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The Effects of Nicotine on Learning and Memory: A Neuropsychological Assessment in Young and Senescent Fischer 344 Rats

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ATTAWAY. C. M.. D M. COMPTON AND M. D. TURNER. *The effects of nicotine in learning and memory: A new ropsychological assessment in young and senescent Fischer* 344 *rats.* PHYSIOL BEHAV **67**(3) 421431. 1999.—The effects of chronic nicotine on the behavioral performance of young (4 month) and old (24 month) Fischer-344 rats were assessed on four behavioral tasks: activity chamber. rotating rod, serial pattern learning. and Morris water maze paradigm. Old and young nicotine-trcatcd rats received an intraperitoneal injection of nicotine (0.20 mg/kg)15 min prior to all behavioral testing. and old and young saline-treated rats received saline injections 15 min prior to all behavioral testing. Nicotine improved motor coordination and increased the general activity levels of the old rats compared to old saline-treated rats. There were no significant differences in the behaviors of the young rats in these behavioral evaluations. In young rats. nicotine improved the acquisition of a serial pattern. suggesting an improvement in working memory or related processes. Nicotine was found to increase swim speed in a Morris water maze paradigm with a hidden platform; however. no beneficial effects of nicotine in reference memory were obtained for either age group. These results suggests that nicotine may not be as beneficial in attenuating age-related learning and memory deficits as once proposed. ©1999 Elsevier Science Inc.

Learning Memory Aging Acetylcholine Nicotine

PRIOR research has documented many age-associated declines in cognitive functioning among older organisms including humans [(5,14), see also, (53)] and nonhuman primates (6,21,25), as well as rodents (19,26,60). Although the exact nature of learning and memory deficits are still the source of some debate (49,50), both working memory and long-term memory appear to be adversely affected by advancing age (51,61). In fact, alteration in the frontal cortical areas and the hippocampus and associated medial temporal cortex have been implicated in the age-associated changes typically associated with working memory function. encoding. and retrieval (36.5 1).

In light of evidence in support of neurochemical abnormalities associated with aging in older adults such as reduced levels of acetylcholine (44) and a loss of nicotinic receptors (1 1), researchers have turned toward the use of drug treatments, particularly, cholinergic agonists. The cholinergic dysfunctions that have been found to correlate with memory loss are associated with reduced levels of acetylcholine (3). Atrophy of cholinergic neurons residing in the medial septal area and the vertical limb of the diagonal band and innervating the hippocampus and related medial temporal cortex (24) are detected in brains of senescent subjects (16.52). However. there is some evidence suggesting that deterioration of cholinergic neurons is not responsible for many of the observed memory deficits (18). Nonetheless, given the observation that substantial degeneration to this system is associated with Alzheimer's disease (12). it has been postulated that by increasing the level of brain acetylcholine, the memory impairments may be attenuated.

Presently, only two cholinergic agonist have been approved by the Federal Drug Administration for the specific treatment of memory impairments associated with Alzheimer disease: Donepezil (Eisai Inc.) and Tacrine (Parke-Davis)

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(Donepezil, Approved, 1907). Both drugs arc cholinesterase inhibitors: they exert their primary actions by increasing the level of acetylcholine within the brain by prolonging its life at the synapse. Although these drugs have been found to reduce memory impairments on some tasks (48). they do not completely eliminate memory deficits, and both drugs produce side effects. For example, in some patients Tacrine has been shown to increase alanine aminotransferase, which may cause liver damage. Donepezil has not been shown to produce liver dysfunction: however, it has been found to produce gastrointestinal-related side effects.

Recently, several cholinergic agonists have been found that increase the ability of rats to perform learning and memory paradigms [e.g.. (26,57)]. Although a compound with well-known CNS properties, one drug that has shown promising. albeit mixed results is nicotine. Nicotine has been shown to enhance cognitive functioning in humans on a variety of tasks [(17,47,59); for a review. see (22,58)], and investigations of nicotine's or nicotine agonist's ability to improve mnemonic functioning have proved beneficial (2,8,31,43,46,59). For example, in an investigation of the effects of nicotine, mecamylamine, a nicotinic antagonist, and scopolamine on working and reference memory in a 16-arm radial maze in adult female Sprague-Dawley rats, a low dose (0.2 mg) of nicotine improved working memory but not reference memory errors (29.30). Latency to respond was decreased by high (0.4 mg) and low (0.2 mg) nicotine treatments. Further, Newhouse and colleagues (40) found that mecamylamine impaired the performance of young subjects in a similar fashion to what occurs in the beginning stages of Alzheimer disease. For example, the mecamylamine-treated group had slower acquisition of a repeated acquisition task (evidenced in more errors), they had more false alarms in a recognition task, slower reaction times, and no impairment of retrieval.

Thus, considerable research supports nicotine as a possible treatment for age-associated memory disorders; however, not all investigators have found beneficial effects of nicotine in similar paradigms or paradigms designed to assess similar functions. Even in cases where an effect has been found, conflicting information about the nature of the memory-enhancing effects have been reported. For example, Arendash et al. (1) found nicotine had no effect on working memory, yet improved the reference memory of senescent Sprague-Dawley rats in a 17-arm radial maze. This is in direct contrast to investigations by Levin and colleagues (28), where nicotine was found to improve working memory but not reference memory in adult Sprague-Dawley rats in a 16-arm radial maze. Although Arendash et al.'s elderly rats had a high level of working memory performance, 85% correct, nicotine did not improve their performance to the level of the young rats, 95% correct.

The goal of the present experiment was to conduct a neuropsychological test battery in young and senescent Fischer 344 rats to determine the effects of nicotine upon their performance. Fischer 344 rats provide a good model for studying age-associated memory deficits in rodents (56). For example, they experience age-associated neuroanatomical abnormalities similar to what occurs in elderly humans (7). In the present experiment, Fischer 344 rats were tested in two experimental paradigms to assess mnemonic functions: a serial pattern learning task and a spatial reference memory task. Prior research has shown that nicotine can produce alterations in psychomotor performance and general activity levels in rats. The effects of nicotine on these measures were also assessed on a motor coordination task and a measure of general activity.

