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RAPID COMMUNICATION

Scopolamine Suppresses Both Locomotion and Object Contact in a Free-Exploration Situation

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RENNER, M. J., D. L. DODSON AND P. A. LEDUC. *Scopolamine suppresses both locomotion and object contact in a free-exploration situation.* PHARMACOL BIOCHEM BEHAV **41**(3) 625-636, 1992.—It was recently reported by Buhot et al. that presession cholinergic disruption with scopolamine decreases time spent in proximity to novel objects while increasing locomotor behavior. Male Long-Evans rats (*Rattus norvegicus*, 80 days old) were given low-light access to an arena containing objects but were not forced to remain in the arena. On day 1, each subject was injected with saline (SAL). This session was used for familiarization with the apparatus and procedure. On days 2 and 3, four groups were given saline (SAL) or scopolamine (SCO, 1 mg/kg or 0.25 mg/kg), resulting in SAL-SAL, SAL-SCO, SCO-SAL, and SCO-SCO groups. Videotapes of these sessions were scored according to a standard protocol that allows separate quantification of locomotion, general activity, and object interaction behaviors. Scopolamine suppressed object investigation (both gross contact measures and indices of interaction character) whenever present. In contrast to Buhot et al. (using a forced-exploration situation), in this free-exploration context SCO also suppressed locomotor behavior. This study supports the conclusion that anticholinergics impair information gathering instead of affecting memory directly, which calls into question memory-related explanations of cholinergic treatments.

Scopolamine Exploration Curiosity Learning Memory *Rattus norvegicus* Investigatory behavior Cholinergic

CONSIDERABLE evidence suggests that anticholinergic agents impair some aspect of the learning and memory process (3) and that cholinergic abnormalities are associated with human memory impairments such as Alzheimer's disease (11). There is, however, disagreement about the specific role the cholinergic system plays in learning and memory. Some argue that scopolamine is amnestic, perhaps through an effect on working memory (5,12), while other evidence suggests that its role may be concerned with attentional and cognitive processes involved with the learning events serving memory formation (4,7,18).

Exploratory behavior in the open field is a complex behavioral phenomenon that reflects learning processes in a naturalistic environment (14,15). Further, the patterns of behavior rats employ during investigation of stimulus objects provide measures that differ from indices of exploration based on gross activity, such as locomotion or rearing (16). Thus, it seems likely that pharmacological study of this naturally occurring form of learning will provide insights from a new perspective into the contribution of the cholinergic system to memory processes, as well as information about whether the neural foundations of exploration and investigation are in common with more traditional task-based forms of learning.

A review of the effects of anticholinergic drugs on various forms of exploratory behavior has also addressed the limitations of forced-exploration paradigms in providing an account of exploration (9). These testing situations rely solely on activity-contaminated measures of exploration. In general, in forced exploration both nonspecific activity and ambulation increase when rats are given anticholinergic drugs, possibly reflecting a generalized CNS activation (9). Ambulation effects of scopolamine are, however, dose dependent, with increases at higher doses (1–2 mg/kg) and decreases at lower doses (0.1, 0.25 mg/kg) (10). In contrast, the frequency and

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duration of a nonspecific behavior, rearing, decreased with scopolamine administration (10). Thus, the use of behavioral measures such as ambulation and nonspecific activity in studying drug effects during exploration provides information about the motoric effects of the drug; however, the drug's effects on the cognitive aspects of exploration are not addressed.

The effects of anticholinergic drugs on exploration have been examined using other experimental paradigms. Although scopolamine reduces preferences for novelty (8), whether this reflects interference with a central cholinergic mechanism or peripheral influences is unclear (9). Anticholinergic drug effects on preference for environmental complexity (defined as spatial change) are not consistent. When employing the "head-poke" test of exploration, scopolamine has been found to reduce the typical within-session decline in head-poke frequency (usually attributed to habituation) (19), while others found no change in head-poke frequency with scopolamine (6,17).

It has recently been reported that, in a forced-exploration situation, presession cholinergic disruption with scopolamine decreases the time spent in proximity to novel objects while increasing locomotor behavior (2). This could provide a useful measure of attentional processes in a spontaneous situation, outside the context of specific tasks. The limitations of the forced-exploration situation, however, limit the confidence that can be placed in this conclusion.

The present study examines the influence of cholinergic disruption on unforced exploration of an open field containing stimulus objects. Use of this experimental paradigm has several advantages over activity-only methods for examining exploratory behavior. First, it allows for the examination of behaviors that are not activity contaminated, as well as more traditional measures such as locomotion and general behaviors (e.g., sniffing, grooming, rearing). More specifically, in this experiment the effects of the anticholinergic drug scopolamine on the number and duration of object interactions, as well as the behaviors used during these interactions, were examined. Second, by introducing two novel stimulus objects on day 2 of testing and then using the same stimuli on day 3, the effects of scopolamine on both the acquisition of and retrieval of information related to object characteristics can be examined.

Three groups were administered scopolamine 12 min prior to gaining access to the arena on either day 2, day 3, or days 2 and 3. If drug administration on day 2 disrupts (or blocks) acquisition of information about the stimulus objects, then rats should respond to these objects as if they were novel when tested in the arena on day 3. If rats given scopolamine on day 3 react to the stimulus objects as if they are novel, then retrieval of previously learned information was disrupted. The final drug condition (scopolamine on days 2 and 3) was used to control for possible state-dependent effects: If scopolamine induces state-dependent memory, subjects given scopolamine on both days should behave more like subjects given saline both days than like either of the groups switched between saline and scopolamine.

METHOD

Subjects

Forty male, Long-Evans hooded rats (Charles River Laboratories) were approximately 80 days of age and weighed an average of 362 g at the time of testing. Prior to the start of the experimental procedures, rats were housed in groups of four in standard laboratory stainless steel rack cages. Subjects were maintained on a 12 L:12 D cycle with lights on at 0700 and given free access to food and water at all times except during the observation period.

