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Locomotor Activity in Female Rhesus Monkeys: Assessment of Age and Calorie Restriction Effects

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As a component of a long-term, longitudinal study of aging in this primate model, the objective of the current experiment was to assess age and diet effects on locomotor activity in a cross-sectional analysis. By attaching a motion detection device to the home cage, locomotor activity was monitored over a week in a group (N = 47) of female rhesus monkeys (*Macaca mulatta*) 6–26 yrs of age. About half these monkeys composed a control group fed a nutritionally fortified diet near ad libitum levels, whereas an experimental group had been fed the same diet at levels 30% less than comparable control levels for approximately 5 yrs prior to testing. Among control monkeys, a marked age-related decline in activity was noted when total activity was considered and also when diurnal and nocturnal periods of activity were analyzed separately. When comparing activity levels between control and experimental groups, only one significant diet effect was noted, which was in the youngest group of monkeys (6–8 yrs of age) during the diurnal period. Monkeys in the experimental group exhibited reduced activity compared to controls. Body weight was not consistently correlated to activity levels. In some older groups, heavier monkeys tended to show greater activity, but in younger groups the opposite pattern was observed.

DECLINE in locomotor activity is a robust feature of aging that has been documented in many invertebrate (houseflies, fruitflies, nematodes) and vertebrate (gerbils, rats, mice, dogs, monkeys) species [see (1,2) for reviews], including man [see (3) for review]. In humans, the decline can be observed during adolescence and appears to continue throughout the life span (4,5) with various plateaus and periods of accelerated decline late in life that differ by gender (6). Whether the phenomenon of age-related decline in activity is related primarily to environmental or genetic factors in humans remains a highly controversial area of research (3).

Caloric intake is a major environmental variable that can affect the rate of aging of many short-lived species (7–9). When regimens of calorie restriction (CR) are implemented in laboratory rodents to limit intake 20–50% less than typical or near typical ad libitum (AL) consumption of a healthy diet, median and maximum life span can be extended; the onset of age-related disease delayed and the incidence reduced; and the age-related functional decline in many physiological systems can be retarded (7–9).

Beyond the vast literature that documents the effects of CR on aging, a major question has been the relevance of this diet manipulation on aging and age-related chronic disease in long-lived species, particularly humans. To address this question, several studies have been initiated in nonhuman primates that apply various CR regimens in different species begun at different ages (10–13). In 1987, the National Institute on Aging (NIA) began a CR study in rhesus (*Macaca mulatta*) and squirrel monkeys (*Saimiri sciureus*) by gradually imposing a 30% CR in different life-span representative groups: juveniles, young adults, and old adults. Summaries of findings from this extensive study can be found elsewhere (12,14,15). In general, retardation of aging in several age-related parameters has been reported, primarily in rhesus monkeys (14,15). Another conclusion emerging from this study is that the physiological response of rhesus monkeys to CR is very similar to what has been observed in rodents (e.g., reduced circulating glucose, increased insulin sensitivity, and lower body temperature), which indicates a major alteration in metabolic response (14,15).

Several studies of CR in rodents have examined locomotor activity. Results from studies using electronic devices to monitor activity in the home cage of mice (16,17) and rats (18,19) indicated higher levels of activity among animals on CR compared to AL controls. A longitudinal analysis of home cage activity in rats confirmed the progressive decline in spontaneous movement in AL controls but not in CR groups (20). Weed and colleagues (21) utilized electronic sensors to examine home cage locomotor activity among a group of adult male rhesus monkeys in the NIA study. The conclusions of this investigation were that within the limited age range analyzed (8–13 yrs), there was evidence of an age-related decline in activity. In addition, results indicated an increased activity among CR monkeys, but this effect was observed only in one group of monkeys examined (10–12.2 yrs), not in a younger group (8.2–8.4 yrs). In general, the results of this study analyzing age and diet effects were limited regarding their generalization. Thus, the current study was planned to address this issue in a broader perspective.

Specifically, we examined locomotor activity in the home cage in a large sample of female rhesus monkeys ($N = 47$) with a much broader age range (6–26 yrs) than Weed and colleagues (21) had employed. We hypothesized that activity would decline with age and would be higher in the experimental group compared to controls. The current study was designed to provide the most extensive analysis conducted to date to assess age-related changes in activity in nonhuman primates conducted with reliable instrumentation under controlled conditions.

