Charles IV	90	—	58	94	98	—	58	40*
Dopey	96	—	76	—	73.6*	85	—	—
Tiny	98	—	92	96	100	—	48	—
Mean	96.3	97.5	74.4	96	89.0	57.8	58.3	49.2
Median	97	98	76	96	96	60	59.5	52.5

*Monkey would not complete entire 50-trial test.
†Monkey would not work at all.

not controlled, an accurate assessment of the influence on these behavioral processes will be greatly obscured and the conclusions drawn likely misleading.

EXPERIMENT 2: EFFECTS ON SHORT-TERM MEMORY

Because the results of Experiment 1 indicated that other research using the DMS procedure may be inappropriate for studying the effects of cholinergic blockade on STM, Experiment 2 was designed to provide a more conclusive evaluation of these effects.

METHOD

Animals

Three naive, male adolescent rhesus monkeys were used. These monkeys were food deprived approximately 23 hr before testing each day and were given water ad lib in their home cage. They had been given 1 to 3 months training in the apparatus described below before Experiment 2 was initiated.

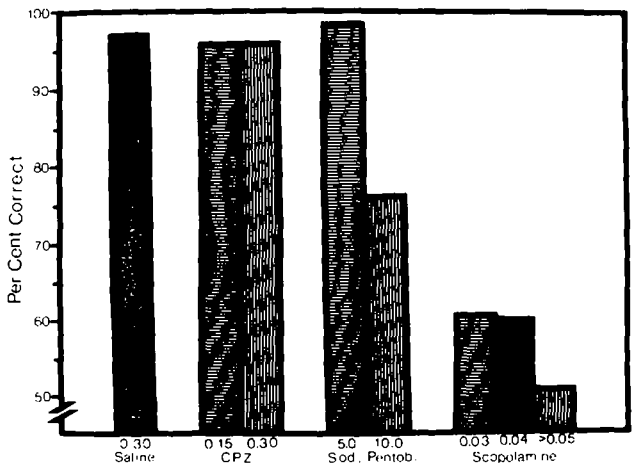

FIG. 2. Histographs depicting median percent correct achieved with postacquisition injections of scopolamine and reference drugs. Numbers immediately above each drug indicate the dose administered (m/k).

Apparatus

The apparatus, illustrated in Figs. 3 and 4, was a totally automated, computer-controlled primate testing device.

Its basic configuration includes an array of stimulus-response (S-R) panels, somewhat similar to those used independently by Pribram [26] and Medin. [9,21] It consists of 9 individual S-R panels, arranged in a 3 x 3 matrix, equally spaced 3 in. apart, center to center. The use of 9 individual panels was intended to increase the measuring sensitivity of the testing procedure by increasing the range of possible above-chance scores (i.e.; chance = 1/9 or 11.1%, vs. the conventional 50%). The S-R panels are arranged in the form of a relatively small matrix to minimize the problem of monkeys using overt body orientation (in lieu of convert memory mechanisms) to bridge the gap between the processing of the information and the opportunity to respond, as reportedly occurs in the two-choice delayed-response (DR) procedure. [13] Careful closed-circuit television observation of all monkeys performing in the apparatus confirmed that apparent overt cues such as these are not used in this test situation.

Each of the 9 S-R panels is approximately 2.5 cm square and is constructed from clear plastic, frosted on one side. A small magnet is attached to the bottom of each panel (back side), and a reed switch is mounted directly below each magnet (inaccessible to the monkey). The S-R panels are hinged at the top, and whenever one is pushed, the switch associated with it closes, allowing automated monitoring of each response. A plastic cube mounted directly behind each S-R panel is designed to accommodate a standard 190-mg Noyes monkey reinforcement pellet which is delivered via a tube entering the side of each cube. When delivered, the reinforcement rests directly behind the correct panel for that trial and is exposed whenever the correct panel is pushed. Each plastic cube fits inside an Industrial Electronics Engineer stimulus display unit (IEE Series 10,000) which is focused to project its image on the frosted door. The single most important advantage of this arrangement is that almost limitless stimulus flexibility is offered, and at the same time the usually contradictory benefits of total automation and close stimulus-response-reinforcement spatial contiguity can also be enjoyed (see Meyer, Treichler,

