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Motor Slowing and Parkinsonian Signs in Aging Rhesus Monkeys Mirror Human Aging

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Motor slowing is a universal feature of human aging, and parkinsonian signs are commonly expressed in human senescence. In the present study, age-associated declines in motor functions in 31 female rhesus monkeys were quantified by activity monitors and an automated test panel, and the incidence of parkinsonian signs was scored using a movement dysfunction assessment scale. Activity levels in middle-aged monkeys (12–17 years old) were less than half that of young animals (5–8 years old) and were further depressed in aged monkeys (21–27 years old). Movement dysfunction scores increased significantly with increasing age. Two or more parkinsonian signs were exhibited by 20% of the middle-aged monkeys and 36% of the aged monkeys. Slowing performance times on fine-motor hand tasks correlated significantly with increasing age. Motor learning was seen in all age groups, but improved faster in the young monkeys. The data suggest that aging rhesus monkeys provide an appropriate model to analyze the biological processes leading to motor slowing and the expression of parkinsonian signs in human senescence.

A pronounced slowing of motor functions (bradykinesia) characterizes advanced human age (1). Although primarily associated with senescence, the onset can be traced back to around age 20, when simple (single-choice) reaction times begin to slow at a rate averaging 3%–5% per decade (2). Multiple-choice reaction times slow at an even faster rate (2–4). Motor movements, once initiated, also become increasingly bradykinetic with age (5). In addition to motor slowing, movement dysfunctions are increasingly prevalent after age 65. In a recent survey of over 14,000 Europeans, the incidence of Parkinson's disease rose from 0.6% in the 65–69 age range to 3.6% by age 80 (6). The expression of milder movement dysfunctions, often called "parkinsonian signs," is even more prevalent in the elderly population. Nearly 15% of individuals between 65 to 75 years old living independently in a Boston suburb were found to display two or more parkinsonian signs: bradykinesia, rigidity, gait disturbances, and tremor (7). The incidence rose to over 50% in those aged more than 85 years.

For over four decades, behavioral testing in humans has suggested that the slowing of motor functions with age is primarily caused by changes in "central processes initiating, shaping and monitoring movements" (3). Because Parkinson's disease results from the degeneration of dopamine neurons in the substantia nigra leading to profound dopamine deficiencies in the basal ganglia (8,9), there has long been the suspicion that the mechanisms underlying motor declines in normal aging involve central dopaminergic mechanisms. However, there are distinct differences between Parkinson's disease and age-associated changes in movement functions. For instance, dopamine levels are fivefold or more higher in the substantia nigra and putamen of normal age-matched controls than in Parkinson's patients (10,11). In addition, although some studies have shown a decline in dopamine receptors and the dopamine transporter in the basal ganglia in aging in both humans and rhesus monkeys (12–16), the changes are complex, and the overall effects on function are not clear. Therefore, to sort out the central nervous system mechanisms contributing to motor declines, we have begun to utilize rhesus monkeys as a model of motor slowing in human aging with the goal of identifying the pathways and neurotransmitter systems involved.

Although motor functions in aging nonhuman primates have not been extensively studied, a slowing of motor functions has been seen by some investigators (17–19), but not by others (20,21). Differences between laboratories in motor functions tested, in testing methodology, and small sample sizes may account for the difficulties in detecting age-related changes. Because some motor functions, such as reaction time, show consistent gender differences in humans (2), gender may be an important variable in assessing movement functions in nonhuman primates. Thus, to increase the power of detecting age-associated changes, the present study used only female rhesus monkeys and a sample size of at least ten animals in each group. The test battery included an automated Movement Assessment Panel (MAP) that has been shown to reproducibly and reliably measure coarse- and fine-motor movements in young rhesus monkeys and robustly distinguish age-associated declines in humans (22,23). General changes in movement behavior were evaluated by measuring home-cage activity levels, and parkinsonian signs were rated using a motor dysfunction assessment scale.