Apparatus

Experimental sessions were conducted in an open-field arena (91 cm square) with clear Plexiglas sides (55 cm in height) as illustrated in Fig. 1. The wooden floor of the arena was painted medium gray and divided into four equal zones (45 cm square) by black paint lines 1 cm wide. A circular opening (8.5 cm dia) centered along one wall provided entry into the arena. Clear polycarbonate tub cages (19 × 36 × 24 cm; Nalgene), each with a fastenable circular opening (7.5 cm dia) at one end, were used to house subjects individually. Each subject had the option of entering the arena from its home cage or remaining out of the arena.

Subjects' behaviors were videotaped under red light with a low-light video camera, the signal from which was routed through a character generator that placed real time, elapsed time, and date on the video image and recorded on a VHS videocassette recorder. Transcription of videotapes was accomplished using an MS-DOS computer system and software by Renner (unpublished).

Stimulus objects were of two general types: Manipulable (M) objects were small and light enough to be moved by the subject; nonmanipulable (N) objects were large and heavy and could not be moved. Manipulable objects used in this study were a wad of paper and a wooden cylinder (4 cm dia, 5 cm long) that had been flattened on one side and scored with drill holes and saw cuts. Nonmanipulable objects were a large granite rock (1600 g) and a wooden block (8.5 × 8.5 × 20 cm).

Drug treatment consisted of scopolamine hydrobromide (Sigma Chemical Co., St. Louis, Missouri) dissolved in 0.9% NaCl at concentrations of 1.0 and 0.25 mg scopolamine/1 ml saline.

Procedure

Nine days prior to testing, subjects were group housed for 7 days in an "enriched condition" (EC) consisting of a large cage (40 × 40 × 60 cm), each of which contained several stimulus objects (chosen from a pool of junk objects kept in the laboratory), some of which were replaced each day [this treatment is described fully in Bennett and Rosenzweig (1)]. Each subject was handled daily to habituate it to human contact. Subjects were then placed in individual tub cages and moved to the testing room 48 h prior to data collection. Twenty-four h prior to testing, subjects were weighed and randomly assigned to one of four experimental groups.

The four treatment conditions used in this study are detailed in Table 1. Data collection took place over three consecutive nights. Observations were carried out under direct dim red illumination (two 25-W lamps) and indirect dim white lighting (one 10-W white bulb in a metal reflector) 2 cm from a wall. Observations began approximately 1 h after the beginning of the dark phase of the subjects' light–dark cycle (13).

Testing was conducted in a small room containing only the open-field arena, videocameras, and a rack with the tub cages used to house subjects. All other necessary equipment was housed in an adjacent room so that the experimenter was

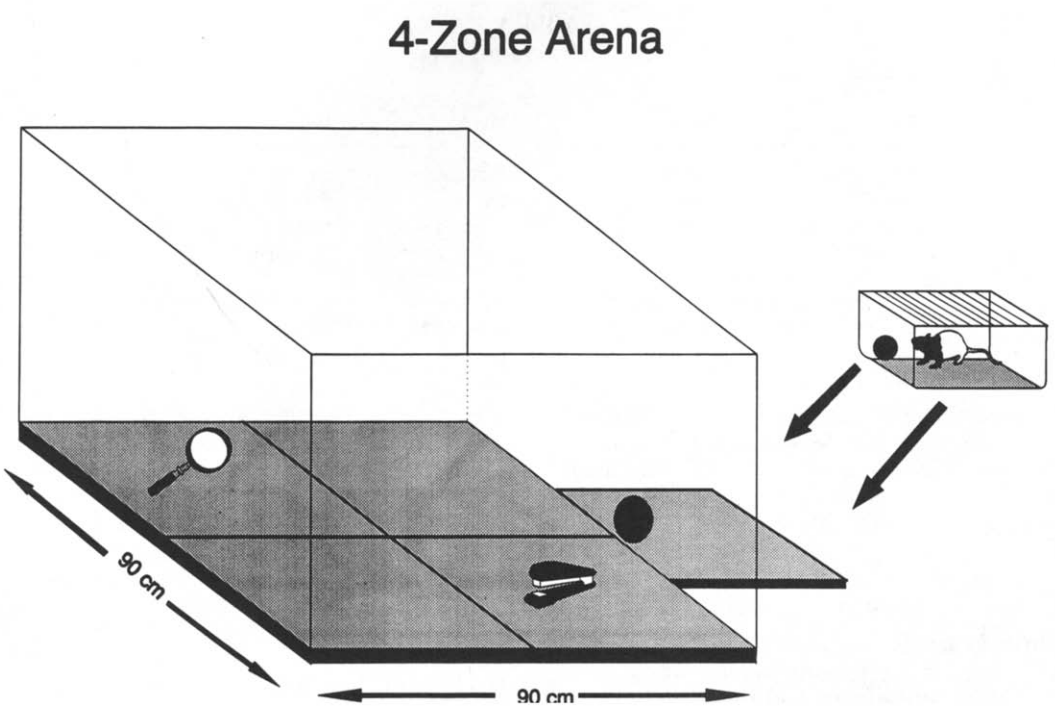

FIG. 1. Schematic diagram of the arena used for behavioral observations in this experiment. Objects shown are for illustration only; actual objects used are described in the text.

never present during actual testing. Each subject was injected with saline (SAL) and 12 min later given access to the arena for 10 min. Subjects were than randomly divided into four groups, with half given SAL and half given scopolamine (SCO, 0.25 or 1.0 mg/kg) on days 2 and 3, resulting in SAL-SAL, SAL-SCO, SCO-SAL, and SCO-SCO groups.