MATERIALS AND METHODS

Subjects

Thirty-two experimentally naive Fischer 344 rats, 4 (n = 16) and 24 (n

in-a nicotine-treated (NIC) group. Thus. the experiment
chided four groups hereafter designated as (a) a young-NIC group (Y-NIC: n = 8), (b) a young-SAL group (Y-SAL: n = 8). (c) a senescent-NIC group (0-NIC: n = 8). and a senescent-SAL group (O-SAL, n = 7). During the course of the investigation, one rat was determined to be too unhealthy to complete all phases of the study.

The SAL groups received an i.p. injection of saline (0.20 mg/ kg; 40 mg/mL conc.) 15 min prior to all behavioral testing, and the NIC-treated groups received an i.p. injection of NIC (0.20 mg/kg) dissolved in bacteriostatic water 15 min prior to all behavioral testing. Two replications were conducted in the following order: (a) replication l-MWM. rod test, activity chamber, runway task; and (b) replication 2-runway task, activity chamber, rod test. and MWM.

Apparati and Procedures

Activity chamber. The activity chamber was a cubic box (30 x 30 x 30 cm), of which the floor was made of wood paneling, three of the four walls were made of steel. and one wall and the ceiling were made of transparent Plexiglas. When the rat moved, a cork beneath the apparatus would move. connecting a circuit wired to an animal activity monitor (Lafayette Instruments, Inc., model 86010). The monitor counted the number of times the circuit was completed.

The activity level of each rat was measured in the activity chamber on two trial sessions lasting 5 min on 2 consecutive days. Each rat was placed into the activity chamber. and the door was closed. The counter was placed on zero, and the rat was allowed to freely explore the box for 5 min. Between each trial, the activity chamber was thoroughly cleaned to prevent odors from previous rats from interfering with the activity of rats on subsequent trials.

Rotating rod test. In our rotating rod test, a motor rotated a pole (10 cm in circumference and 162 cm long) five rotations per minute. The pole was wrapped with tape to help prevent the rat from slipping. The rod was elevated 100 cm above the floor, and approximately 15 cm of foam padding was placed beneath the apparatus to prevent injury in case a rat fell.

The electronic motor was turned on 1 min prior to the beginning of the trial to allow the rat to acclimate to the sound of the motor. A trial began when the rat was placed onto the rod and the experimenter saw that all four feet were securely placed on the rod. The experimenter counted the number of slips and falls for a 1-min period. A slip was defined when the rat fell off of the rod but was still able to hold on through one rotation. A fall was defined when the rat completely fell off of the rod. When a rat slipped or fell, it was repositioned on the rod.

Serial pattern learning. The base and the sides of the runway (179 cm long and 14 cm in height) were constructed of wood, and the top of the apparatus was constructed of Plexiglas. The box was divided into three compartments. The middle compartment (120 cm long) was painted a flat gray. The side compartments were designated as the start box (28 cm long) and the goal box (29 cm long), with one painted white and the other painted black, respectively. The three chambers were separated by two wooden guillotine doors, and the interior and exterior of each door was painted its respective color. The doors could be raised or lowered by a pulley system as needed. When the start box door was raised, a timer (Lafayette Instruments Inc., model 20225) was automatically activated. When the rat entered the goal box, a photobeam was interrupted, stopping the timer. All food rewards (Noyes; .045 g) were placed in a ceramic dish located in the goal box.

The serial pattern learning paradigm had been previously designed (9). Before actual testing began in the runway task, the rats were pretrained for 5 min a day for 2 consecutive days. During this time, the guillotine doors were opened, and the rat was allowed to freely explore the apparatus. The goal box contained seven food pellets that the rats were allowed to eat at their leisure.

At the beginning of each experimental testing trial. the rat was placed into the start box and the two guillotine doors were raised. For each trial, the latency to reach the goal box was measured across four reward conditions presented in the following order: 14, 0, 3, and 7 pellets. After the rat entered the goal box, the door was lowered, enclosing the rat in the compartment until all of the food was consumed. In the zero-pellet reward condition the rats were confined in the goal box for 30 s. On any trial, if the rat did not reach the goal box within 60 s, it was gently placed there and confined in the compartment for 30 s or until all food was consumed (if applicable).

Morris water maze. The Morris water maze (MWM) was constructed of a circular, galvanized steel tank (145 cm in diameter and 69 cm in height). The tank was painted white and filled with water (room temperature), and a white platform (30 cm in height, and 1.5 cm x 10 cm wide) was submerged in the water approximately 6 inches (15.24 cm) from the side of the tank. To obscure the platform, the water was made opaque with nontoxic, white Arista II tempura paint (ABC School Supply, Inc., Hazelton, PA). The platform was determined not to be visible by the experimenter. To designate where the start locations and platform would be located, the tank was labeled by direction (North, Northeast, East, Southeast, South. Southwest, West, and Northwest). All behavioral data was compiled and stored by a video tracking system (San Diego Instruments: San Diego, CA.). A Burle video camera (model TC655EAC) was mounted 8 feet above the center of the tank, and images were displayed on a Javelin Electronic monitor (model BWM9). The camera sensitivity to contrast could be controlled via a track level console (model SA-3), and the contrast images of the swim path and the tank were transformed and stored by a computer.

The procedures for the MWM task were adapted from Compton, Griffith et al. (10). At the beginning of each trial, the rat was placed into the maze with its nose facing the wall of the tank. At this time, the computer was activated. On each trial, latency to reach the platform, and the total distance swam were recorded by the computer. The trial was terminated when the rat reached the platform or a ceiling of 120 s had been reached. In the latter case, the rat was guided by hand through the water to the platform. Once the rat was on the platform, it was allowed to rest for an intertrial interval (ITI) of 30 s before the start of the second trial. This general description of the training procedure remained constant throughout testing; however, rats were required to perform two different phases of the Morris water maze task: (a) constant start, and (b) novel start.

Constant-start training. The first phase of training. constant start. consisted of four trials per day. The start location was constant across all trials and was located at the west side of the maze (see Fig. 1A). The escape platform was always located in the Northwest portion of the maze. To reach the criterion, the rat had to make three of four trials with a latency period of less than 10 s for 2 consecutive days. Once criterion was achieved, the rat began the second phase of the paradigm, novel-start testing.

Novel-start (probe) testing. During the novel start phase. the platform remained in one location, Northwest, but the start location varied in a pseudorandom fashion on the third and sixth trials. That is to say, the rat would always start from the west location on trials 1, 2, 4, and 5, but on trials 3 and 6. the rat would start from a new location, either North, Southeast, Northeast, Southwest. South, and East. respectively (see Fig. 1B). For example, on Day 1 of novel start training, the start location for trial 3 would be North, and the start location on trial 6 would be South. The rats performed 6 trials per day for 3 consecutive days.