Materials and Methods

Animals

Thirty-one adult rhesus monkeys (*Macaca mulatta*), ranging in age from 5 to 27 years old, were used in the study. The animals were obtained from a commercial supplier (Covance, Alice, TX). Nineteen of the animals were bred at the supplier's facility and their date of birth documented. Twelve of the animals had been purchased from other vendors by Covance; three of the older animals in this group were wild caught and their age estimated from dentition. Upon entry into this study, the animals were housed in individual cages with one wall consisting of clear plastic Lexan to permit videotaping. They were maintained on a 12-hour light/dark cycle with water available ad libitum. Food was available continuously, except for a 3-hour period on test days when MAP testing was in process (see later). In addition to standard primate biscuits, the diet was supplemented daily with fresh fruits and vegetables. All testing was conducted in the Laboratory Animal Facilities of the University of Kentucky, which are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Veterinarians skilled in the health care and maintenance of nonhuman primates supervised all animal care. All protocols were approved by the University of Kentucky's Animal Use Committee.

General Assessment

The animals were divided into three age groups: young adults, 5 to 8 years old ($n = 10$); middle-aged adults, 12 to 17 years old ($n = 10$); and aged adults, 21 to 27 years old ($n = 11$). For entry into the study, animals had to be healthy, research naïve, and display a normal range of upper and lower limb movements. Because many group-housed rhesus monkeys experience hand injuries from fighting, any impairments to digits were noted. Only animals with the ability to maneuver and retrieve small food objects were studied. Home-cage activity levels were continuously recorded over a 30-day period from infrared monitors mounted on the outside of the Lexan wall (24). Each time that the animal crossed in front of the beam was logged into a computer, with activity levels analyzed by the DATAQUEST program (Data Science International, St. Paul, MN).

Standardized Rating of Movement Dysfunctions

A movement dysfunctions rating scale (Table 1) was developed based on our parkinsonian rating scale described in detail elsewhere (24,25). Motor dysfunctions were rated independently in quarter-point increments by two observers from videotapes of 2 days of standardized behavioral tests of animals in their home cage. Each standardized test began at 1:30 PM with a technician entering the room and placing a small food item (e.g., grape or a marshmallow) on a ledge above the cage door to elicit standing and reaching movements. The animal was then videotaped for 15 minutes with no one in the room. The technician then reentered the room and tested food retrieval from a panel attached to the front door of the home cage (a nonautomated version of the automated MAP described below). Arm and hand use in retrieving the food items were rated from the videotapes. The same sequence of taping was then repeated at 2:30 PM.

Monkey-Automated MAP Testing

To measure coarse-motor movement times of the large arm muscles in reaching and fine-motor movement times of the small hand muscles in retrieving food items from a receptacle, an automated clear Lexan MAP (Figure 1A) was attached to the door opening of the home cage (22). The monkeys were preadapted to the test panel by placing it on their home cage for 10–15-minute periods for 5 to 6 days and adding small food items to the food receptacle. When the animals were routinely retrieving food from the receptacle, active testing began. A day's testing session consisted of 12 trials, six on each side alternating between the right and left hand. Monkeys were given 45 seconds to retrieve food before the trial was aborted and the tester moved on to the other side.

Three tests of increasing levels of difficulty were evaluated in the present study (Figure 1B–D). The platform test was the simplest (level I difficulty) and involved the removal of a small food item, such as a lifesaver, from a level platform in the food receptacle. Level II and III tests were modified from the visuospatial orientation task of Bachevalier and coworkers (17) and entailed retrieving a lifesaver threaded on a rod in the food receptacle. The level II task required maneuvering the lifesaver up a straight rod. The most difficult task, level III, required the animal to thread the lifesaver over a question mark–shaped rod in the receptacle. For each trial, the *coarse-motor performance time* was recorded as the time for the limb to move from the armhole portal to the food receptacle portal and then back from the receptacle portal into the cage. The time the hand was in the receptacle retrieving the food reward was considered to represent the *fine-motor performance time* and was *not* included in the coarse-motor performance time measurements. Testing was repeated for a total of 10 days before progressing to the next level of difficulty. The performance of the young monkeys served as a baseline and is published elsewhere (22).

