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# PSYCHOMOTOR AND SPATIAL MEMORY PERFORMANCE IN AGING MALE FISCHER 344 RATS

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**Abstract—**Psychomotor and spatial memory performance were examined in male Fischer 344 rats that were 6, 12, 15, 18, and 22 months of age, to assess these parameters as a function of age and to determine at what age these behaviors begin to deteriorate. Complex motor behaviors, as measured by rod walk, wire suspension, plank walk, inclined screen, and accelerating rotarod performance, declined steadily with age, with most measures being adversely affected as early as 12 to 15 months of age. Spatial learning and memory performance, as measured by the working memory version of the Morris water maze (MWM), showed decrements at 18 and 22 months of age (higher latencies on the working memory trial), with some change noticeable as early as 12–15 months of age (no improvement on the second trial following a 10-min retention interval); these differences were not due to swim speed. Therefore, complex motor and spatial memory behaviors show noticeable declines early in the lifespan of the male Fisher 344 rat. This cross-sectional age analysis study using the latest behavioral techniques determines the minimal age at which psychomotor and spatial learning and memory behaviors deteriorate; this information is important when planning for longitudinal studies where interventions are tested for their efficacy in preventing or restoring age-related behavioral deficits. *Published by Elsevier Science Inc.*

**Key Words: Morris water maze, learning, cognitive behavior, motor behavior, age-related changes, cross-sectional study**

## INTRODUCTION

THE FISCHER 344 (F344) rat has been used frequently in aging studies (Weindruch and Masoro, 1991), due to its availability from the aging colony at the National Institute of Aging (Spangler *et al*., 1994) and the extensive age-related database available for this strain. However, a recent cross-sectional age analysis study using the latest, sensitive, behavioral techniques has not been conducted in this species to determine the minimal age at which psychomotor and spatial

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learning and memory behaviors begin to deteriorate. A current study is essential, because it has been found that Fischer 344 rats have grown faster, attained higher body weights, and developed more tumors over the years, which has led to a decreasing survival trend over time (Rao *et al*., 1990). This decreasing trend in survival is probably due to an increase in body weight, increase in severity of age-related nephropathy due to a protein-rich diet, and changes in criteria for moribund sacrifice of aged animals (Rao *et al*., 1990). Additionally, we believed that information on behavioral changes with age was necessary and important for the planning of longitudinal studies in our and other's laboratories to test interventions using long-term dietary antioxidants (e.g., beta-carotene, ascorbate, α-tocopherol) or phytochemicals (e.g., flavonoids) for their efficacy in preventing or restoring age-related deficits in these behaviors.

Aged rats show decrements in performance on tasks requiring coordinated control of motor and reflexive responses, such as suspension time on a horizontal wire or inclined wire mesh screen, and the length of time an animal can traverse/balance on a wooden rod or plank (Dean *et al*., 1981; Joseph *et al*., 1983; Joseph and Lippa, 1986; Ingram *et al*., 1994), and on cognitive tasks that require the use of spatial learning and memory, i.e., the ability to acquire a cognitive representation of location in space and the ability to effectively navigate the environment (for reviews, see, Barnes, 1988; Gallagher and Pelleymounter, 1988b; Brandeis *et al*., 1989; Ingram *et al*., 1994). Age-related deficits in motor performance are thought to be the result of alterations in the striatal dopamine (DA) system; the striatum shows marked neurodegenerative changes with age (Joseph, 1992). Memory alterations appear to occur primarily in secondary memory systems, possibly due to the decline in the functioning of the central cholinergic system, and are reflected in the impaired storage of newly acquired information (Bartus *et al*., 1982; Joseph, 1992).

The objective of the present study was to assess complex motor behavior and spatial learning and memory of Fischer 344 rats as a function of age. Therefore, a cross-sectional age analysis was performed using rats that were 6, 12, 15, 18, and 22 months of age, to determine at what age these behaviors begin to deteriorate.

## MATERIALS AND METHODS

### *Animals*

The subjects consisted of five age groups of male Fisher 344 rats (Harlan–Sprague–Dawley, Indianapolis, IN): 6 month ($n = 10$), 12, 15, 18, and 22 month ($n = 6$ for each group), weighing between 290 and 460 g. The rats were individually housed in stainless steel mesh suspended cages, provided food and water *ad libitum*, and maintained on a 12-hour light/dark cycle. All animals were observed daily for clinical signs of disease.