RESULTS

General Activity and Motor Coordination

Effects of NIC on general activity levels and motor coordination in young rats. As expected, NIC increased the genera1 activity of the young rats (see Fig. 2). Analysis of the data with

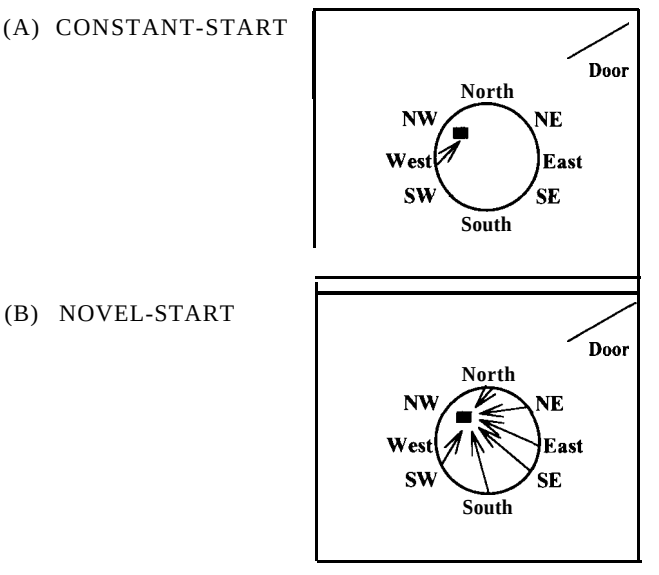

FIG. 1. Schematic of the Morris water maze testing environment depicting the start positions and platform location. (A) Constant-start testing phase. (B) Novel-start (probe) testing phase.

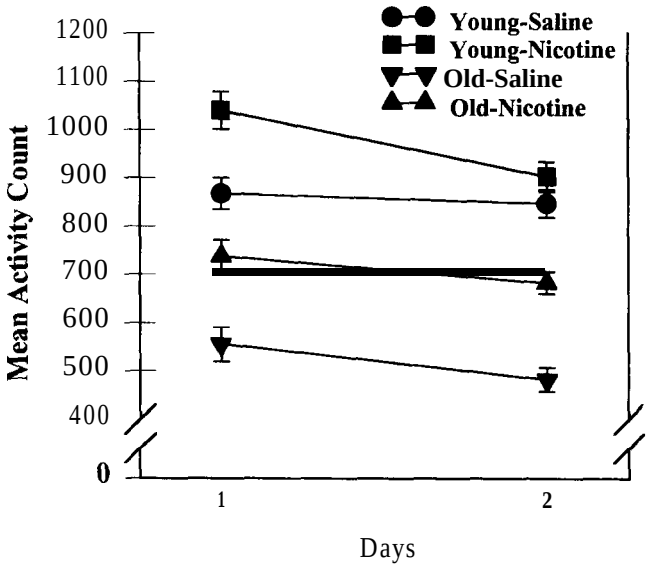

FIG. 2. Comparison of the mean activity counts across the 2-day assessment period for all of the treatment conditions.

a 2 (group) X 2 (days) mixed ANOVA revealed significant main effects of drug group, $F(1, 14) = 7.61$, $p < 0.05$, and assessments, $F(1, 14) = 8.61$, $p < 0.05$. However, these results must be considered within the context of a significant group X days interaction, $F(1, 14) = 4.62$, $p < 0.05$. During the first assessment period, the Y-NIC rats were significantly more active than the Y-SAL rats, but the groups were comparable by the second assessment period (see Fig. 2).

Kinesis was evaluated by recording the number of slips and falls on the elevated rod test. The data are presented in Fig. 3A. Separate one-way ANOVAs revealed that the two groups had a comparable number of slips; however, the NIC-treated rats had significantly more falls from the rod during testing, $F(1, 14) = 14.93$, $p < 0.005$.

Effects of NIC on general activity levels and motor coordination in senescent rats. Like the young animals, significant differences in activity were observed as a function of NIC, $F(1, 13) = 37.36$, $p < 0.001$ (see Fig. 2). The drug group x days interaction was nonsignificant. A main effect of Assessments was observed, $F(1, 13) = 5.08$, $p < 0.05$. Thus, both the NIC- and SAL-treated animals had differing levels of activity, and these levels decreased at comparable rates across the assessment period (see Fig. 3B).

As can be seen in Fig. 3B, analysis of the kinesis indicators revealed that the senescent SAL-treated rats fell significantly more often than the NIC-treated rats, $F(1, 13) = 6.78$, $p < 0.05$. Although the NIC-treated rats had somewhat more slips on the rotating rod, the differences were nonsignificant.

Serial Pattern Learning

The effects of NIC on serial pattern learning in young rats. To meet the assumptions of the analysis of variance (ANOVA), the data were transformed using the reciprocal (X = 1/X) transformation. For purposes of analysis, the serial pattern learning data were collapsed into one block of 6 days (block 1) and thereafter in blocks of 3 days. Application of a three-way (groups X elements X blocks) mixed ANOVA to these data (Fig. 4A): revealed a significant main effect for