Statistical Analysis

Home-cage activity levels were evaluated by a one-way analysis of variance (ANOVA) followed by Dunnett's T3 Multiple Comparison Test assuming unequal group variances. Overall age effects on motor dysfunction scores were assessed by a Kruskal-Wallis test because of the nonparametric distribution of the data. Pairwise group differences were subsequently analyzed using the Mann-Whitney *U* test. The coarse- and fine-motor performance times were averaged over six trials in the monkeys. Coarse-motor performance time was the total time for a trial minus the fine-motor movement time. Because hand preference in rhesus monkeys is task and situation dependent (26), the right and left arms were tested separately, and the results were averaged for each subject. A repeated measures ANOVA was performed using test day, motor component (coarse or fine), and level of task difficulty as within-subject variables. Bonferroni's multiple comparison test was used as the post hoc criterion. Improvements in motor functions (motor learning)

Table 1. Nonhuman Primate Motor Dysfunction Assessment Scale[†]

1. General movement speed (walking, reaching, head movements, etc.)
   0. Normal
   1. Slightly slower in movements
   2. Markedly slower in movements
   3. Markedly slower in movements, episodes of freezing or akinesia
2. Rigidity
   A. Upper limbs
      0. Normal
      1. Decrease in limb extension and/or capacity and frequency of limb use
      2. Severe decrease in limb extension and/or capacity and frequency of limb use
      3. Unable or refuses to extend or use the limb (including walking)
   B. Lower limbs
      0. Normal
      1. Diminished capacity of limb use in walking and in limb extension while standing up
      2. Severe decrease in capacity of limb use and extension while standing up
      3. Unable or refuses to use limb (including walking and standing up)
3. Tremor
   A. Upper limbs (as judged by food pick-up test)
      0. Absent
      1. Occasionally present
      2. Present much of the time
      3. Continuously present
   B. Lower limbs
      0. Absent
      1. Occasionally present
      2. Present much of the time
      3. Continuously present
4. Fine-motor function of hands (as judged by food retrieval test)
   0. Normal use
   1. Moderate impairment in ability to retrieve food
   2. Severe impairment in ability to retrieve food
   3. Unable or refuses to retrieve food
5. Balance
   0. Normal balance
   1. Upper limbs needed to steady balance while standing
   2. Major lapses in balance during activities
6. Posture
   0. Normal
   1. Stooped posture
   2. Arched posture

[†]Normal baseline is considered to be the average movement behavior of a young adult (5–8-year-old) rhesus monkey. Ratings were made in quarter-point increments.

over the 10 days were determined separately for each age group by Dunnett's Multiple Comparison Test using day 1 as the control. Least-squares regression analysis was used to determine the correlation between age and fine-motor performance time on the three retrieval tasks. In all analyses, a $p \leq .05$ was considered significant.

Results

General Assessment

The most active animals during the daily observation periods were the young adult monkeys. The aged animals were not only more sedate but could be identified by their relatively unkempt fur and stooped posture. Daily home-cage activity levels recorded over a 30-day test period (Figure 2) confirmed the hypothesis of an age-related effect ($p \leq .0001$ for the overall ANOVA). Middle-aged monkeys were less than half as active as young animals. Activity levels declined even further in the aged monkeys ($p \leq .001$ in all paired post hoc tests). Although the aged monkeys were significantly less physically active, 8 out of the 11 monkeys still displayed regular menstrual cycles (data not shown).