### *Psychomotor testing*

A battery of tests of psychomotor behavior were performed over a period of five consecutive days. Performance on all these tasks has been shown to deteriorate with age (Dean *et al*., 1981; Ingram, 1983; Joseph *et al*., 1983; Joseph and Lippa, 1986; Joseph, 1992; Ingram *et al*., 1993, 1994). These tests were administered in the following order, with no less than a one-hour break between tasks.

*Rod walking.* The ability of rats to balance on a stationary, horizontal rod measures psychomotor coordination, and the integrity of the vestibular system. Animals were placed in the center of a rod (100 cm long, 26 mm in diameter, positioned 23 cm above the table surface),

parallel to it, and their latency to fall off the rod onto a cushion below was recorded (max score = 60 s). If the rats fell immediately after being placed on the rod, they were given another opportunity.

*Wire suspension/wire hanging.* The prehensile reflex refers to an animal's ability to grasp a horizontal wire (12 gauge) with its forepaws and to remain suspended; it is a measure of muscle strength. Rats were raised to an elevated taut horizontal wire (55 cm above the table top) and the forepaws of each rat were placed on the wire. Each was given one trial, with the total hanging time in seconds recorded (max score = 60 s).

*Plank walk.* Balance and coordination were measured by exposing the rats to one trial on each of three horizontal planks (wide = 38 mm; medium = 25 mm; narrow = 13 mm), each 100 cm long, placed 34 cm above the table top. The order of plank widths that the animal was given was randomized and counterbalanced across groups. Latency to fall (max score = 60 sec), distance traveled (in cm), and number of turns on the planks were recorded and averaged for each trial.

*Inclined screen.* This test measured muscle tone, strength, and balance. Each rat was placed in one of six separate compartments of a wire mesh that was tilted 60° to the horizontal plane of the floor. Latency to fall from the screen (max score = 600 s) was recorded.

*Accelerating rotarod.* Fine motor coordination, balance, and resistance to fatigue were quantitated by measuring the amount of time that a rat could remain standing on a rotating, accelerating rod (Ugo Basile, Italy). The rod is a drum, 7 cm in diameter, that is machined to provide traction. Each rat was placed on the rod at 2 rpms until it maintained its grip and orientation without assistance. The rod then accelerated steadily for five minutes (by 2 rpms every 30 s) until it reached 20 rpms. Latency to fall (maximum = 300 s) was recorded.

### *Cognitive testing*

The working memory version of the Morris Water Maze (MWM), with a 10-min intertrial interval, was performed to test spatial learning and memory (Morris, 1984; Brandeis *et al*., 1989). The MWM is a paradigm that requires the rat to use spatial memory to find a hidden platform just below the surface of a circular pool of water, and to remember its location from the previous trial (Morris, 1981, 1984). Therefore, the rat must use distal cues to effectively locate it. Accurate navigation is rewarded by escape from the pool. Performance on the maze, including the working memory paradigm, has been shown to deteriorate with aging (Gage *et al*., 1984; Rapp *et al*., 1987; Gallagher and Pelleymounter, 1988b; Brandeis *et al*., 1989; Van der Staay and de Jonge, 1993; Ingram *et al*., 1994), due to a specific deficit in the ability of aged rats to utilize spatial information (Rapp *et al*., 1987).

*Procedures.* The maze consisted of a circular black fiberglass pool (134 cm in diameter × 50 cm in height), filled to a depth of 30 cm with water maintained at 23°C. The pool was divided into four equal-size quadrants. The circular escape platform (10 cm in diameter) was colored black and, therefore, hidden from sight. The platform was submerged 2 cm below the surface of the water in the center of one of the quadrants; its location was changed to a different quadrant for each session of testing. The maze was placed in a room with the lights dimmed, and there were numerous extramaze cues on the walls.

MWM testing was performed daily for four consecutive days, with a morning and an afternoon session, two trials each session, with a 10-min intertrial interval between the two

trials. At the beginning of each trial, the rat was gently immersed in the water at one of four randomized start locations (located 90° apart on the perimeter of the pool). Each rat was allowed 120 s to escape onto the platform; if the rat failed to escape within this time, it was guided to the platform. Once the rat reached the platform, it remained there for 15 s (trial 1; reference memory or acquisition trial). At the end of each trial, the rat was towel dried, returned to its home cage (where a heat lamp was available), and 10 min elapsed before the next trial (trial 2; working memory or retrieval trial), which used the same platform location and start position as trial 1. Performance on each test was videotaped and analyzed with image tracking software (HVS Image, Hampton, UK). This software provided dependent measures such as latency to find the platform (s) and swimming speed (cm/s).