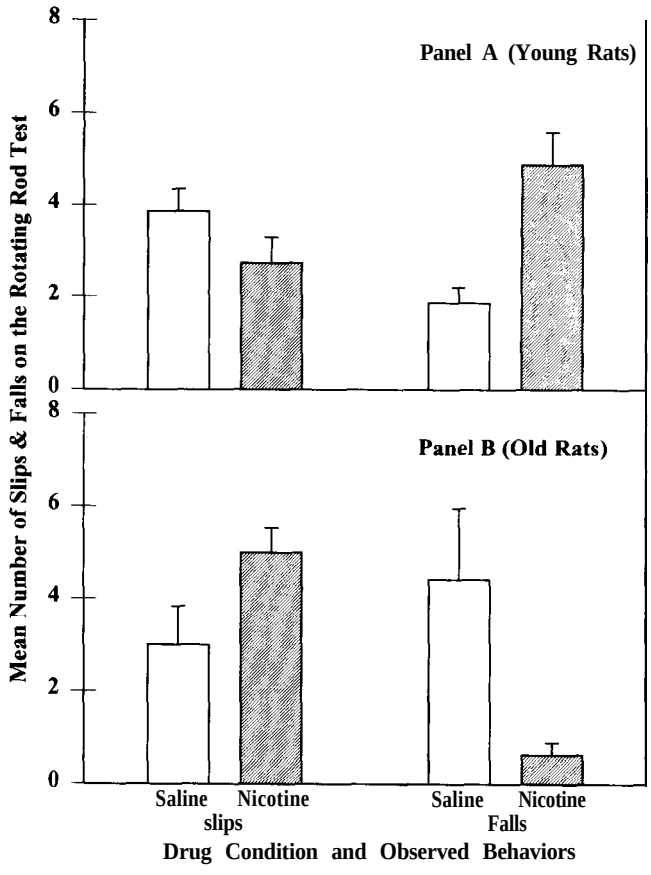

FIG. 3. Mean number of slips and falls on the rotating rod test. (A) Comparison of the NIC- and SAL-treated young rats. (B) Comparison of the NIC- and SAL-treated old rats.

blocks of training, $F(7, 98) = 24.05$. $p < 0.001$, but not the group X blocks interaction, $F(7, 98) = 0.45$. NS. This main effect was the result of a reduction in running times with continued training. The main effect of elements of the stimulus series was significant, $F(3, 42) = 163.76$. $p < 0.001$, as was the group X elements interaction, $F(3, 42) = 24.51$, $p < 0.001$. The main effect of elements reflects differences in running times as a function of the anticipated series element, with a significant group X elements interaction suggestive of group differences in element discriminability. However, the above must be considered in light of the significant group X blocks X elements interaction, $F(21, 294) = 1.90$, $p < 0.05$. The primary statistical result of this analysis can be communicated most effectively through further consideration of this three-way interaction. To achieve this goal, within group analyses of the tracking abilities of each group were examined using Tukey_A tests ($p < 0.05$). For the purposes of the present experiment, accurate responding or 'tracking" of the individual elements of the series was designated as running significantly slower on the zero- than on the three-pellet elements, significantly slower on the three- than on the seven-pellet elements. and significantly slower on the 7- than on the 14-pellet elements.

Tracking in the Y-NIC group developed rapidly (see Fig. 4A). Significant differences in running times between the 14- and 3-, 7- and O-pellet elements were observed in block 2.

Running times to the three rewarded elements of the series (14.7. and 3 pellets) all differed significantly from the O-pellet element by block 3 of training. With the exception of the thee- and seven-pellet elements, from block 3 to block 6 running times to each element of the series were significantly different. Finally, on blocks 6 and 7, all running times as a function of series element were significant.

Tracking in the Y-SAL group developed normally, albeit at a slower pace. First, as can be seen in Fig. 4A, running times to the three rewarded elements of the series were not significantly different from the zero-pellet element until block 6 of training. Earlier in training while some significant differences among the elements were observed, these differences suggested only the rudiments of tracking ability. Specifically, the 14-pellet element significantly differed from the other three elements (block 5). the zero- and three-pellet elements (block 3). The 14- and 7-pellet elements also differed in block 5. However, full tracking was not established until block 7 of training.

The** effects of **NIC on serial pattern learning in senescent rats. As can be seen in Fig. 4B, unlike the young rats, the senescent rats required significantly more training to master the series, and even at the end of training tracking was inferior to that of the young animals. A mixed ANOVA applied to the data revealed a main effect of blocks of training, $F(7, 77) = 19.64$, $p < 0.001$, and elements, $F(3, 33) = 3.30$, $p < 0.05$. Closer examination of this interaction with Tukey, tests revealed the following within-groups differences. Collapsing the data across blocks, the animals were able to discriminate between the rewarded and nonrewarded elements of the stimulus series. No effect of NIC on performance was observed (i.e., all $ps > 0.05$).

Morris Water Maze Assessment

Constant-start training: young rats. For purposes of analysis, the escape latencies were transformed (X = l/X). A mixed two-way ANOVA on the escape latencies for the first 12 trials of training revealed that both groups reduced latencies as a function of training. $F(11, 154) = 6.00$, $p < 0.001$ (see Fig. 5A). However, Y-SAL animals had significantly shorter escape latencies than the Y-NIC animals. The group X trials interaction was nonsignificant. As can be seen in Fig. 5B, an analysis of the distances traversed by each group revealed similar results. Consistent with the above, both groups improved (i.e., swim distances decreased) as a function of training, $F(11, 1.54) = 5.61$, $p < 0.001$. with Y-NIC rats swimming significantly further than the Y-SAL rats, $F(1, 14) = 62.06$, $p < 0.001$. Thus, the differences in escape latencies observed in the early stages of constant-start training are at least in part a function of the differences in swim path length. On the basis of a significant group x trials interaction. $F(11, 154) = 2.99$, $p < 0.001$, each of the 12 trials were examined individually using Tukey, tests. Group differences in distance traversed developed on trial 5 of training and continued through trial 12 (see Fig. 5B). As a result of the longer swim path and higher es-

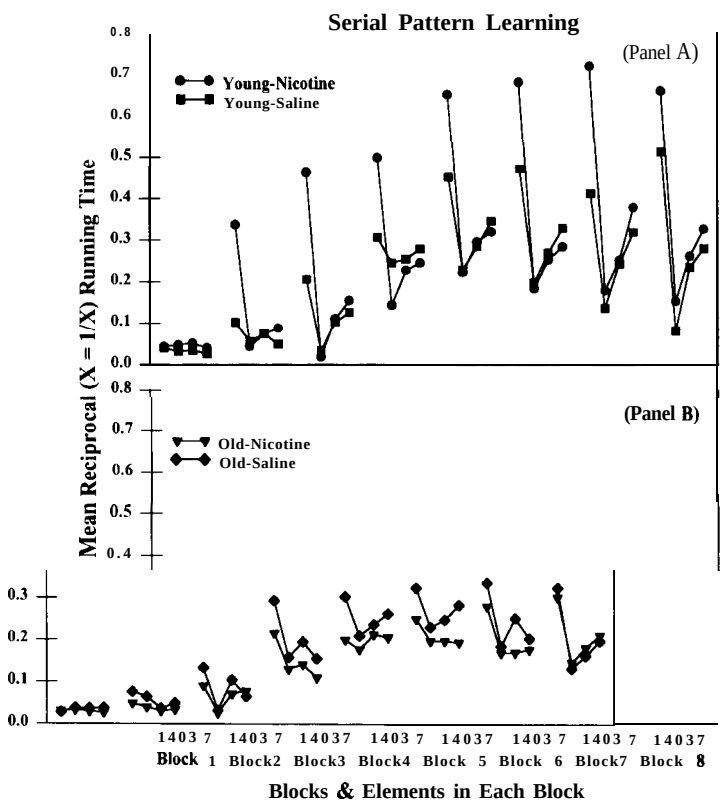

FIG. 4. Serial pattern learning. Mean reciprocal (X = X/l) running time across each trial (14-, 0-, 3-, and 7-elements) for eight blocks of training. (A) Comparison of the NIC- and SAL-treated young rats. (B) Comparison of the NIC- and SAL-treated old rats.