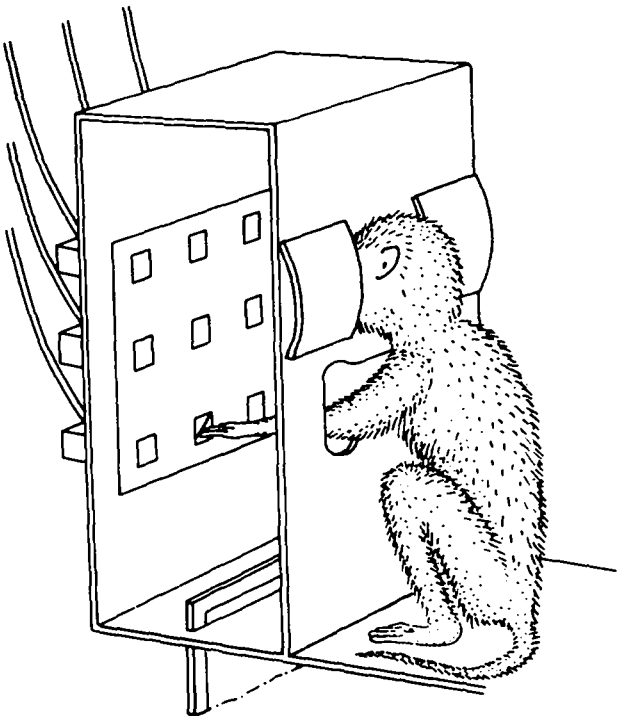

FIG. 3. Artist's conception of monkey making choice response in the automated apparatus used to measure short-term memory (STM). An indirect delayed response procedure was used.

and Meyer, [23] for excellent review of these problems).

A partition similar to that employed by Meyer [24] separates the monkey from the S-R matrix. An inverted U cutout allows the monkey to reach through the partition to execute choice responses, and a viewing window equipped with a photo-electric device not only allows the monkey to self-initiate the stimulus presentation but also can be used to force him to look for a predetermined period of time before the trial will progress. The self-initiation and forced-looking procedures have been shown to greatly increase stimulus control in the two-choice discrimination learning paradigm, allowing precise intratrial manipulation [4, 6, 7, 18, 19, 20] as well as tachistoscopic presentation of the stimuli. [2,5] This arrangement was incorporated into the present apparatus to increase the likelihood that the monkey will process the necessary stimulus information before the retention interval is initiated. Also, by precisely manipulating the stimulus information presented before the delay, it is possible to study mechanisms of information processing during STM in a manner similarly accomplished in the discrimination learning paradigm (for recent review, see Bartus and LeVere [7]).

A one-way viewing mirror-window, or screen (similar to that originally used by Fuster, [14] and later adopted for STM by Ruggiero [30]) separates the S-R panels from the viewing partition. When this mirror is back-lit, it appears transparent, allowing the monkey to view the matrix; when it is not back-lit it is opaque, visually isolating the matrix from the monkey. Thus, this mirror-window serves the dual functions of the opaque and transparent barriers required in most other primate testing devices. In the normal, resting position (i.e., while separating the S-R matrix from the monkey), the mirror is actually raised, and at the end of the