### *Statistical analyses*

For each behavioral measure, one-way between-subjects analysis of variance (ANOVA) models comparing five age groups were performed using Systat (Evanston, IL) to test for statistical significance at the $p \leqslant 0.05$ level. For the MWM, trials were included in the model as a within-subjects, repeated-measures variable. Post hoc comparisons, to determine differences among age groups, were performed using Fischer's LSD post hoc analysis.

## RESULTS

Performance on most motor tests decreased with increasing age (Fig. 1). In the rod-walking test, ANOVA showed a significant effect of age, $F(4, 29) = 2.64$, $p \leqslant 0.05$. Post hoc testing showed that latency to fall was shorter for the 12-month ($p < 0.05$), 18-month ($p < 0.05$), and 22-month ($p < 0.05$) groups than for the 6-month group; latency for the 15-month group was not different than the 6-month group. Performance in the wire suspension test decreased linearly with age, $F(4, 29) = 5.25$, $p < 0.01$; latency to fall was shorter for the 15-month ($p < 0.05$), 18-month ($p < 0.01$), and 22-month ($p < 0.001$) groups than for the 6-month group, but the difference was not significant at 12 months. Furthermore, wire hang latency declined significantly from 12 months to 22 months ($p < 0.05$).

In the plank-walk test, ANOVA showed a significant effect of age, $F(4, 29) = 6.66$, $p < 0.01$. Post hoc testing showed that latency to fall was shorter for the 12-month ($p < 0.05$), 15-month ($p < 0.05$), 18-month ($p < 0.001$), and 22-month ($p < 0.001$) groups than for the 6-month group. There were no significant differences among the age groups on plank walk distance and number of turns.

There was a significant age effect associated with the inclined screen test, $F(4, 29) = 5.75$, $p < 0.01$. Post hoc testing showed that latency to fall was shorter for the 15-month ($p < 0.001$), 18-month ($p < 0.05$), and 22-month ($p < 0.05$) groups than for the 6-month group. There was also a significant difference between the 12-month ($p < 0.01$) and the 18-month ($p < 0.05$) groups compared to the 15-month group; latency for the 22-month group was not different from the 15-month group.

In the Accelerating Rotarod, ANOVA showed a significant age effect, $F(4, 29) = 10.16$, $p < 0.001$. Post hoc testing showed that latency to fall was significantly shorter for the 12-month ($p < 0.01$), 15-month ($p < 0.01$), 18-month ($p < 0.001$), and 22-month ($p < 0.001$) groups than for the 6-month group.

These age-related differences in motor testing could not explained by the differences in body weight seen with age, $F(4, 25) = 27.40$, $p < 0.001$. Post hoc testing showed that the 6-month group weighed significantly ($p < 0.05$) less than all other groups, the 12-month old group