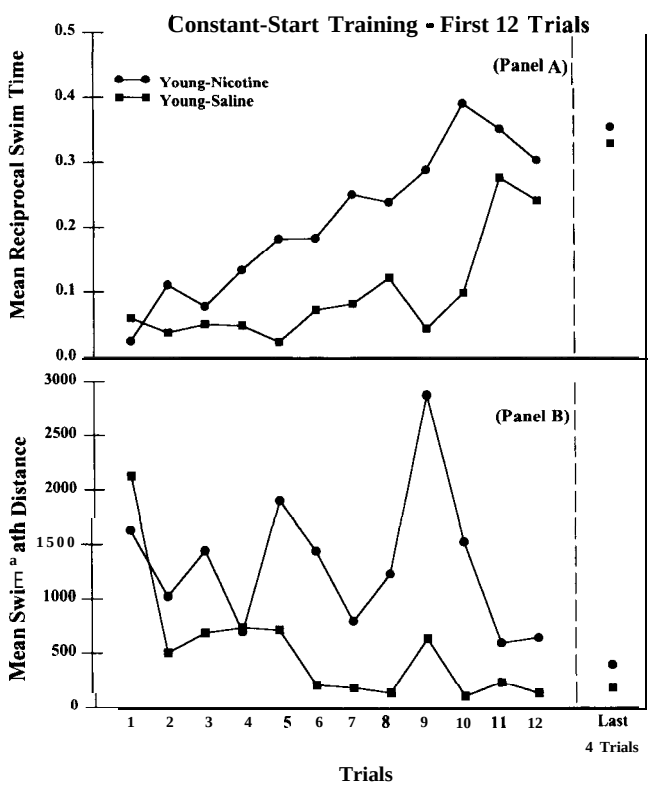

FIG. 5. Morris water maze constant-start training young rats. (A) Comparison of mean reciprocal (X = X/l) swim time for young NIC- and SAL-treated rats. (B) Comparison of mean swim path distance for young NIC- and SAL-treated rats.

cape latencies observed early in training, the Y-NIC rats required significantly more trials (mean = 29.00: SD = 11.46) to reach the performance criterion than the Y-SAL rats [mean = 14.00 trials, SD = 3.02; t(14) = 3.58, $p < 0.005$, two-tailed test]. However, even though earlier group differences were present, consideration of the last four trials of training collapsed showed that both groups had both comparable escape latencies, $t(14) = 0.42$, NS, two-tailed test, and swam comparable distances to the platform, $t(14) = 1.52$, NS, two-tailed test.

Constant-start training: senescent ruts. Examination of the trials through criterion suggested a beneficial effect of NIC on performance. Specifically, 0-NIC rats required approximately one-half the number of trials (mean = 15.50. SD = 2.56) as the O-SAL rats [mean = 30.86. SD= 10.25; $t(13) = 4.11$, $p < 0.001$, two-tailed test]. Once again, the escape latency data were transformed using the reciprocal transformation. The escape latency and swim path distance data are presented in Fig. 6A and B, respectively. Application of an ANOVA to the data from the first 12 trials of training indicated that both groups improved as a function of training, $F(11, 143) = 6.59$. $p < 0.001$, and, overall, both groups learned the location of the platform at similar rates, $F(1, 13) = 1.06$, NS. A group x trials interaction was detected, $F(11, 154) = 2.30$, $p < 0.05$, but Tukey_A tests revealed that this was largely a function of escape latencies on trials 10 and 12.

Although escape latencies were similar across the first 12 trials. the 0-NIC rats swam significantly further than the O-SAL rats, $F(1, 13) = 8.83$. $p < 0.05$. Even so. both groups improved with training, $F(11, 154) = 2.70$. $p < 0.005$. As noted previously, the O-SAL rats required more trials to achieve the performance criterion. However, examination of the data and the joint consideration of both the escape latency and swim path distance data. suggest that differences in swim speed rather than learning per se account for the observed difference between the two groups. At any rate, by the last four trials of constant-start training, both groups had both comparable escape latencies, t(13) = 1.98, NS, two-tailed test. and swam comparable distances to the platform, $t(14) = 1.96$, NS. two-tailed test.

Novel-start (probe) testing: young rats. To allow for the direct comparison of escape latencies and swim path distances across all possible start loci with different minimum swim path distances, all escape latency and swim path distance data were normalized. Normalization involved computation of a ratio of the minimum distance from the start location to the platform in centimeters for each novel start locus to the minimum distance from the start location to the platform on constant-start trials in centimeters.

Analysis of the escape latency data using a mixed three-way ANOVA (groups X trials X probe assessment) revealed the following (see Fig. 7A). The escape latencies for both groups indicated were comparable across the novel-start assessment period, $F(1, 14) = 0.92$, NS. and the group X probe assessments interaction was nonsignificant. The escape latencies differed across the assessment period, trials $F(2, 28) =$