Day 1 was intended to familiarize subjects with the arena and testing procedure; hence, behavioral data were not collected for that day. Data were collected from days 2 and 3. Placement of stimulus objects was counterbalanced so that for half of the subjects (five from each treatment condition) the block was in zone 1 and the cylinder in zone 4; for the remaining subjects, the zone positions were reversed. For any particular subject, the location of the objects was the same on both nights.

The procedure used for each individual test session was the same for all subjects on all three nights. At the start of each session, an experimenter would enter the testing room, take the appropriate tub cage off the rack and open the door on the end of the cage, position the tub cage so that the door fit snugly against the entry to the arena, and exit the room. Video recording was started and continued for 10 min. During this time, the subject was free to remain in the start box (home cage), enter the arena, or return to the start box at any time. At the end of the 10 min, video recording was halted and the subject's tub cage was replaced on the rack. The process was then repeated with the next subject until all subjects had been observed.

Transcription of Videotape

Videotapes of arena sessions were scored according to a standardized protocol [described fully in Renner and Seltzer (16)] that allows for separate quantification of locomotor and object interaction behaviors. Locomotion is scored in terms of latency to enter the arena, number of zone changes within the arena, arena entries, and mean duration of visits to the arena. The number of nose-pokes (defined as any time the tip of the nose breaks the plane of the arena wall) and partial entries (defined as any time the subject enters the arena but has only one to three paws inside the arena) made by the subject were recorded. Except that arena entries were scored as partial until all four paws were inside the arena, location was determined by the position of the subject's head and front paws. General activities, those not related to specific objects in the environment, were also recorded. These include sniffing at the arena walls and floor, grooming, rearing, and propping on the walls of the arena with one or both forepaws. Several other behaviors were scored (e.g., sudden freezing, sudden withdrawal from the arena, jumping up the walls), but occurred so infrequently as to prohibit analysis.

Each second during which the subject was in contact with a stimulus object was transcribed according to which of 10 predefined behaviors were observed. These behaviors included sniffing the object, three forms of forepaw contact, two forms of climbing or entering the object, two forms of mouth contact, and two types of apparently inadvertent contact. In addition, any movement of the object resulting from these interactions was recorded. Operational definitions for each behavior type may be found in Table 1 of Renner and Seltzer (16). From these records, several summary measures of object interaction were derived. Total object contact was defined as the total number of seconds in contact with the object. A bout of interaction was defined as any uninterrupted period of contact, and was considered to have ended when 1 s passed with-

TABLE 1
TREATMENT CONDITIONS

Group	Day 1 (preexposure)	Day 2	Day 3
SAL-SAL	Saline	Saline	Saline
SAL-SCO	Saline	Saline	Scopolamine
SCO-SAL	Saline	Scopolamine	Saline
SCO-SCO	Saline	Scopolamine	Scopolamine

All subjects received a saline injection on day 1, which was used as preexposure to the injections and behavioral procedures. Data were collected on days 2 and 3.

out interaction. The number of different behaviors displayed by the subject was also recorded. An additional measure referred to as the *intensity index* was also used. This measure is the proportion of interaction bouts that included a subset of the possible behaviors requiring higher levels of physical involvement.

RESULTS

Each location and locomotion measure was analyzed using a 4 (groups) × 2 (doses) × 2 (days) model three-way analysis of variance (ANOVA) with groups and doses as between-subjects factors and day as a repeated measure. Latency to enter the arena, shown in Fig. 2, was significantly affected by group, $F(3,32) = 3.72$, $p < 0.05$, drug dose, $F(1,32) = 5.80$, $p < 0.05$, and day, $F(1,32) = 7.10$, $p < 0.05$, with no significant interactions. Number of entries to the arena, also shown in Fig. 2, was significantly affected only by drug dose, $F(1,32) = 8.45$, $p < 0.05$; no other main effects or interactions were significant. Mean length of visits to the arena, shown in Fig. 3, was affected by group, $F(3,32) = 3.33$, $p < 0.05$, with a significant group × day interaction, $F(3,32) = 4.24$, $p < 0.05$. Number of zone changes, as shown in Fig. 3, was also affected by group, $F(3,32) = 9.98$, $p < 0.05$, and there were significant group × day, $F(3,32) = 18.77$, $p < 0.001$, and dose × day interactions, $F(1,32) = 5.16$, $p < 0.05$, as well.

Each object interaction measure was analyzed using a 2 (object types) × 4 (groups) × 2 (doses) × 2 (days) model four-way ANOVA, with object types and days as within-subjects factors and doses and groups as between-subjects factors. For economy and to preserve the readability of the presentation, F values, degrees of freedom, and significance levels for these analyses are presented in Table 2. Any comparison characterized as significant describes means that are different at the $p < 0.05$ level or beyond.

Total contact with the objects, shown in Fig. 4, was significantly influenced by group, day, and object type. In addition, significant dose × day, group × day, group × object, day × object, and group × day × object interaction effects were observed. Number of interaction bouts, shown in Fig. 5, was significantly affected by group and object type. Significant dose × day, group × day, and group × object interactions were also observed.

The number of behaviors displayed during object investigation, shown in Fig. 6, show significant group and object type effects, as well as a group × day interaction and a dose × day interaction. As was found with the other measures of object interaction, the intensity index [a measure of the proportion of bouts including more physically intense forms of interaction behavior; see Renner and Seltzer (16) for the derivation of the measure], shown in Fig. 7, was significantly influenced by object type and group, as well as a dose × day interaction.