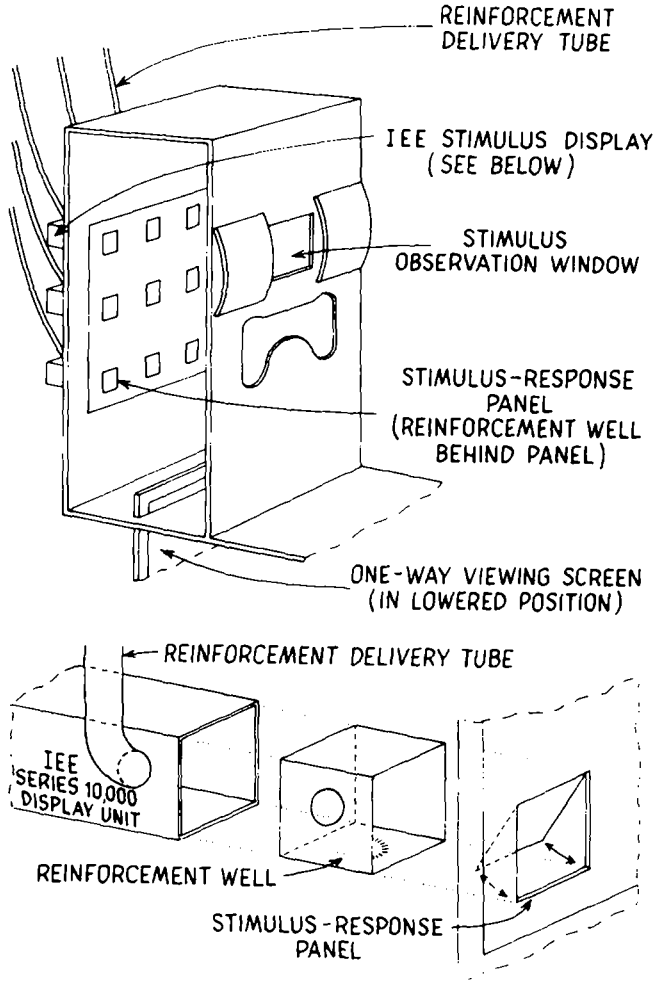

FIG. 4. Schematic diagram illustrating important features of the apparatus shown in Fig. 3. Bottom diagram depicts exploded view of one of the 9 stimulus-response-reinforcement units which make up the S-R matrix.

retention interval, it is rapidly removed from the monkey's way by dropping it, rather than by slowly raising it. This feature was incorporated to allow much shorter and more precise retention intervals to be used.

The entire experimental procedure was controlled using a Data General, Nova 2/10 minicomputer interfaced to the apparatus via BRS/LVE "ACT III" language.

Procedure

An indirect delayed-response (DR) procedure [22] was used because the amount of sensory discrimination required in the DR presumably is not as great as in the DMS. That is, in the DR procedure, the monkey need only perceive where the conditioned stimulus appears and remember this position during the retention interval. On the other hand, the DMS procedure requires that the monkey encode which of 2 or more stimuli occurred before the delay and then discriminate among the alternatives when the retention interval expires. For this reason, the DR test should provide a more accurate assessment of the effects of scopolamine on STM, unconfounded by its effects on visual discrimination.

Each delayed-response trial was initiated when the monkey placed his head into the stimulus observation window. This observing response interrupted an infrared light beam which tiggered a phototransistor located on the other side of the window. When his observing response occurred, lights, mounted behind a translucent panel (above and below the S-R matrix), were illuminated, enabling the monkey to see the stimulus-response matrix. Two hundred msec after the observing response was initiated, a green stimulus, signaling which of the 9 stimulus-response panels had a reinforcement pellet behind it, was flashed for 3 sec on one of the 9 panels of the matrix. After the stimulus presentation period expired, the back-lights and the stimulus light were extinguished so that the monkey could no longer see the correct panel or its position on the matrix. This marked the beginning of the retention interval, during which time the monkey had to retain in memory the information concerning which of the 9 stimulus-response panels hid the reinforcement. When the retention interval timed out, the one-way screen was quickly dropped out of the way, the back-lights illuminated, and the matrix became accessible to the monkey. The monkey then pressed one of the panels, attempting to expose the reinforcement. If the panel was incorrect, a buzzer sounded for 500 msec and the monkey was then allowed another choice. This procedure continued until the monkey finally chose the correct panel. When the correct panel was pushed, the stimulus light was reilluminated, a conditioned reinforcement tone was sounded, and the reinforcement was exposed. At this time the monkey could remove the food pellet from the reinforcement well and eat it. After the monkey removed his face for the observation window, the one-way screen was raised (with the back-lights now extinguished), and intertrial interval initiated. The data from that trial was then stored in the computer. Following this, a new panel was selected for baiting by the computer, and the apparatus was set for the next trial.