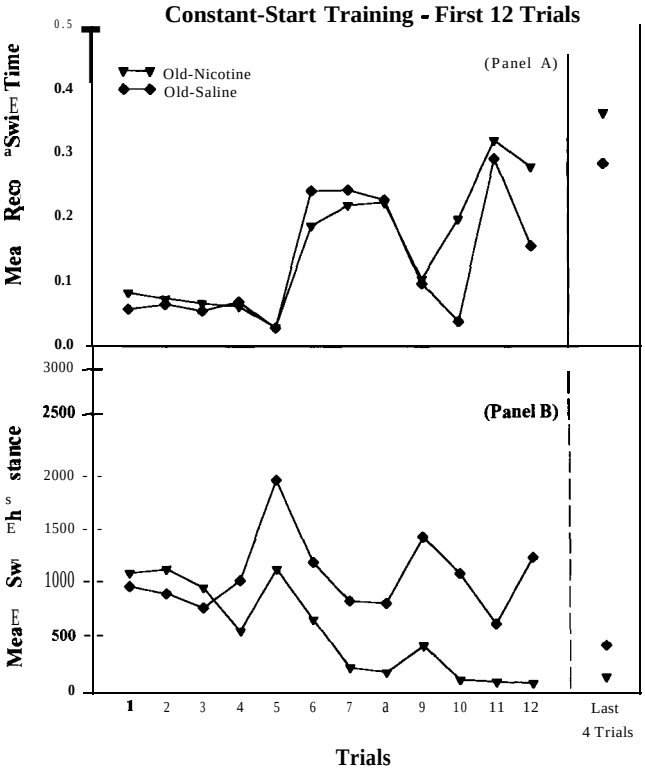

FIG. 6. Morris water maze constant-start training old rats. (A) Comparison of mean reciprocal (X = X/l) swim time for old NIC- and SAL-treated rats. (B) Comparison of mean swim path distance for old NIC- and SAL-treated rats.

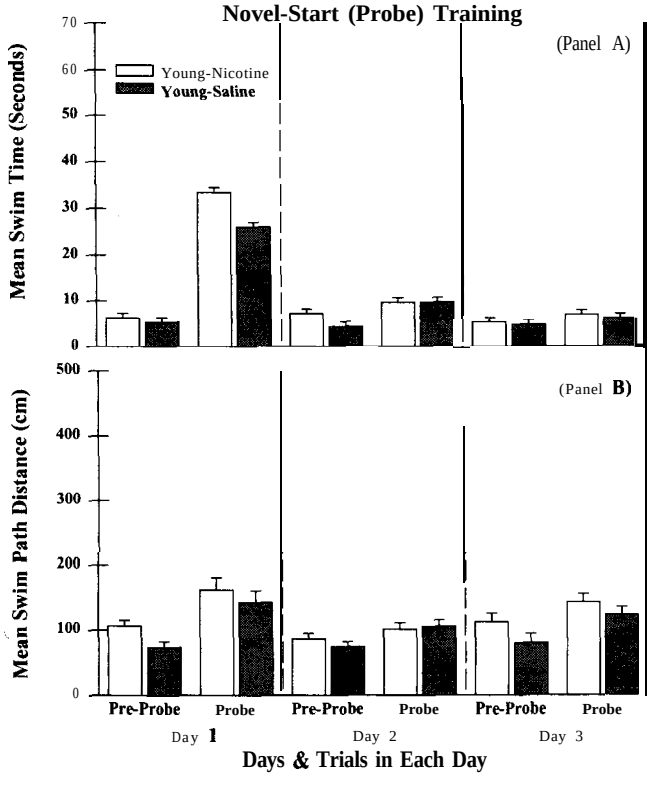

FIG. 7. Morris water maze novel-start (probe) testing for young rats. (A) Comparison of mean swim time on preprobe and probe trials. (B) Comparison of mean swim path distance on preprobe and probe trials.

14.62, $p < 0.001$, as did the difference between the trial preceding a probe and the probe trial, $F(1, 14) = 34.31$, $p < 0.001$. When probe assessments are collapsed across groups. a large disruption in performance is only seen on the first assessment. Here, the difference between the preprobe and probe trials is 23.82 s. $t(15) = 4.45$, $p < 0.001$, two-tailed test. Conversely, even though the differences between the preprobe and probe trials on the second and third assessments were significant, these differences were nonetheless much smaller (means = 3.81 and 1.54 s).

A three-way ANOVA of the swim path distance data (see Fig. 7B) indicated that once again the groups differed across the assessment period (i.e., across trials), $F(2, 28) = 6.58$, $p < 0.005$, and that the distances traversed were longer on novel-start trials than on the preceding probe trial, $F(1, 14) = 23.84$, $p < 0.001$. Consistent with the above and the behavior under constant-start conditions, Y-NIC rats swam significantly further distances than the Y-SAL rats, $F(1, 14) = 5.33$, $p < 0.05$. Neither the group X trials nor the group X probe interactions were significant.

Novel-start (probe) testing: senescent rats. As can be seen in 8A, both groups of senescent rats differed across trials, $F(2, 26) = 14.73$, $p < 0.001$, and placement in a novel-start location had an adverse impact on the escape latencies, $F(1, 13) = 30.81$, $p < 0.001$, especially on the first and second assessments. The main effect of drug group was nonsignificant, as were all of the interactions.

Although the escape latencies of both groups were similar, the 0-NIC animals swam significantly farther than the O-SAL rats, $F(1, 13) = 18.69$, $p < 0.001$. The main effect of trials was nonsignificant, $F(2, 26) = 1.58$, NS, but the distance traversed differed as a function of start location (i.e., constant- versus novel-start, $F(1, 13) = 11.66$, $p < 0.005$). However, the present results must be considered in light of a significant drug group X trials X probe assessment interaction, $F(2.26) = 5.07$, $p < 0.05$. As can be seen in Fig. 8B, within-group comparisons with Tukey, tests revealed that the novel-start location had an adverse effect on the performance of the 0-NIC rats on the first and third assessments (i.e., Days 1 and 3). O-SAL rats were impaired on all three assessments.

Novel-start testing: comparison of senescent versus young rats. Review of the data suggested that although the young rats were initially impaired by the introduction of a novel-start placement (probe assessment 1), they recovered quickly while the senescent rats did not. To explore this issue in further detail. the data for the drug groups were collapsed and the performances of the young and senescent rats compared. Not surprisingly, the escape latencies of the young rats were superior to that of the senescent rats, $F(1, 29) = 8.08$, $p < 0.001$, lending further support for the observation that although initially impaired by the novel-start location. the young rats quickly adapted. In fact, collapsed across assessments, the difference between preprobe and probe performance in the young rats was about 9 s. As seen earlier, the majority of this difference is attributed to the first probe assessment. No comparable level of adaptation to changing task demands was observed in the senescent animals. In fact, collapsed across assessments, the difference between preprobe and probe performance exceeded 22 s!