What at first glance appears to be a complex pattern of results is profoundly simplified by one overriding effect: Both doses of scopolamine resulted in a decrease in exploration for both locomotor activity and object contact. Inspection of Figs. 2–7 reveals a clear pattern: If scopolamine had a suppressive effect, then groups plotted with circles (SAL on day 2) should have higher values than triangles (SCO on day 2) for all variables except latency to enter arena, which should be reversed. Likewise, open figures (SAL on day 3) should be higher than filled figures (SCO on day 3). This pattern held in 41 of 48 possible comparisons of this type. Statistically, within-subjects comparisons were possible for the SAL-SCO and SCO-SAL groups. When scopolamine sessions were compared with saline sessions for the 1.0-mg/kg dose subjects (ignoring day), all means were in the predicted direction except latency to enter the arena (n.s.); zone changes, $t(9) = 2.98$, $p < 0.05$, total contact with the nonmanipulable object, $t(9) = 2.87$, $p < 0.05$, and the number of bouts with the nonmanipulable object, $t(9) = 3.07$, $p < 0.05$, were significantly different. For rats at the 0.25-mg/kg dose, all means were also in the predicted direction and mean length of arena visits, $t(9) = 5.88$, $p < 0.001$, zone changes, $t(9) = 5.60$, $p < 0.001$, total contact with the nonmanipulable object, $t(9) = 4.12$, $p < 0.01$, and number of bouts with both nonmanipulable, $t(9) = 5.17$, $p < 0.01$, and manipulable, $t(9) = 3.25$, $p < 0.05$, objects were significantly different. For SCO-SCO and SAL-SAL groups, between-subjects comparisons were calculated by taking the mean of days 2 and 3 for each subject. All mean differences for 1.0-mg/kg subjects were in the predicted direction, and 11 of 12 measures were significantly different at $p < 0.05$ or better; intensity index for the M object was marginally significant, $t(9) = 2.56$, $p = 0.061$. At 0.25 mg/kg, all means were different as predicted, and visit length, $t(8) = 4.83$, $p < 0.01$, zone changes, $t(8) = 3.40$, $p < 0.05$, total contact with the nonmanipulable object, $t(8) = 4.40$, $p < 0.01$, number of interaction bouts with both the nonmanipulable, $t(8) = 4.26$, $p < 0.01$, and manipulable, $t(8) = 2.87$, $p < 0.05$, objects, and number of behaviors displayed toward the nonmanipulable object, $t(8) = 3.17$, $p < 0.05$, were significantly different.

DISCUSSION

In the testing context used in this study, in which subjects are free to explore or remain out of the arena, scopolamine suppresses both locomotion and investigation of stimulus

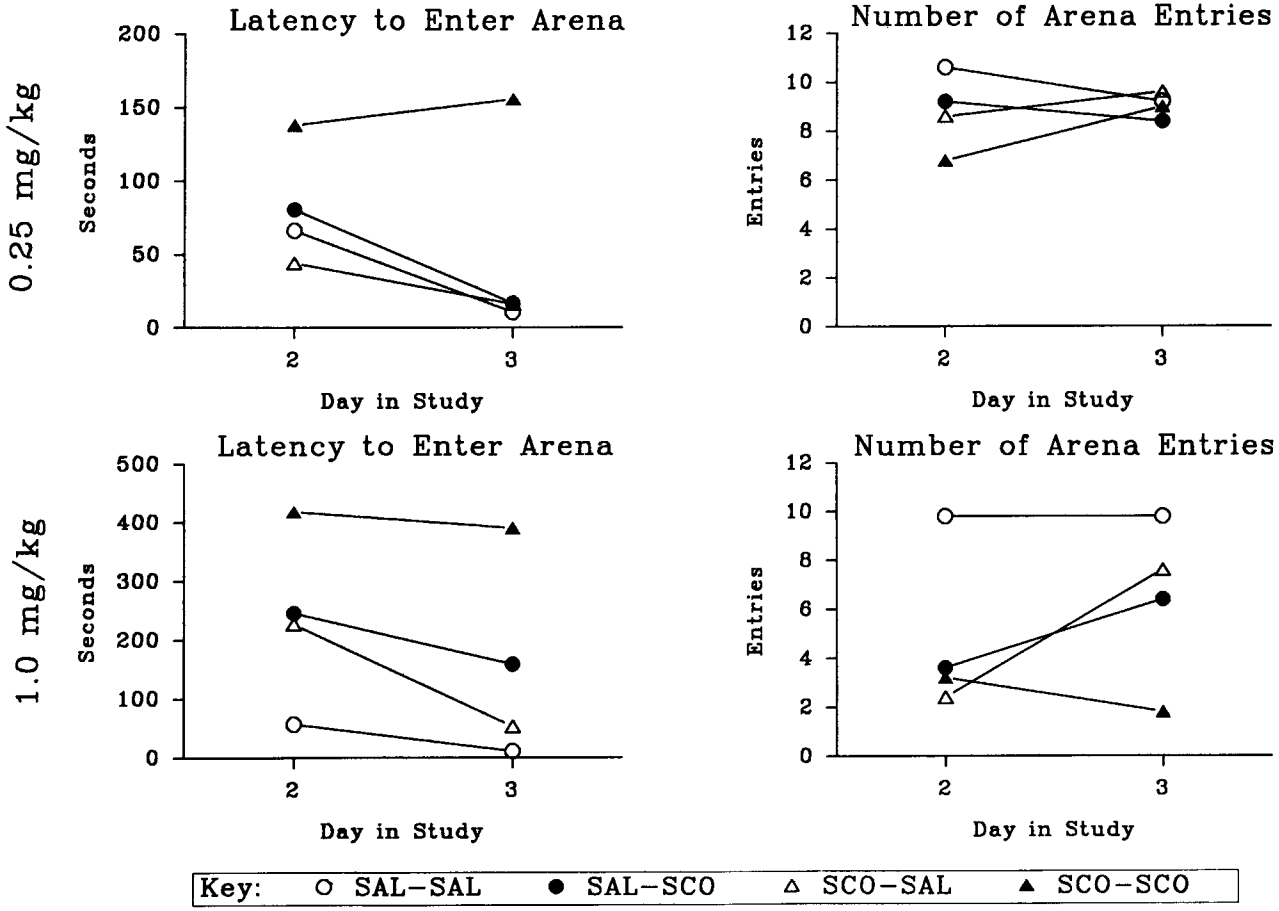

FIG. 2. Latency to enter the arena (left two panels, with 0.25-mg/kg dose above and 1.0-mg/kg dose below) and number of arena entries (right panels).