Methods

Monkeys

Subjects were 47 female rhesus macaques (*Macaca mulatta*). Group ages and experimental design are provided in Table 1. The monkeys had been introduced to the study protocol in January 1992. All were experimentally naive prior to their procurement for the study. The youngest group of monkeys was obtained from Labs of Virginia (Morgan Island, SC) with a mean age of about 2 years upon arrival at the Poolesville, Maryland, NIH primate facility and were thus designated as the juvenile (J) group at the beginning of the study. Another group of monkeys was obtained from a research colony in the People's Republic of China via the Texas Primate Center (Hazelton Research Primates, Alice, TX) or via the U.S. Army Medical Research Institute of Chemical Defense (Aberdeen, MD). They had a mean age of about 9 years at arrival and were thus designated as the adult (A) group. An old (O) group of monkeys was obtained from Labs of Virginia with a mean age of about 17 years upon arrival. A more detailed description of the housing and husbandry of the colony can be found elsewhere (12).

All monkeys in the study were considered healthy as determined by extensive health analysis: three daily checks by trained animal technicians and a complete physical examination conducted annually by a veterinarian assigned to the study. The median life span of rhesus monkeys in other colonies has been estimated to be 24 years with a maximum life span of 37 years (22).

Diet

At the beginning of the study, the monkeys were divided into control (CON) and experimental (EXP) groups. Food allotments for CON groups ($n = 26$) were based on age and body weight in accordance with National Research Council (NRC) recommendations for nonhuman primates (23). Regular measurements of consumption documented actual food intake. Examination of food consumption data over the course of the ongoing study has indicated that CON monkeys were eating at approximately ad libitum levels. All animals received food at approximately ad libitum levels for one month prior to starting on restriction. The EXP groups ($n = 21$) received 30% less ration than age- and body weight-matched CON groups. The target restriction level of 30% was achieved by a gradual reduction (10% per month) of food intake over 3 months. As CON animals grew, intake was adjusted based on NRC requirements for monkeys of a given age and weight. Allotments for EXP monkeys were adjusted to maintain a 30% restriction.

Table 1. Experimental Design with Mean Age (Range), Body Weight (Range), and Daily Food Intake (*SEM*) at Testing

Group	Diet	*n*	Age (years)	Body Weight (kg)	Food Intake (g)
J	CON	8	7.2 (6.2–8.3)	6.56 (3.51–9.94)	164.5 (12.8)
J	EXP	6	7.6 (7.1–8.2)	5.40 (4.03–6.52)	116.1 (5.5)
A	CON	12	14.5 (10.8–18.2)	5.75 (4.03–8.93)	135.2 (7.8)
A	EXP	9	15.2 (11.1–19.4)	4.78 (3.82–5.70)	98.8 (3.8)
O	CON	6	23.6 (21.0–26.1)	7.49 (5.79–9.64)	123.6 (3.9)
O	EXP	6	22.2 (18.2–26.2)	7.22 (3.89–9.84)	104.3 (5.4)

Notes: J = juvenile; A = adult; O = old; CON = control; EXP = experimental.

All monkeys were fed individually, twice a day, at approximately 0700 and 1400 hours. A stainless steel screen was located below each individual cage to catch dropped biscuits. Monkeys could retrieve these biscuits throughout the day. All uneaten food was removed following the afternoon feeding. Each animal received a fruit treat as a supplement once a week and a 5 g treat (Noyes Precision food pellet; a fruit-flavored pellet of the same composition as the monkey biscuits) twice a week.

The diet was formulated at NIH as a modification of their high-fiber diet routinely fed to monkeys. Nutrient content of the diet was based on published estimates of requirements for nonhuman primates (23). All monkeys ate an identical diet that was supplemented with additional vitamins, minerals, and trace elements to prevent nutritional deficiency (12). Young monkeys on the CR regime demonstrated body weight increases and maintained growth, albeit more slowly, since the inception of this study (24,25). Further detailed descriptions of the diet and composition are available in previously published reports (12,26).

Housing

The monkeys resided in stainless steel primate cages measuring $88.9 \times 61.0 \times 68.5$ cm. The cages were located in one of two light- and temperature-controlled vivaria measuring 2.9×8.2 m, where the activity monitoring was conducted. The vivaria had only artificial lighting, maintained on a 12:12 light-dark cycle with lights on at 0600 hours. Room temperature (22–28°C) and humidity (50–60%) were under automatic control. Water was provided ad libitum via automatic filtered watering systems. All testing was conducted within the vivarium. Although some of the monkeys had been paired-housed early in life for socialization, all had been housed individually for at least 5 yrs prior to the study, but had visual, auditory and olfactory—but not tactile interactions—with other monkeys. Only female rhesus monkeys involved in the study were housed in the two single-sex rooms where the activity monitoring occurred.