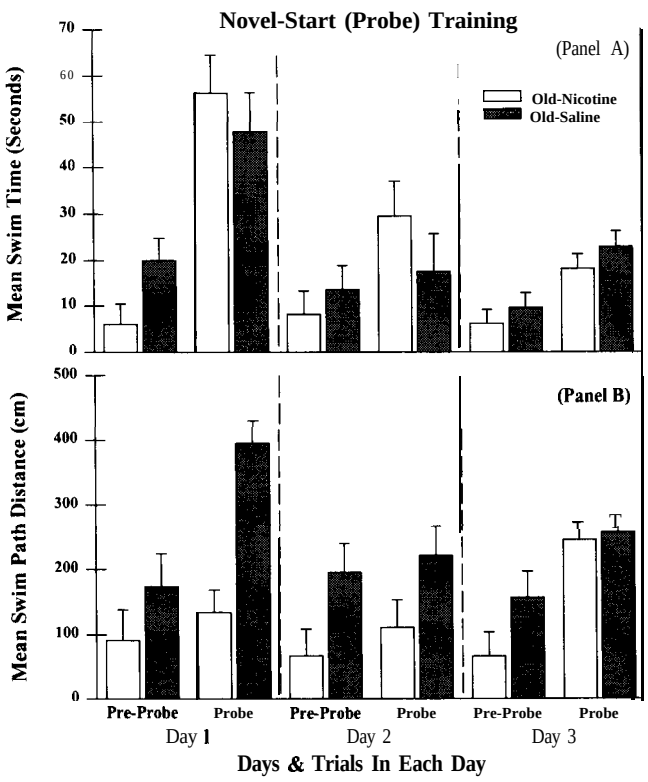

FIG. 8. Morris water maze novel-start (probe) testing for old rats. (A) Comparison of mean swim time on preprobe and probe trials. (B) Comparison of mean swim path distance on preprobe and probe trials.

DISCUSSION

The goal of the present experiment was to investigate the effects of NIC on general activity levels, coordination, and learning and memory performance in young and senescent Fischer 344 rats. Our results suggest that the behavioral effects of NIC depend on at least two variables: age, and the task employed. NIC affected the motor coordination of the young and senescent rats differently. For example, nicotine increased the number of falls in young rats but decreased the number of falls in senescent rats. Furthermore, senescent rats are inferior to young rats in finding a submerged platform in a Morris water maze task despite the treatment condition. These results are consistent with prior research demonstrating impairments in the ability of senescent rats on paradigms designed to test learning and memory functioning (25). NIC only improved the performance of the young rats in the serial pattern learning paradigm.

NIC increased the general activity level of the young rats, especially during the first assessment period. This is consistent with findings that NIC increased arousal levels (4.5) and alertness (23). NIC did not affect the general activity level of the senescent rats, and both SAL- and NIC-treated senescent rats reduced their level of activity across the assessment period. Further, the present results differ from those of Meguro et al. (35) who have reported that NIC did not increase the general activity levels of senescent rats. Prior research suggests that NIC can alter motor coordination without directly affecting learning and memory systems. For example, a common measure of mnemonic functioning in rats is their latency to respond to target stimuli. NIC could decrease latency by altering psychomotor functioning without affecting learning and memory systems.

NIC was found to facilitate the acquisition of a serial pattern learning task in young rats compared to age-matched controls. Although both SAL- and NIC-treated animals learned the task. NIC pretreatment increased the rate in which the rats learned. This is consistent with prior research demonstrating NIC produces faster learning in rats (1,46).

By the end of training, both NIC- and SAL-treated senescent rats had not developed full tracking behavior, although they could distinguish between the rewarded (14, 7, and 3 pellets) and nonrewarded (0 pellets) elements of the series. These results suggests that the rats were able to form a memory of the ordered sequence of events. They learned that the first trial was rewarded. followed by a rewarded trial (trial 2). followed by a nonrewarded trial (trial 3), followed by a rewarded trial (trial 4). In other words, the rats were able to remember two distinct categories: rewarded and nonrewarded. However. they were unable to distinguish and/or remember within category differences in the rewarded condition. Although NIC has been found to facilitate learning in senescent rats (1,35), there is evidence suggesting that the facilitation effects are test specific (41).

In light of this evidence, the ability of NIC to improve the performance of young rats in the serial pattern learning paradigm may not be the direct result of improved learning per se, but the result of improved attention that would affect the rate in which the rats were able to distinguish between the four reward conditions. Prior research has documented improved attention in subjects administered NIC (4,47,58). The senescent NIC-treated rats may have also experienced improved attention: however, their working memory deficit could have precluded behavioral demonstration of the improvements in attention. The serial pattern learning paradigm employed in the present study was not sensitive enough to differentiate between attention and working memory processes.

It has been postulated if nicotinic agonist can reverse neurochemical abnormalities in cholinergic transmission associated with age-associated memory declines, then nicotine should reverse cognitive impairments induced by a cholinergic antagonist that mimic age associated memory impairments. For example, mecamylamine and scopolamine have been found to produce memory impairments in humans (13.40). In an investigation of the effects of nicotine, mecamylamine, and scopolamine on working and reference memory in a 16-arm radial maze in adult female Sprague-Dawley rats, a low dose (0.2 mg) of nicotine improved working memory but not reference memory errors (29). Latency to respond was decreased by high (0.4 mg) and low (0.2 mg) nicotine treatments, and the latency to respond was increased by high (I .0 mg) and low (0.05 mg) scopolamine treatments and low mecamylamine treatments (1.25 mg). Scopolamine also increased the number of working memory errors but not the number of reference memory errors. Although nicotine did not attenuate the scopolamine-induced deficit, it did attenuate the mecamylamine (1.25 mg)-induced deficits observed in working memory errors. This supports the assumption that nicotinic and muscarinic receptors are involved in different aspects of memory processes. and nicotine can reduce drug induced memory impairments.

Nonetheless, considerable research supports both muscarinic and nicotinic receptor functions in learning and memory. and it may be tentatively concluded that each plays distinct roles in these processes. For example, Granon et al. (20) postulated that nicotinic and muscarinic blockade may affect different aspects of memory. They used the nicotinic antagonist neuronal bungarotoxin and dihydro-β-erythroidine, and the muscarinic antagonist. scopolamine, to determine the effects of nicotinic and muscarinic cholinergic receptor function in the prelimbic frontal cortex in a matching-to-sample task (MTS) and a nonmatching-to-sample task (NMTS) in Long–Evans rats. They found that neuronal bungarotoxin produced an adverse effect on working memory and impaired the rodents' ability to perform a MTS but not a NMTS task. Dihydro-B-erythroidine did not effect working memory in either paradigm. A high dose of scopolamine hydrochloride impeded the performance of rats in both the MTS and NMTS tasks. Reference memory was not affected by any of the drug treatments. It has been postulated the MTS task requires more effort because proper responding interferes with the rat's natural tendency to alternate. On the basis of their work and others, the authors suggest. nicotinic and muscarinic receptors are involved in two distinct processes of memory. The nicotinic receptor is important for tasks where effortful processing is required to make a response. while the muscarinic receptor is important in overall working memory.