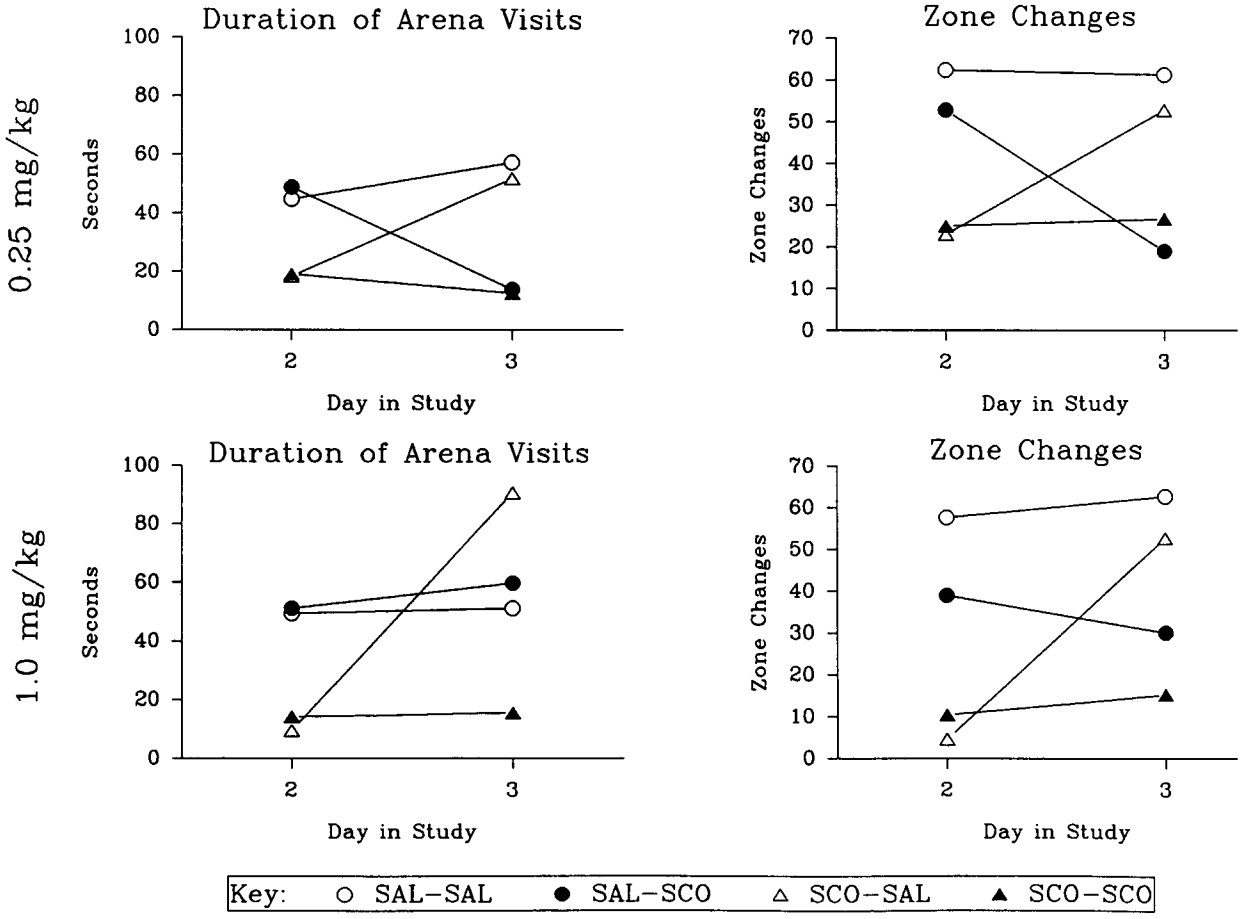

FIG. 3. Mean length of visits to the arena (left) and number of zone changes (right).

TABLE 2

F-VALUES AND SIGNIFICANCE LEVELS FOR 4 (GROUP) × 2 (DOSE) × 2 (DAY) × 2 (0BJECT) FOUR-WAY ANOVA PERFORMED ON EACH OBJECT-RELATED DEPENDENT VARIABLE

Variable	Dose	Group	Dose × Group	Day	Dose × Day	Group × Day	Dose × Group × Day	Object	Dose × Object	Group × Object	Dose × Group × Object	Day × Object	Dose × Day × Object	Group × Day × Object	Dose × Group × Day × Object
Degrees of freedom	1,32	3,32	3,32	1,32	1,32	3,32	3,32	1,32	1,32	3,32	3,32	1,32	1,32	3,32	3,32
Total contact	0.22	14.06§	0.61	4.61†	8.73‡	16.90§	0.57	71.59§	0.24	6.48†	0.34	4.19†	0.52	7.58‡	0.20
Number of bouts	0.49	13.96§	0.34	2.77	4.88†	19.24§	1.85	42.72§	1.26	3.94†	0.04	0.18	0.04	3.92†	0.49
Number of behaviors	1.73	10.24§	0.84	2.98*	6.85†	7.11‡	0.66	61.50§	.014	1.69	0.56	0.69	0.10	0.68	0.40
Intensity index	0.23	5.02‡	2.55*	0.35	11.00‡	2.35*	0.02	77.32§	0.02	2.01	0.39	2.76	0.63	0.11	0.49

†$p < 0.05$; ‡$p < 0.01$; §$p < 0.001$; *$p < 0.10$.