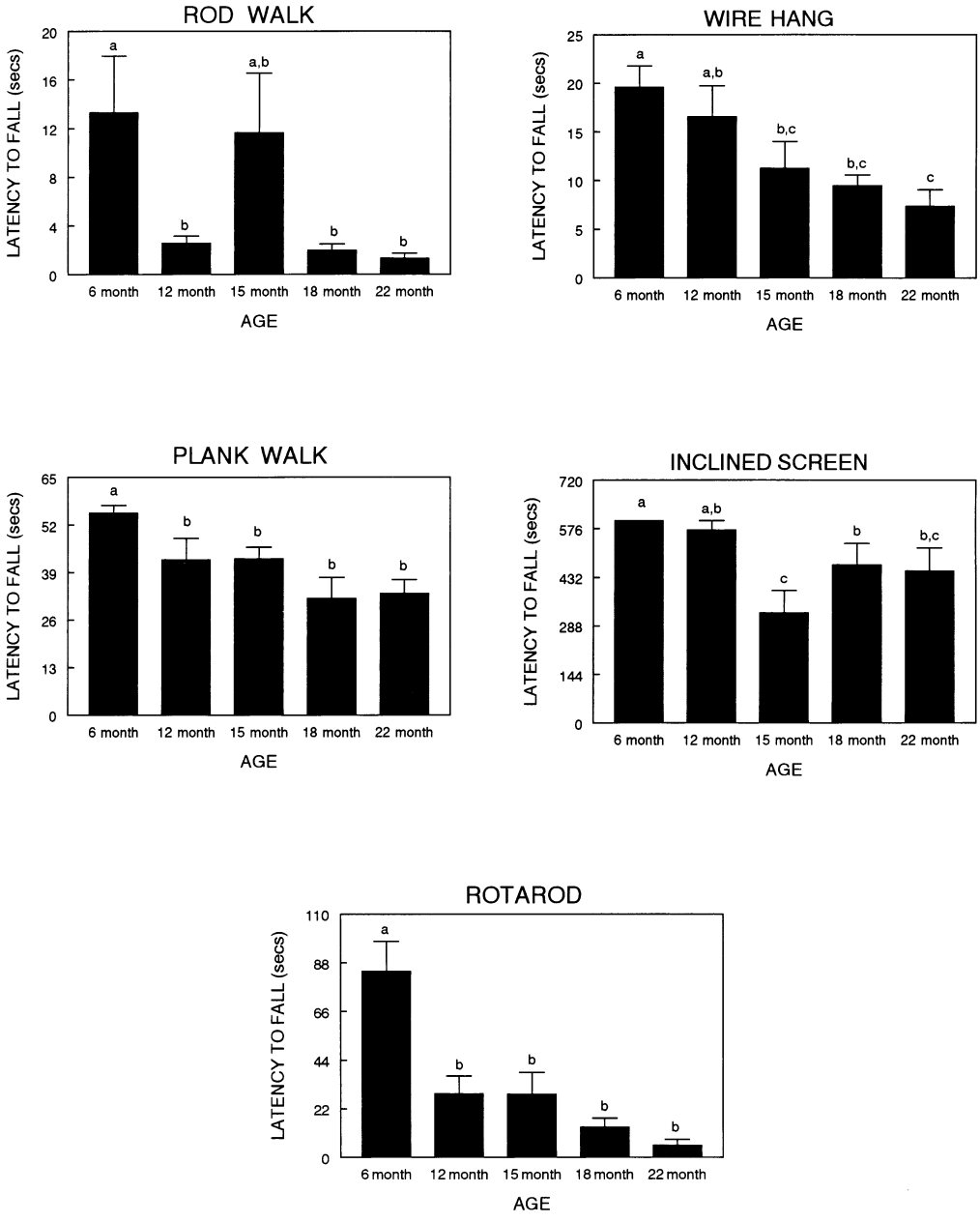


FIG. 1. Latency (mean + SEM: s) to fall in the rod walk, wire suspension, plank walk, inclined screen, and rotarod tests for five different age groups (6, 12, 15, 18, and 22 months). Means with different letters are significantly different from each other ($p < 0.05$, Fischer's LSD).

weighed less than all older groups, and there were no differences in weight between the 15, 18, and 22 month old groups. However, the age-related decline in motor performance was still intact on most tasks after statistically adjusting (using analysis of covariance) for body weight.