Retention intervals of 0, 2.5, 5.0 and 10 sec were used for all 3 monkeys. These intervals were quasi-randomly intermixed within each session to control for possible confounding effects of satiation, fatique, rate of drug metabolism, etc. For 10 trials immediately preceding presentation of these intervals, as well as for 10 trials immediately following, a continuous stimulus presentation condition was presented. In this treatment, the stimulus light remained on during the time the monkey could respond, therefore eliminating all requirements of STM, while still demanding the same use of visual-coordinative mechansims (e.g., visual acuity, eye-hand coordination, etc.) needed to perform in the apparatus.

Several doses of scopolamine were administered to each monkey over several days of testing. Each dose was titrated for each monkey with the aim of either demonstrating or refuting the existence of an interaction between the dose of scopolamine and the length of the retention interval.

RESULTS

The results of this experiment, depicted in Fig. 5, A, B and C, consistently demonstrate that as the retention interval increases, the deficits from scopolamine increase. Furthermore, this retention deficit is clearly dose-related, for the higher dose of scopolamine produced even greater impairments than did the low dose. Thus, very little or no effect is found at the control interval, or the zero second

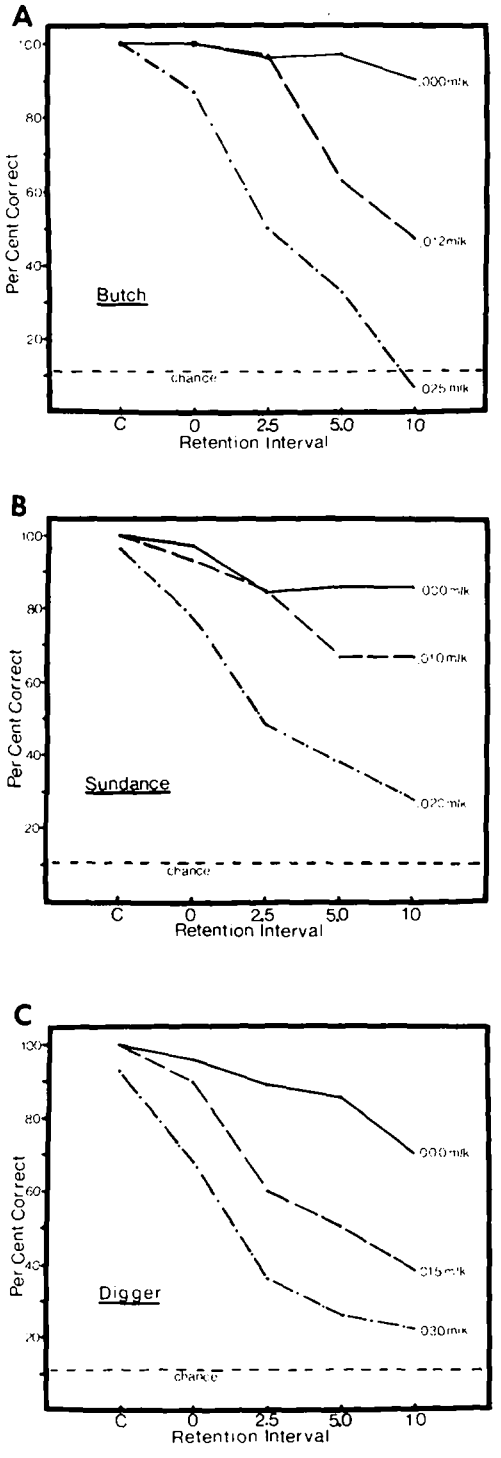

FIG. 5, A, B and C. Graphs depicting individual monkey's performance at various retention intervals under 2 doses of scopolamine and a saline control condition (0.000 m/k). The treatment labeled "C" was a control condition where the stimulus was continuously present during the opportunity to respond. The other 4 conditions (0, 2.5, 5.0 and 10) refer to the duration (in sec) that expired between when the stimulus went off and when the opportunity to respond occurred.

retention interval under the low dose of scopolamine, but as the retention interval increases, the monkeys' performance becomes progressively more impaired. At the higher doses of scopolamine, the detrimental effect is observed sooner (i.e., at even shorter intervals) and the deficit on the longest intervals approaches chance levels.