Motor dysfunction scores increased significantly with increasing age (Table 2; Figure 3). Agreement between the motor dysfunction ratings of the two observers was judged to be very good with an intraclass correlation coefficient of 0.91 ($p \leq .0001$), and mean values were used in the main analysis. A nonparametric Kruskal-Wallis test demonstrated an overall age effect ($p \leq .0001$), with motor dysfunction scores increasing significantly with age (Figure 3). None of the 5–8-year-old animals exhibited movement impairments and, thus, had much lower scores than either the middle-aged or aged monkeys ($p \leq .001$). In contrast, many of the middle-aged and aged animals displayed parkinsonian signs—bradykinesia, rigidity, tremor, and postural instability—although the scores for the middle-aged group were lower ($p \leq .001$) than those of aged monkeys. A parkinsonian sign was considered "prominent" if it was rated as higher than 1.0 on the movement dysfunction rating scale. Two of the middle-aged monkeys and four of the aged ani-

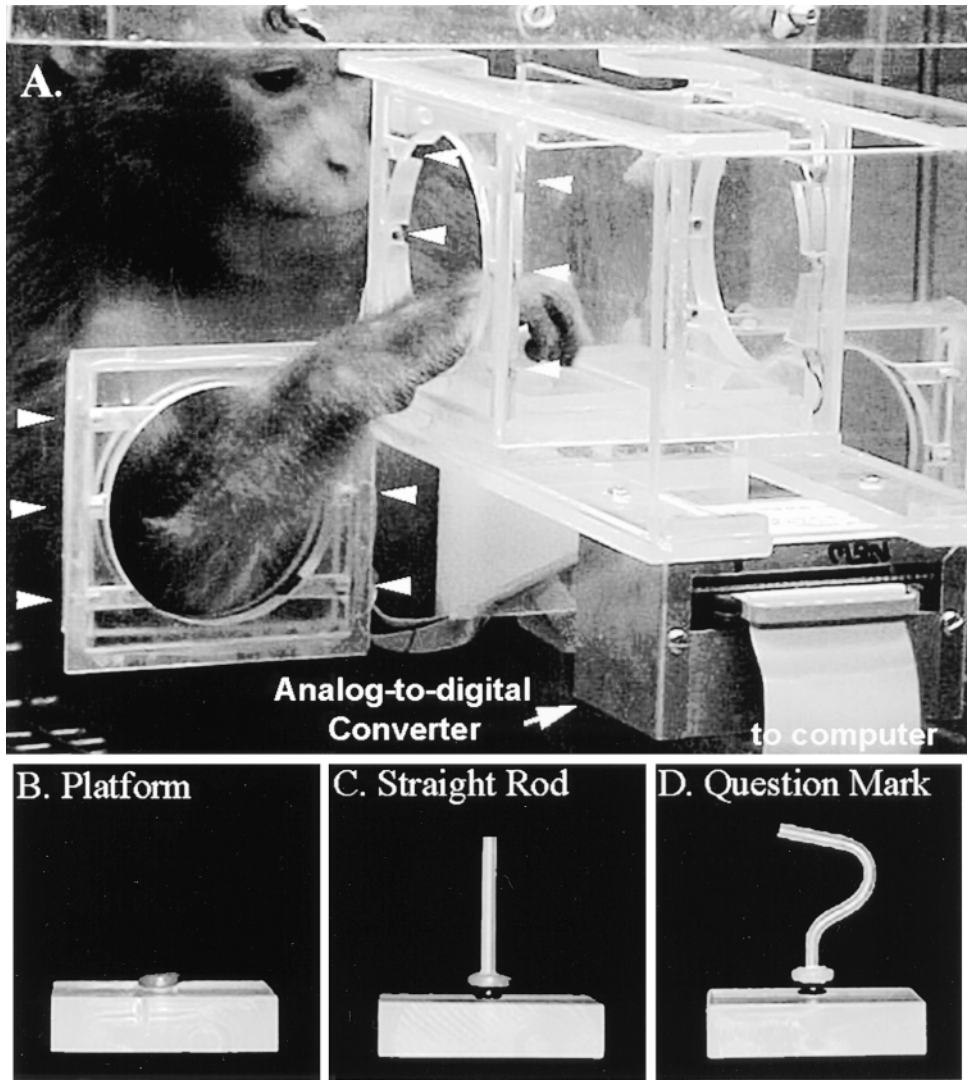

Figure 1. **A**, The Movement Assessment Panel (MAP) was used to record the time to reach from the cage into a receptacle and retrieve a food reward. Here, a rhesus monkey is grasping a lifesaver in the right receptacle of the MAP. Movement times were measured by arrays of photodiodes (*arrowheads*) around the armhole portal and the receptacle portal. Food retrieval from the receptacle was tested using three tasks of increasing levels of difficulty: **B**, platform, **C**, straight rod, and **D**, question mark rod.

mals displayed prominent bradykinesia along with either rigidity (two middle-aged and three aged animals) or tremor (one old animal). Another two middle-aged animals and five aged monkeys expressed one prominent parkinsonian feature. In six of the seven animals, this feature was bradykinesia. The remaining animal, an aged monkey, showed a pronounced rigidity in its lower limbs.