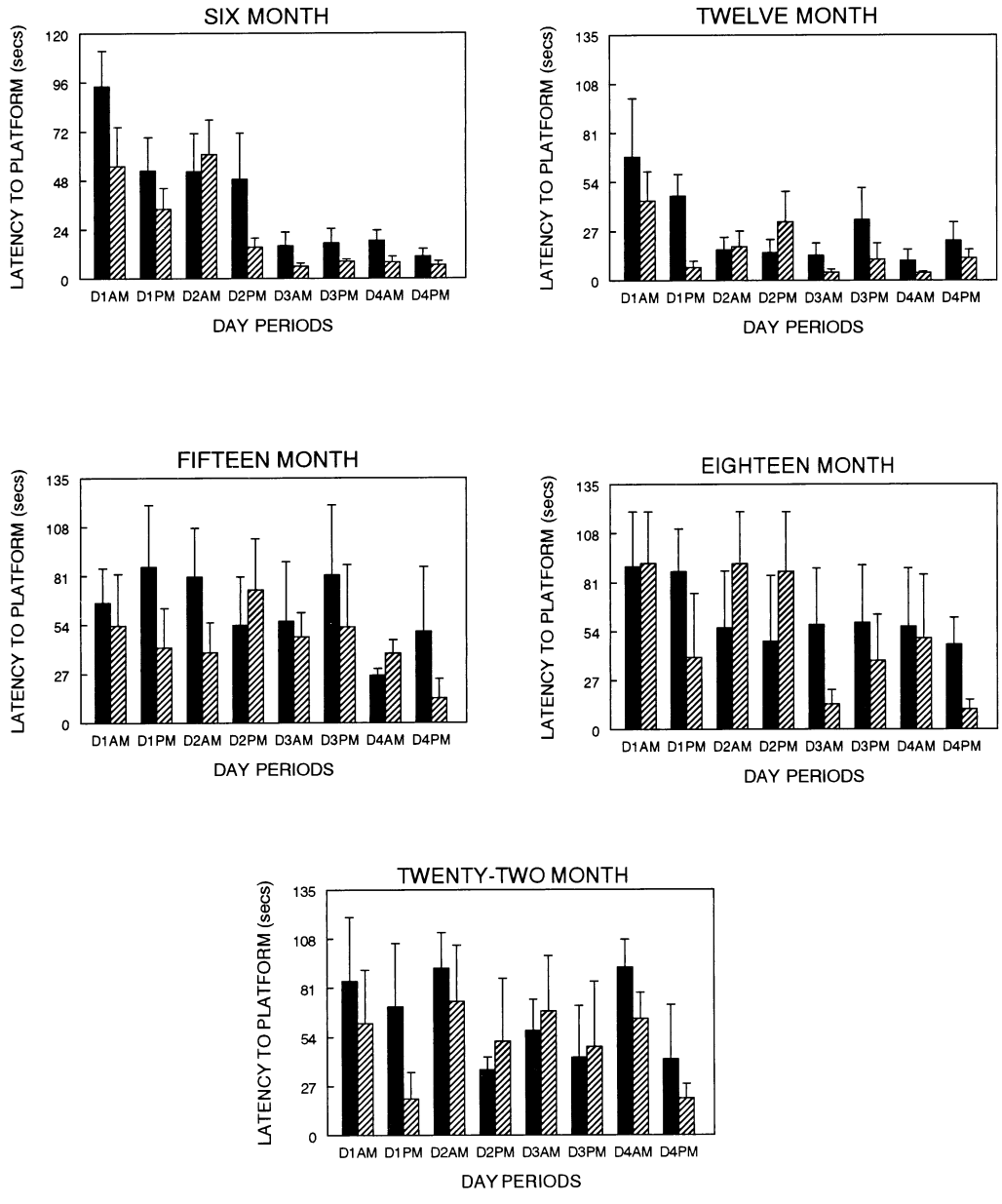


FIG. 2. Latency (mean + SEM: s) to find the hidden platform in the Morris Water Maze for 6-, 12-, 15-, 18-, and 22-month-old male Fischer rats for each day (1–4) and session (morning = a.m. or afternoon = p.m.). Trial 1 (■) and trial 2 (▨) were separated by a 10-min intertrial interval.

In the MWM (Fig. 2), the latency to find the platform was calculated separately for trial 1 and trial 2. For trial 2, ANOVA showed a significant effect of age, $F(4, 13) = 3.02$, $p \leqslant .05$, and trials, $F(7, 91) = 4.76$, $p < 0.001$, but the age × trial interaction was not significant. Post hoc analyses showed that trial 2 latency was significantly longer for the 18-month ($p < 0.05$) and

the 22-month groups ($p < 0.05$) compared to the 6- and 12-month groups; latency for the 12- and 15-month groups was not significantly different from the 6-month group. However, there was a trend for the latency of the 15-month group to be higher ($p = 0.07$) compared to the 12-month group. These differences in latency were not due to swim speed, as there was no significant age effect on this measure for trial 2 ($p = 0.18$). Additionally, the age effect or age $\times$ trial interaction for latency to reach the platform on trial 1 did not reach significance ($p = 0.16$); however, there was a significant trial effect, $F(7, 91) = 3.34$, $p < 0.01$, with latency to find the platform improving over time.

To see if the different age groups improved their performance from trial 1 to trial 2 (as the working memory hypothesis predicts) (Van der Staay and de Jonge, 1993) separate *t*-tests between the two trial latencies were performed for each age group. Only the 6-month group had a significant difference between trial 1 and trial 2, $t(5) = 2.50$, $p \leqslant 0.05$; (trial 2 latencies significantly less than trial 1), showing that these young rats demonstrated one-trial learning, even with the 10-min retention interval. This one-trial learning was not found in the other age groups (12, 15, 18, and 22 months), because significant improvement was not seen between the two trials.