A three-way analysis of variance was performed to test the reliability of these results. This test revealed highly significant main effects attributed to the dose of scopolamine ($F(2,4) = 78.62$, $p<0.001$) as well as length of retention interval ($F(4,8) = 53.48$, $p<0.001$). More importantly, however, a significant interaction between dose and retention interval was also found ($F(8,16) = 10.79$, $p<0.0001$), demonstrating greater disruptive effects of scopolamine as the monkey is required to retain information in STM for longer periods of time.

Finally, it should be noted that when the monkeys were tested under doses higher than those illustrated in Fig. 5, A, B and C, their performance at all retention intervals, including the continuous presentation control condition, exhibited a dose-related decline. When the dose was raised about 0.075 m/k, the monkeys' response rate on the self-initiated trials became very sporadic (often ceasing altogether), and their performance accuracy fell to near chance levels.

DISCUSSION

Others have suggested that cholinergic mechanisms are directly involved in the expression of recent, or STM. [1, 11, 25] The data reported here support this idea by demonstrating that the longer information must be held in STM, the more disruptive are the effects of scopolamine. However, a question which must be considered is whether the observed effects are actually the result of an anti-cholinergic influence on the central nervous system or whether peripheral, autonomic effects might be responsible.

We believe the evidence is substantial that the peripheral autonomic effects of anticholinergic drugs cannot account for these deficits. For instance, Bohdanecky, *et al.* [8] reported that although scopolamine impaired performance at all retention intervals in the DMS, methscopolamine bromide (which does not easily pass the blood-brain barrier) did not substantially impair response accuracy at any retention interval. Thus, the impairments they reported must have been the result of an action on the central nervous system. Evans, [12] also studying monkeys, found scopolamine disrupted accuracy on visual discrimination, whereas methscopolamine bromide produced no such effect. Furthermore, unpublished pilot tests conducted in our laboratory with methylatropine iodide (another quaternary anticholinergic with restricted transport across the blood-brain barrier) demonstrated that when the dose was raised high enough to produce impairments, accuracy on the DR paradigm described earlier was affected equally across all retention intervals. Roberts and Bradley [28] found a similar general effect with methylatropine nitrate when testing primate memory in a Konorski-type delayed discrimination procedure. From these studies it seems apparent that the peripheral autonomic effects of anti-cholinergics do not readily impair primate performance; furthermore, the impairments that do eventually occur are equally severe across all test conditions, suggesting that a general effect on motivation is responsible. The interaction between dose of scopolamine and retention interval makes it equally unlikely that effects on nonmemorial, central nervous system mechanisms (such as attention or perception) could be responsible for these behavioral impairments. Rather, the disruption of STM by interference with central cholinergic mechanisms essential to the process remains the most parsimonious interpretation of these observations.

Various features of the test apparatus developed and used here provide certain advantages for behavioral and pharmacological studies of primate STM not previously available to other investigators. Perhaps the most important advantage to demonstrating a specific disruptive effect on STM by anti-cholinergic drugs was the elimination of drug-induced, confounding discrimination impairments. The results of Experiment 1, together with previously published research, [12, 15, 16] demonstrate how extremely low doses of scopolamine can severely impair discrimination performance, even in situations where stimulus control is usually very good. For this reason, tests such as the DMS, which require extensive use of discrimination abilities, are not ideal for testing specific drug effects on memory. Obviously, they can measure little about how much a monkey remembers if, because of certain effects of the drug, the monkey is unable to accurately encode the sample stimulus or discriminate among the choice alternatives. Thus, if performance becomes universally poor in this situation when an anti-cholinergic is administered, one might reasonably conclude that motivation, attention, or perception may have been affected, but one can conclude little about what specific effects on memory processes may have also occurred. Care should therefore be given in interpreting whether drug effects, as measured in these situations, have any specific effect on STM.

In summary, the results of this study demonstrate a clear interaction between the effects of an anti-cholinergic and the length of the retention interval. This interaction provides evidence that one specific result of cholinergic blockade is the impairment of performance in situations where information must be held in memory for short periods of time. On the basis of these data, it seems reasonable to conclude that acetylcholine is not only involved in the acquisition and long-term retrieval of newly-learned habits, as previously reported, [10] but is also intimately involved in the expression of primate STM as well.

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