Although most animals readily learned to use the testing panel, one aged monkey never acquired the platform task and was not tested further. One additional old animal failed to acquire the straight rod and question mark rod tasks. Maneuvering food over the question mark route was difficult for some animals in all three age groups. One additional old monkey, one young animal, and two middle-aged monkeys failed to learn the question mark rod test. For those animals that did perform the tasks, the time taken for performing the coarse-motor component of each task was similar in all three age groups. Although the greatest range in movement times was seen in the aged animals, there was significant overlap with the other age groups (Figure 4).

In contrast, the fine-motor components of the tasks clearly separated the age groups (Figure 5). In the overall ANOVA, the main effects of age group, test day, and level of task difficulty were all highly significant ($p \leq .0001$). In addition, in evaluating the interactions between the main effects, age by task difficulty, and test day by task difficulty were also highly significant ($p \leq .0001$). Young rhesus monkeys were significantly faster than middle-aged and aged monkeys on all three tasks. The middle-aged animals, in turn, showed faster performance times on the platform and straight rod tasks than the old monkeys. Their performance times overlapped on the question mark test.

Because of high variability, the age by test day interaction did not reach statistical significance using ANOVA.

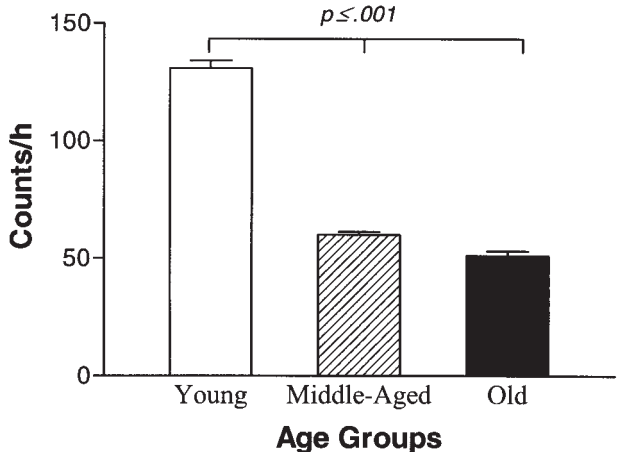

Figure 2. Average daily home-cage activity levels for each age group over a 30-day period demonstrated that there was an overall decline in activity with age ($p \leq .0001$). In all of the pairwise post hoc tests, the differences between groups were highly significant ($p \leq .001$). The error bars indicate the mean ± standard error of the mean.