## DISCUSSION

For the five motor tests examined in this study, performance decrements were seen on 100% of them for both the 18- and 22-month-old rats, 80% for the 15-month-old group, and 60% for the 12-month-old group. Therefore, these tests are sensitive enough to measure age-related deficits in motor behavior, which are evident for some parameters as early as middle-age (12 to 15 months) in male, F344 rats. For the MWM, decrements in spatial working memory are visible at 18 and 22 months of age, with some change noticeable as early as 12–15 months of age (i.e., no difference in latency between trials 1 and 2); therefore, the MWM paradigm used in this study is sensitive enough to test the nature of cognitive dysfunction in senescence.

The present results obtained for the motor tests are comparable to those from other, similar studies. One study (Spangler *et al*., 1994) found age-related changes in motor performance on a battery of behavioral tests (inclined screen, rod suspension, rotorod) for three different age levels (7, 13, and 24 months) of F344 rats; however, this study did not determine which age groups were different from each other. Another study (Wallace *et al*., 1980b) examined motor behaviors in different age groups of F344 rats and found that responses requiring a greater degree of motor coordination, balance, or strength (i.e., wire hang, rotorod, plank walk, descending a wire mesh pole) declined systematically and quite precipitously with aging, and that performance on these behaviors dropped sharply beginning in midlife (between 8 and 14 months of age). However, this study did not examine an intermediate age group (such as 12 months in the present study), so it is not possible to determine at what age these behaviors significantly declined. In male CD-COBS rats, tests of motor behavior (plank walking and rotarod) were significantly impaired in a 12-month-old group compared to a 4-month-old group (Pitsikas *et al*., 1990), but this study did not test the F344 strain of rats, and F344 rats seem to be affected by normal aging at a younger age than other strains (Arbel *et al*., 1994).

A few investigations (Rapp *et al*., 1987; Aitken and Meaney, 1989; Brandeis *et al*., 1990; Pitsikas *et al*., 1990) have tested middle-aged rats in the MWM, and only one group has done a cross-sectional aging study using the F344 rat to assess how early these changes start to reliably occur (Frick *et al*., 1995). Some of these studies have reported impairments in spatial memory performance beginning at a relatively early age for different species of rat (12-month

Long–Evans rats, Aitken and Meaney, 1989; 12 month CD-COBS rats, Pitsikas *et al*., 1990; 18–19-month Wister rats, Brandeis *et al*., 1990). In one study that did use the F344 rat (Wallace *et al*., 1980a), spatial memory, as measured by performance in an eight-arm radial maze, declined gradually with age, with some changes evident as early as 14 months of age. Another study (Walovitch *et al*., 1987) found performance impairments (i.e., increased shocks, errors, and run time) in a complex 14-unit T-maze in middle-aged (12–16 month) F344 rats compared with young animals (three months). The one cross-sectional age study (Frick *et al*., 1995) using the Fischer 344 rat assessed spatial reference and working memory in the MWM in 4-, 11-, 17-, and 24-month old animals. Aging significantly affected performance in all measures of reference memory, as both 17- and 24-month-old rats showed deficits in the MWM. Rats in the 11-month-old group had a mild spatial reference memory deficit, as indicated by a decrease in the number of platform crossings on a probe trial. However, spatial working memory deficits, as assessed by latencies to the platform on trial 2 of a repeated acquisition task, were present only in 24-month-old rats. This finding is in contrast to the findings of the current study, perhaps because the intertrial interval used by Frick and colleagues was only 3–4 min, not 10 mm. The longer the delay between trial 1 and 2, the more difficult the task, and increasing task demand increases the likelihood of observing spatial working memory deficits at younger ages (Frick *et al*., 1995), as was seen in the current study.

It is important to note that, in this study as well as others (Markowska *et al*., 1989), there are individual differences in behavioral performance (as seen by the variability within groups), with some animals being significantly impaired at earlier ages and others not greatly impaired with age. The variability observed in the pattern of age-related decline in behavior can be due to either genetic or environmental factors or to their interaction (Ingram, 1985). This result that not all rats are impaired similarly at a given age could also be due to the fact that aging probably does not affect all systems uniformly and with the same pattern of timing across all individuals (Ingram *et al*., 1994). Behavioral aging is highly individualized in animal models, as well as human studies, with individual differences seen between tests measuring similar performance parameters (e.g., motor tests) and between separate types of tests (i.e., psychomotor and spatial memory tests) (Markowska *et al*., 1989). Therefore, many studies using aged rats divide them into two groups, "impaired" and "nonimpaired," as only "impaired" rats (i.e., rats with a learning decrement) are likely to improve from treatments being evaluated for their beneficial responses to age-related behavioral deficits (Arbel *et al*., 1994; Gallagher and Pelleymounter, 1988a; Quirion *et al*., 1995). However, what is clear from this and other studies is that age affects overall performance, so that differences due to age are evident (Ingram *et al*., 1981).