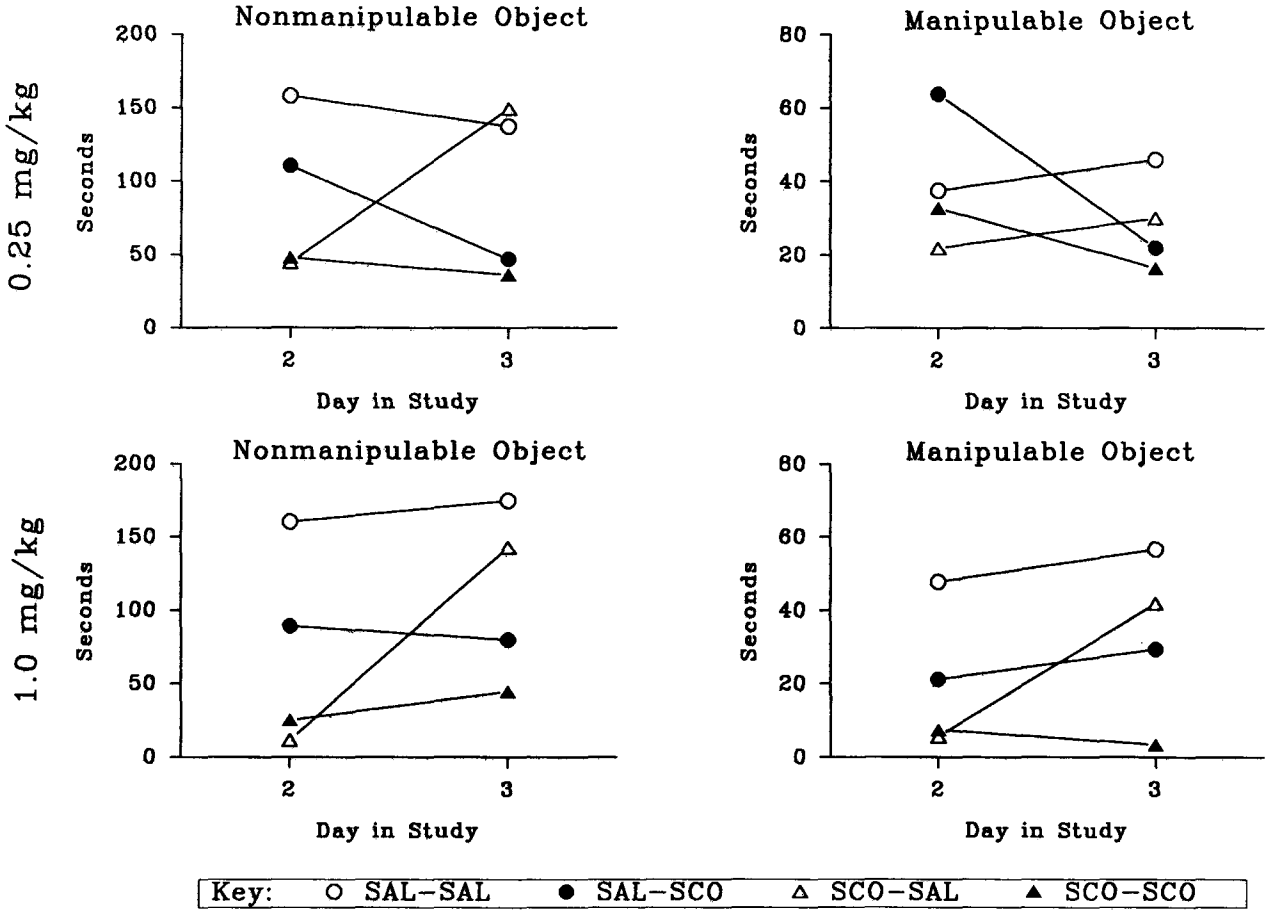

FIG. 4. Total time of object contact, with nonmanipulable object in the left panels and manipulable object in the right panels. Note the differences in scale between the graphs for the types of objects.