The results of the Morris water maze suggests that NIC does not facilitate spatial reference memory in Fischer 344 rats. By the end of the constant-start phase of training in the Morris water maze. both the young NIC- and SAL-treated rats had learned the location of the platform (i.e., met criterion). However, the NIC-treated rats required more trials to reach criterion. In part, their longer latencies were a result of longer swim paths. The results for the constant-start phase of training for the senescent rats were similar to that of the young; however, the senescent NIC-treated rats required fewer trials to meet criterion than the senescent SAL-treated rats. Like the young NIC-treated rats. the senescent NIC-treated rats swam a further distance than age-matched controls: however. the senescent NIC rats swam significantly faster than controls resulting in shorter latencies, despite a further distance swam. Although not directly assessed in the present experiment, it is interesting to note that prior research has found that senescent Fischer 344 rats had impaired swimming ability (32).

In the novel phase of training. the young NIC- and SAL-treated rats improved across the assessment period, albeit differentially. Although the rats had longer latencies on the probe trials, they did decrease across probe trials, suggesting that they had learned the placement of the platform. Overall, the senescent rats did not differ as a function of drug group, and experienced longer latencies on the probe trials. However, where as the senescent SAL rats were impaired on all three probe assessments, the senescent NIC rats were only impaired on the first and third assessments. Once again, the senescent NIC rats swam further than the senescent SAL rats.

NIC pretreatment has been found to decrease processing speed and reaction time (4). We found that NIC pretreatment reduced the senescent NIC-treated group's latency to reach the platform in the MWM; however, these improvements were at the expense of a greater number of errors in correct path choice, as assessed by distance traversed. This last measure is indicative of a reference memory deficit that was evident in both SAL- and NIC-treated senescent rats. Although the young rats did not demonstrate a memory deficit, it is of interest to note NIC did not improve the young rats' performance. In fact. during the acquisition phase of testing. NIC pretreatment significantly increased escape latencies compared to SAL pretreatment.

Recent investigations of the role of acetylcholine in learning and memory have found support for a cholinergic involvement in attentional processes [for a review. see (14)]. The

frontal cortex has been strongly implicated in attentional processes (42). and medial prefrontal lesioned rats have been found to require more trials to develop effective strategies in a place learning task in a Morris water maze paradigm (IO). The lesioned rats had both longer swim distances and greater latencies to reach the platform compared to controls. As previously noted. research suggested that cholinergic neurons with in the nucleus basalis of Meynert that project to the frontal cortex were strongly implicated in spatial learning (39). However. Torres et al. (55) found that lesions limited to cholinergic neurons with in the nucleus basalis of Meynert did not impair spatial learning. This suggests that the reference memory deficits experienced by the senescent NIC- and SAL-treated rats in our study may not be the direct result of a dysfunction limited to the cholinergic system. Furthermore. more selective lesions of the nucleus basalis of Meynert have been found to impair visual attention as assessed in a serial reaction time task (37), and the administration of NIC or physostigmine eliminated the impairment (38).

In their review article, Everitt and Robbins (15) presented information that suggest that the septum and its major projection. the hippocampus, are not as strongly implicated in spatial reference memory as once thought, but rather, spatial working memory. Chronic NIC has been shown to improve performance in a working memory version of the eight-arm radial maze. Selective lesions of cholinergic neurons in the septum did not impair the performance of rats in a Morris water maze task. a reference memory task (33). Furthermore, septal lesions produce impairments in the ability of rats to perform a delayed nonmatching-to-position task. suggesting a deficit in short-term memory (34).

Although both the Morris water maze and serial pattern learning paradigm can be used to assess learning and memory functions in the rat, they are both testing different constructs. Nicotine has been shown to increase arousal levels (45), and research has shown that arousal levels and task difficulty are correlated for mnemonic tasks (60). Increased arousal narrows attentional capacity and is beneficial in less complex tasks. Consequently, NIC may enhance the focus of attention. This would be beneficial to rats in the serial pattern learning paradigm because the animal has one pathway, and it must form an internal representation of the different rewards and remember their sequence. Learning the pathway to the food reward is fairly simple. There is only one choice without backtracking. An increased focus of attention may not improve the performance of rats in our version of the Morris water maze. Here, the animal is given an almost infinite number of pathways (i.e.. the animal can turn 360 degrees at any point in the maze) and a large number of extramaze cues that the animal must process and learn in relation to the location of the platform.

In conclusion, NIC was found to differentially affect young and senescent Fischer 344 rats. NIC increased general activity levels, motor coordination. and swim speed in senescent rats compared to aged-matched controls. These differences may be the result of NIC's modulatory role on dopamine release, Young rats treated with NIC had faster acquisition of a serial pattern learning task compared to young SAL-, senescent SAL-. and senescent NIC-treated rats. The performance of young SAL rats was also superior to the senescent SAL- and senescent NIC-treated rats. It was concluded that the beneficial effects of NIC were the result of increased attentional capacity or enhanced working memory processes. NIC did not improve spatial reference memory in a Morris water maze task. Taken together, the present study suggests that NIC may produce only limited improvements in learning and memory in Fischer 344 rats.

Thus, the cognitive enhancing properties of NIC or its affects on psychomotor performance do not appear to be a universal phenomenon generalizable across experimental paradigms. Methodological, strain, or sex differences might account for the inconsistencies in NIC research (27). As previously stated, NIC is a potentially harmful drug that can produce many negative side effects (54). In light of this evidence, it is imperative that we fully understand the specific cognitive-enhancing effects of NIC before using it as a treatment for memory disorders, especially with the elderly. Future research should be designed to ascertain which aspects of cognition NIC specifically effects, memory or attention. and whether or not the improvements in cognitive functioning outweigh the potential risks associated with NIC treatments.

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