Therefore, psychomotor and spatial working memory behaviors show declines early in the lifespan of the male F344 rat, between 6 and 12 months of age, as changes in both these parameters were noticeable at 12 months of age in the present study (an age when age-related declines in visual ability may be just starting to appear, DiLoreto *et al*., 1995a, b). This information is important when planning for longitudinal studies where interventions such as antioxidants or phytochemicals are tested for their efficacy in preventing age-related behavioral deficits in F344 rats. If prevention of these adverse changes is the desired goal, then these interventions should be initiated early in the life of the rat, i.e., six months of age.

## REFERENCES

AITKEN, D.H. and MEANEY, M.J. Temporally graded, age-related impairments in spatial memory in the rat. *Neurobiol. Aging* **10,** 273–276, 1989.

ARBEL, I., KADAR, T., SILBERMANN, M, and MEANEY, M.J. The effects of long-term corticosterone administration on hippocampal morphology and cognitive performance of middle-aged rats. *Brain Res.* **657,** 227–235, 1994.

BARNES, C.A. Aging and the physiology of spatial memory. *Neurobiol. Aging* **9,** 563–568, 1988.

BARTUS, R.T., DEAN, R.L., BEER, B., and LIPPA, A.S. The cholinergic hypothesis of geriatric memory dysfunction. *Science* **217,** 408–417, 1982.

BRANDEIS, R., BRANDYS, Y., and YEHUDA, S. The use of the Morris water maze in the study of memory and learning. *Int. J. Neurosci.* **48,** 29–69, 1989.

BRANDEIS, R., DACHIR, S., SAPIR, M., LEVY, A., and FISHER, A. Reversal of age-related cognitive impairments by an M1 cholinergic agonist, AF102B. *Pharmacol. Biochem. Behav.* **36,** 89–95, 1990.

DEAN, R.L., SCOZZAFAVA, J., GOAS, J.A., REGAN, B., BEER, B., and BARTUS, R.T. Age-related differences in behavior across the life span of the C57BL/6J mouse. *Exp. Aging Res.* **7,** 427–451, 1981.

DILORETO, D., ISON, J.R., BOWEN, G.P., COX C., and DEL CERRO, M. A functional analysis of the age-related degeneration in the Fischer 344 rat. *Curr. Eye Res.* **14,** 303–310, 1995a.

DILORETO, D.A., MARTZEN, M.R., DEL CERRO, C., COLEMAN, P.D., and DEL CERRO, M. Müller cell changes precede photoreceptor cell degeneration in the age-related retinal degeneration of the Fischer 344 rat. *Brain Res.* **698,** 1–14, 1995b.

FRICK, K.M., BAXTER, M.G., MARKOWSKA, A.L., OLTON, D.S., and PRICE, D.L. Age-related spatial reference and working memory deficits assessed in the water maze. *Neurobiol. Aging* **16,** 149–160, 1995.

GAGE, F.H., DUNNETT, S.B., and BJORKLUND, A. Spatial learning and motor deficits in aged rats. *Neurobiol. Aging* **5,** 43–48, 1984.

GALLAGHER, M. and PELLEYMOUNTER, M.A. An age-related spatial learning deficit: Choline uptake distinguishes "impaired" and "unimpaired" rats. *Neurobiol. Aging* **9,** 363–369, 1988a.

GALLAGHER, M. and PELLEYMOUNTER, M.A. Spatial learning deficits in old rats: A model for memory decline in the aged. *Neurobiol. Aging* **9,** 549–556, 1988b.

INGRAM, D.K. Analysis of age-related impairments in learning and memory in rodent models. *Ann. NY Acad. Sci.* **444,** 312–331, 1985.

INGRAM, D.K. Toward the behavioral assessment of biological aging in the laboratory mouse: Concepts, terminology, and objectives. *Exp. Aging Res.* **9,** 225–238, 1983.

INGRAM, D.K., JUCKER, M., and SPANGLER, E.L. Behavioral manifestations of aging. In: *Pathobiology of the Aging Rat*, vol. 2, Mohr, U., Cungworth, D.L., and Capen, C.C. (Editors), pp. 149–170, ILSI Press, Washington, DC, 1994.