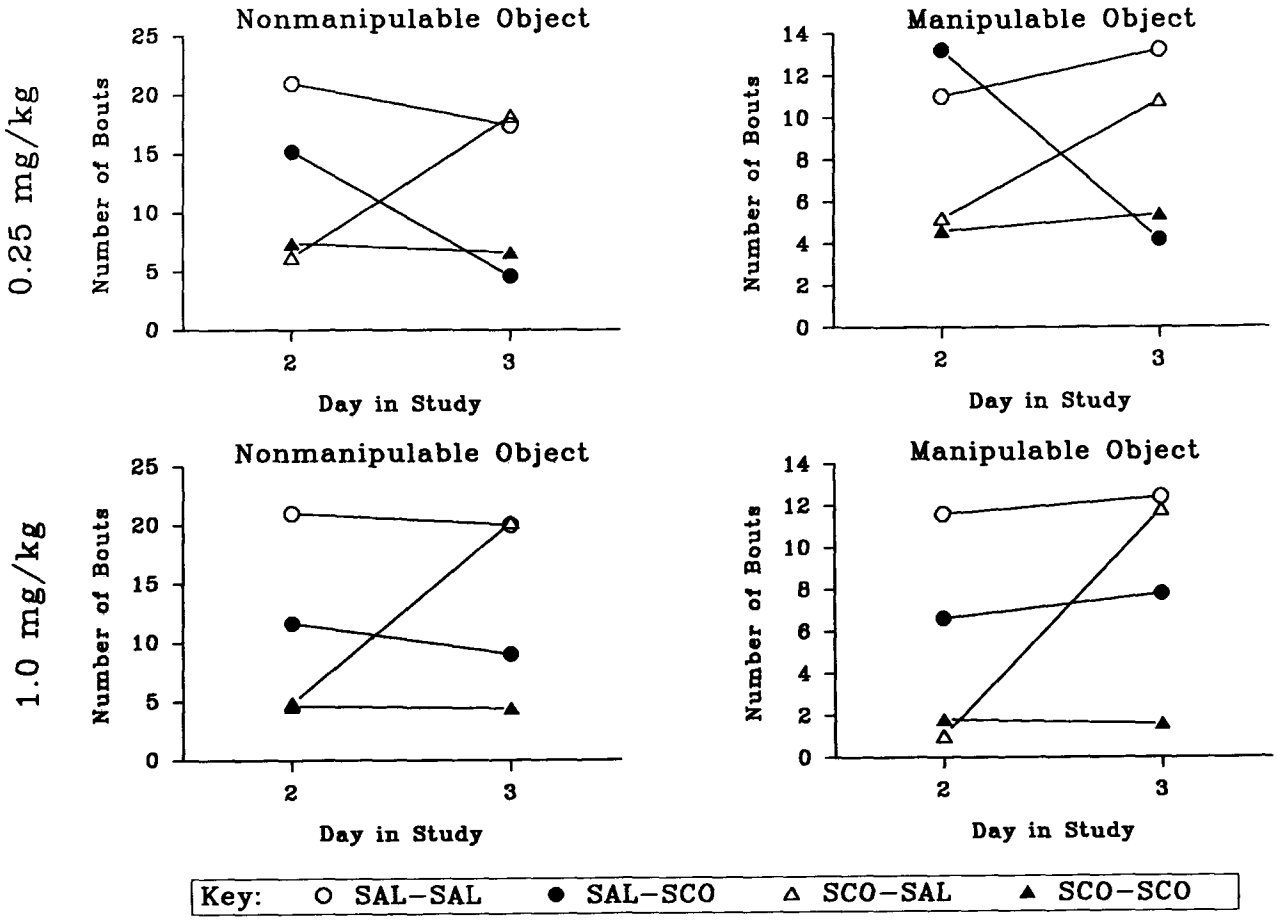

FIG. 5. Number of bouts of object interaction, with nonmanipulable object in the left panels and manipulable object in the right panels. Note the differences in scale between the graphs for the types of objects.

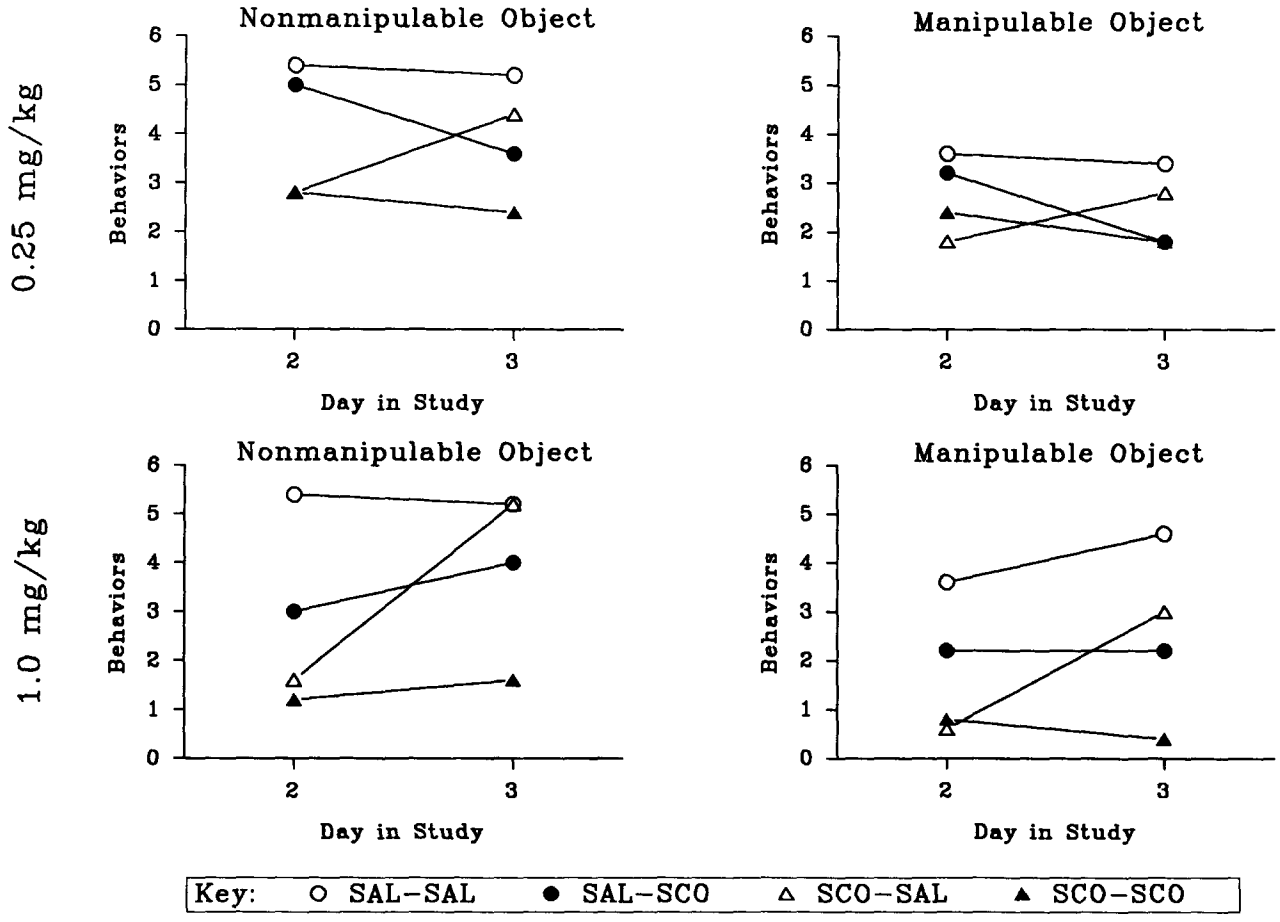

FIG. 6. Number of discriminable behaviors displayed during object interaction, with nonmanipulable object in the left panels and manipulable object in the right panels.