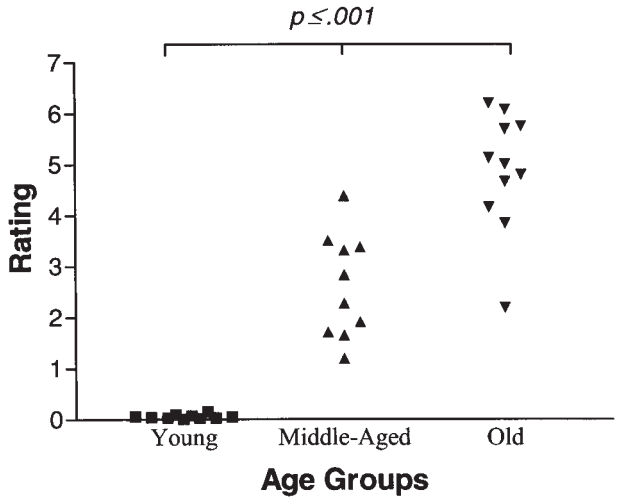

Figure 3. Movement impairments were scored from standardized videotaped tests using the Nonhuman Primate Motor Dysfunction Assessment Scale (Table 1). Impairments were not seen in the young age group, which formed the baseline for the rating scale. A nonparametric Kruskal-Wallis test showed an overall age effect in motor dysfunction scores ($p \leq .0001$). In all of the pairwise tests, the differences between groups were highly significant ($p \leq .001$).

Therefore, to determine if there were changes in performance times with repeated testing, performance times on each subsequent day of testing were compared with day 1 of testing within each age group using Dunnett's Multiple Comparison Test. Over the 10 days of testing, significant improvements in performance time with practice (i.e., motor learning) were seen in all three age groups on the straight rod and question mark tasks (Figure 5). The improved times were achieved earlier in the young adults than in the two older age groups.

As expected from the group averages, the fine-motor performance times of the individual animals strongly correlated with age, with the best correlations seen on the platform and straight rod tasks ($p \leq .0001$; Figure 6). Although the older animals were slower as a group, the performance times of some middle-aged and aged monkeys overlapped with those of young animals.

Discussion

In correspondence with human aging, the rhesus monkeys in this study displayed age-associated slowing of motor functions. The progressive functional declines were evident in middle-aged animals and were further advanced in aged animals. Changes in motor functions included the following: (i) decreased home-cage activity levels; (ii) increased expression of parkinsonian features with advancing age; (iii) slower fine-motor movement times with advancing age; and (iv) age-associated differences in motor learning. These results complement and extend previous reports of

Table 2. Motor Function Rating Scores for Each Age Group

Age/Feature	Young	Middle-Aged	Aged
Bradykinesia	0	1.10 ± 0.06	1.19 ± 0.08
Rigidity			
Upper limb	0	0.11 ± 0.06	0.42 ± 0.07
Lower limb	0	0.51 ± 0.14	0.97 ± 0.09
Tremor			
Upper limb	0	0.06 ± 0.04	0.38 ± 0.11
Lower limb	0	0	0
Fine-motor (hand)	0	0.48 ± 0.08	0.88 ± 0.08
Balance	0	0.06 ± 0.04	0.22 ± 0.05
Posture	0	0.30 ± 0.08	0.80 ± 0.06
Total	0	2.61 ± 0.35	4.86 ± 0.35

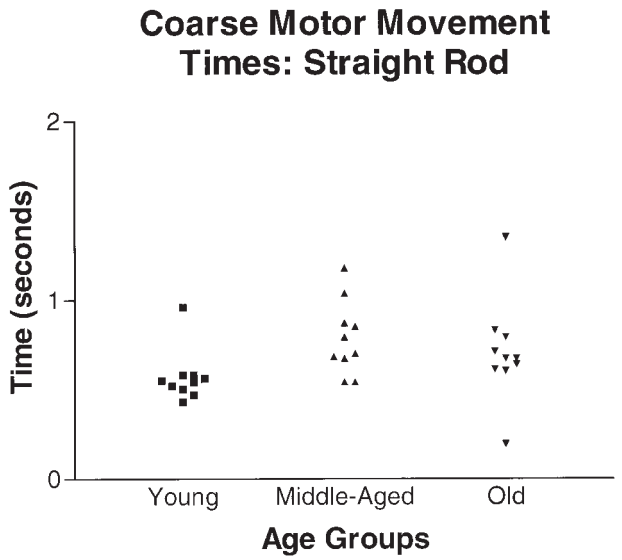

Figure 4. No significant difference was seen between the three age groups on the coarse-motor components of the three tasks. Here, the average coarse-motor performance time for each group over a 10-day period on the straight rod task is shown.