INGRAM, D.K., LONDON, E.D., REYNOLDS, M.A., WALLER, S.B., and GOODRICK, C.L. Differential effects of age on motor performance in two mouse strains. *Neurobiol. Aging* **2,** 221–227, 1981.

INGRAM, D.K., WIENER, H.L., CHACHICH, M.E., LONG, J.M., HENGEMIHLE, J., and GUPTA, M. Chronic treatment of aged mice with L-deprenyl produces marked striatal MAO-B inhibition but no beneficial effects on survival, motor performance, or nigral lipofuscin accumulation. *Neurobiol. Aging* **14,** 431–440, 1993.

JOSEPH, J.A. The putative role of free radicals in the loss of neuronal functioning in senescence. *Integr. Physiol. Behav. Sci.* **27,** 216–227, 1992.

JOSEPH, J.A., BARTUS, R.T., CLODY, D., MORGAN, D., FINCH, C., BEER, B., and SESACK, S. Psychomotor performance in the senescent rodent: Reduction of deficits via striatal dopamine receptor up-regulation. *Neurobiol. Aging* **4,** 313–319, 1983.

JOSEPH, J.A. and LIPPA, A.S. Reduction of motor behavioral deficits in senescent animals via chronic prolactin administration—II. Non-stereotypic behaviors. *Neurobiol. Aging* **7,** 37–40, 1986.

MARKOWSKA, A.L., STONE, W.S., INGRAM, D.K., REYNOLDS, J., GOLD, P.E., CONTI, L.H., PONTECORVO, M.J., WENK, G.L., and OLTON, D.S. Individual differences in aging: Behavioral and neurobiological correlates. *Neurobiol. Aging* **10,** 31–43, 1989.

MORRIS, R. Developments of a water-maze procedure for studying spatial learning in the rat. *J. Neurosci. Meth.* **11,** 47–60, 1984.

MORRIS, R.G.M. Spatial localization does not require the presence of local cues. *Learning Motiv.* **12,** 239–261, 1981.

PITSIKAS, N., CARLI, M, FIDECKA, S., and ALGERI, S. Effect of life-long hypocaloric diet on age-related changes in motor and cognitive behavior in a rat population. *Neurobiol. Aging* **11,** 417–423, 1990.

QUIRION, R., WILSON, A., ROWE, W., AUBERT, I., RICHARD, J., DOODS, H., PARENT, A., WHITE, N., and MEANEY, MJ. Facilitation of acetylcholine release and cognitive performance by an $M_2$-muscarinic receptor antagonist in aged memory-impaired rats. *J. Neurosci.* **15,** 1455–1462, 1995.

RAO, G.N., HASEMAN, J.K, GRUMBEIN, S, CRAWFORD, D.D., and EUSTIS, S.L. Growth, body weight, survival, and tumor trends in F344/N rats during an eleven-year period. *Toxicol. Pathol.* **18,** 61–70, 1990.

RAPP, P.R., ROSENBERG, R.A., and GALLAGHER, M. An evaluation of spatial information processing in aged rats. *Behav. Neurosci.* **101,** 3–12, 1987.

SPANGLER, E.L., WAGGIE, KS., HENGEMIHLE, J., ROBERTS, D., HESS, B., and INGRAM, D.K Behavioral assessment of aging in male Fischer 344 and Brown Norway rat strains and their F1 hybrid. *Neurobiol. Aging* **15,** 319–328, 1994.

VAN DER STAAY, F.J. and DE JONGE, M. Effects of age on water escape behavior and on repeated acquisition in rats. *Behav. Neural Biol.* **60,** 33–41, 1993.

WALLACE, J.E., KRAUTER, E.E., and CAMPBELL, B.A. Animal models of declining memory in the aged: Short-term and spatial memory in the aged rat. *J. Gerontol.* **35,** 355–363, 1980a.

WALLACE, J.E., KRAUTER, E.E., and CAMPBELL, B.A. Motor and reflexive behavior in the aging rat. *J. Gerontol.* **35,** 364–370, 1980b.

WALOVITCH, R.C., INGRAM, D.K, SPANGLER, E.L., and LONDON, E.D. Codergocrine, cerebral glucose utilization and maze performance in middle-aged rats. *Pharmacol. Biochem. Behav.* **26,** 95–101, 1987.

WEINDRUCH, R. and MASORO, E.J. Concerns about rodent models for aging research. *J. Gerontol.* **46,** B87–B88, 1991.