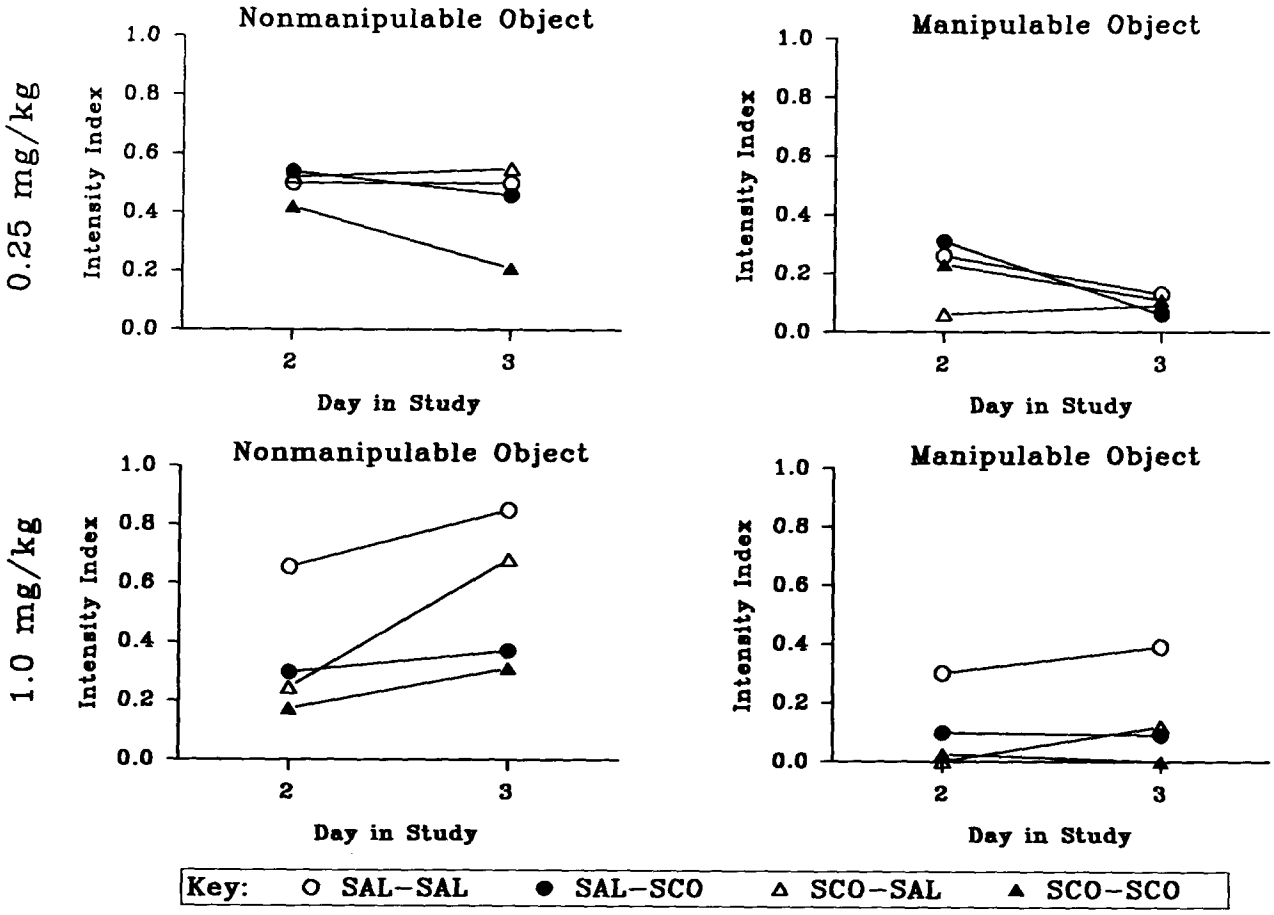

FIG. 7. Intensity index (proportion of bouts including at least one behavior classified as high involvement; see text for discussion), with nonmanipulable object in the left panels and manipulable object in the right panels.

objects. This effect is not apparently dose dependent, as both 0.25- and 1.0-mg/kg doses of scopolamine produced this effect. Visual inspection of Figs. 2–7 confirms the pattern shown by the statistical analyses: Whenever scopolamine was present, locomotor behavior and object contact were markedly reduced. As a result, the animal had less interaction with its environment, and therefore had scant raw materials for memory, that is, it had reduced its exposure to the sensory information from which memories are constructed.

These results point to an important methodological issue and underscore that the experimental context in which behavioral data are gathered must be given proper consideration. The behaviors displayed by rats in the forced-exploration situation of the open-field test, as it is typically used, include a significant component of escape or escape-related behaviors. Use of the forced-exploration testing context, therefore, imposes at least some stress on experimental subjects, and this must be considered for proper interpretation of the experimental results. When identically treated animals are placed in a similar situation, but under free-choice conditions, their behaviors are often markedly different. For example, Hughes et al. (10) found a biphasic effect of scopolamine on ambulation, with decreases at low doses and increases at high doses; in the free-exploration context used in this study, scopolamine at either dose suppressed locomotion.

This study replicates and extends the conclusions of Buhot et al. (2) that anticholinergics may impair information gathering instead of affecting memory directly. These data are also consistent with the assertion that scopolamine affects cognitive and attentional processes rather than memory (4,7,18). According to our data, an animal may in fact fail to form memories while under the influence of scopolamine, but this apparently amnestic effect is the result of the animal's failure to expose its receptors to the stimuli from which a memory might be formed. As such, scopolamine affects the animal's exploitation of the opportunity for encoding object information rather than causing any direct disruption of memory processes, such as consolidation of memory for object characteristics.

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