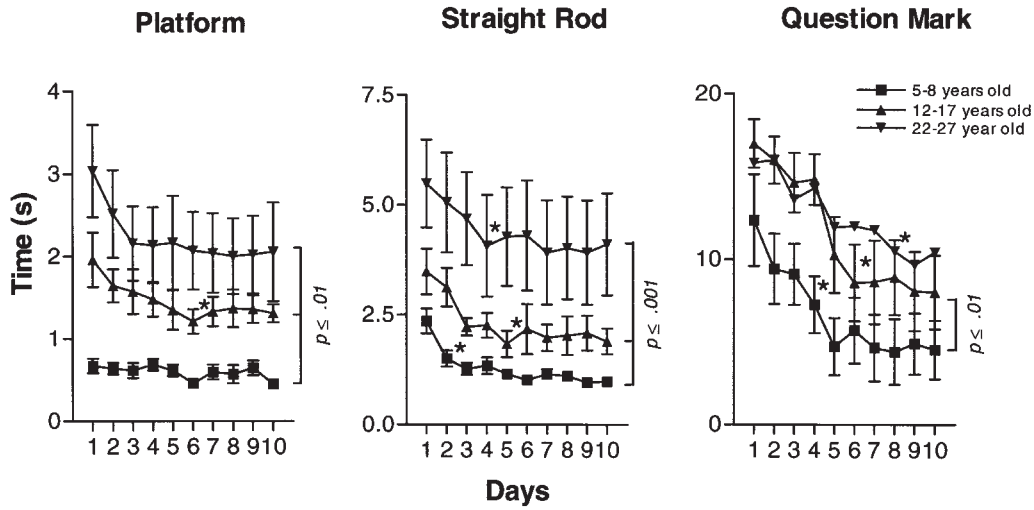

Figure 5. Fine-motor performance times, as assessed by the three tasks, showed significant age-associated differences. The three age groups differed significantly from one another in both the platform ($p \leq .01$) and straight rod tasks ($p \leq .001$). The young adults were significantly faster ($p \leq .01$) than the two older groups on the question mark task, the most demanding of the three tasks. The performance times of the middle-aged and aged animals overlapped on this task. The performance times of each age group improved significantly with repeated testing on the straight rod and question mark rod tasks. The first day on which performance times were significantly lower than day 1 of testing (Dunnett's Multiple Comparison Test, $p \leq .01$) are marked by a star. The young animals reached this criterion before the older monkeys.

declines in activity levels (25) and fine-motor movements in aged rhesus monkeys (17,18).

Comparative ages between humans and rhesus monkeys have been estimated based on ages at puberty and menopause, and longevity. Female rhesus monkeys enter puberty 3–4 years after birth and experience menopause between 25 to 30 years of age (27–29). The oldest rhesus monkeys survive into the 35–40-year age range (20,30). With human puberty occurring between ages 9 to 12 years, and the oldest humans living for just over 120 years (31), 1 year of rhesus life would approximately equal 3 human years. The threefold faster rate of aging in rhesus monkeys is consistent with a recent magnetic resonance imaging study in which age-associated declines in rhesus brain parenchymal volume were found to proceed at three times the human rate (32). The timing of menopause does not fit within this

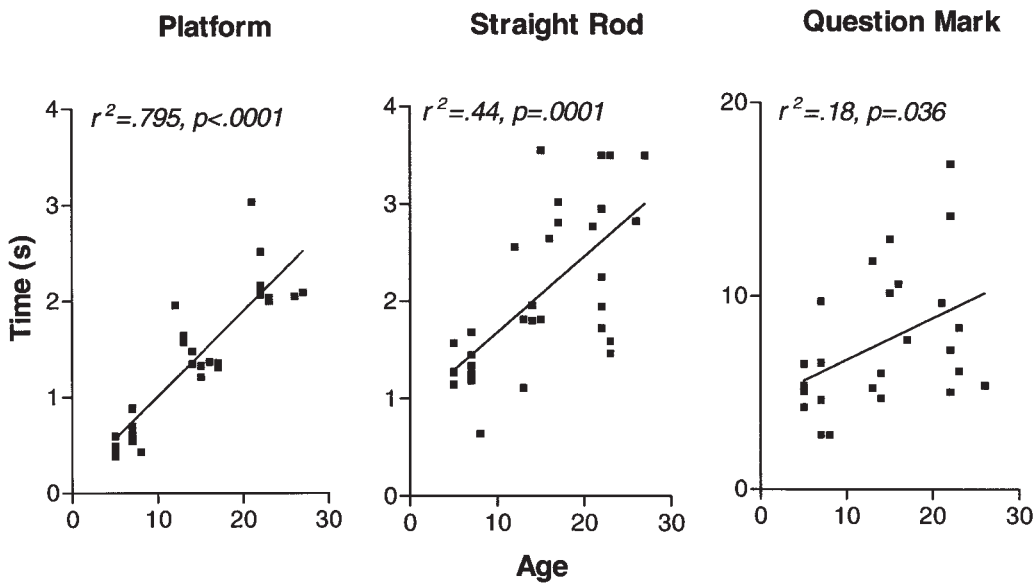

Figure 6. Fine-motor performance time correlated with increasing age on all three tasks. The average time for each animal is shown for days 6–10 of testing, when performance times had stabilized.

scheme and would suggest a reproductive aging ratio closer to 1 year in the rhesus for every 2 human years. But, whichever comparative aging scale is used, the pronounced motor slowing in 12- to 17-year-old rhesus monkeys and the presence of parkinsonian signs in this age group suggest that the decline of motor functions in middle-aged monkeys is relatively accelerated compared with humans.

Performance times on the two most difficult retrieval tasks improved significantly with learning in all three age groups of monkeys. The young animals were not only initially faster in performing the tests, their movement times improved faster than in the older animals. On the question mark task, the middle-aged group initially could not be distinguished from the aged animals. However, by the sixth day of testing, the middle-aged monkeys were significantly faster in food retrieval. The aged monkeys did not reach this level of improvement until the eighth day of testing. The improved performance times in all three age groups, indicating motor learning, suggest that central nervous system processes rather then peripheral factors regulate the speed of motor functions. This is consistent with converging evidence from other studies showing that administration of either levodopa or GBR-12909, two drugs that increase available dopamine levels in the brain, significantly improved fine-motor performance in aged monkeys (33).

Determining the effects of peripheral factors on motor functions in aging rhesus monkeys requires further study. As discussed earlier, rhesus monkeys usually do not undergo menopause until their mid-20s, and eight of our 21–27-year-old monkeys displayed regular menstrual cycles. However, the changing endocrine status of both the middle-aged and aged animals may have influenced their speed in completing the motor tasks. It was clear that performance times on MAP tasks were not correlated with past hand injuries. Hand injuries involving the digits are common in the aged monkeys. Because all animals had been selected for their ability to retrieve small food items, those monkeys with prior injuries had developed effective compensatory strategies.

Although central dopaminergic pathways are implicated in the movement dysfunctions of aging because of their resemblance to parkinsonian features, dopaminergic changes in the central pathway regulating movements are complex, and their effects on motor performance are not well understood. The present study demonstrates that aging rhesus monkeys display many aspects of age-associated declines in human movement functions. The data suggest that aging rhesus monkeys provide an appropriate model to analyze central morphological, physiological, and molecular processes leading to motor slowing and the expression of parkinsonian signs in human senescence.

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