Activity Sensors

Activity data were collected using four activity sensors that had been custom designed for this study (infrared and microwave motion detectors, C & K systems intrusion detection units, model DT450, Folsom, CA). Each monitor was attached to the front of the monkey's home cage. These sensors transferred digitized signals to an IBM XT computer that then recorded and tabulated, via a custom-designed pro-

gram, the detection of whole body movements. Data were collected as single events and blocked into 5-second increments across 1-minute sessions. Thus, a count of 12 for a 1-minute session would represent virtually constant activity, whereas a count of 6 would indicate that the monkey was moving about half the time monitored. If motion was detected during the sampling period, the computer program scored this as a single activity event. These summary counts were then accumulated across 24 hr for analysis of circadian patterns. Before each session the sensors were calibrated to record only gross motor movements of the center of gravity. Calibration was accomplished by adjusting the sensitivity of the sensor to detect a 20–30 cm deflection of the experimenter's arm movement in the center of the cage. Calibration was checked by observing a monkey in the test cage and then verifying the visually obtained activity score against the sensor recording. Movements such as scratching and grooming were not detected. Other details of the apparatus can be found in Weed and colleagues (21).

Procedure

At least one week prior to testing, the platforms used to mount the activity unit were attached to the top of each home cage without the actual units present, which allowed habituation of the monkey to the apparatus. Activity monitors remained visible for all monkeys throughout the entire testing procedure. Following this habituation period, activity monitors were activated for 7 days, with 6 full days of data collection. Thus, adaptation and testing conditions were the same for all monkeys and occurred during the period May 1997 to August 1997.

The order of testing was pseudorandomized across the experimental groups. During any week of testing, two pairs of CON and EXP monkeys were always included. The order of testing across weeks was randomized across the age groups. Specifically, the random order was always selected within triplet pairs of J, A, or O groups, again with CON and EXP groups paired within the age groups. To assess the reliability of the measurements, a subsample (9 CON; 6 EXP) of monkeys from one of the vivaria were retested one week after their first test.

Statistical Analysis

Data from hours of 0800, 0900, and 1000 were excluded from the analysis because colony husbandry occurred at this time. Daily human activities have been shown to inflate activity scores artificially (27). Activity monitors were reset at this same time. Reliability of the activity measurements was assessed with a subset of the monkeys by calculating the correlation between activity counts obtained during one week with those collected during the following week and then controlling for possible effects of age by using a partial correlation with age as the covariate. The relationship between age and mean total daily activity counts in the control groups was assessed by linear regression. Separate regression analyses examined the relationships between age and activity during diurnal and nocturnal hours and addressed the possibility of age effects on the circadian distribution of activity. Diet effects on activity within each age group were assessed using an analysis of variance with repeated measures (ANOVA–RM) on hourly activity counts. The Bonferroni *t* test was used to compare control and experimental groups at each hour. Additional ANOVAs were conducted to identify possible age and diet effects on activity by collapsing across hours both within the diurnal and nocturnal time periods. Finally, a correlational analysis was used to examine possible relationships between activity counts and body weight of the monkeys within various groups. Statistical significance was accepted as $p < .05$.

Results

The data obtained from the activity sensors demonstrated several important features. First, reliable measures of activity could be generated for both CON and EXP groups. This conclusion is supported by the appearance of the data in Figure 1, in which data have been collapsed across age groups. What is observed is a clear circadian pattern of activity typical for rhesus monkeys. With light onset at 0600 hours, activity rises dramatically toward a peak at the first mealtime around 0700 hours. Activity declines somewhat through the day with a plateau around the second mealtime, about 1400 hours. After this event activity declines, with a sharp offset at lights-off at 1800 hours. Almost no activity is detected during the nocturnal period, with the exception of a few individuals.

Reliability of the data collected was further confirmed with a specific assessment. For 15 monkeys, the 1-week test was repeated. The test–retest correlation for this group was very high, $r(13) = .83$, $p < .01$. The correlation remained high even when the effects of age were partialed out, $r(12) = .81$, $p < .01$.

Regarding age effects, the results were consistent. Figure 2 presents the regression of age on activity for the CON groups. A significant age-related decline is evident, $r(1,24) = .54$, $p = .004$ (Figure 2A). The activity level of every monkey over 17 yrs of age is less than that of every monkey under 10 yrs of age. The greatest variability in results was observed in the A group of monkeys between 10 and 17 yrs of age. The monkey with the lowest activity level was from this group. This monkey was retested approximately 3 weeks later, and its low level of activity was repeated (data not shown).

To examine possible age effects in circadian patterning of behavior, the regression of age on activity was repeated with diurnal and nocturnal periods analyzed. The regression was again significant for the diurnal period ($r = .51$, $p = .008$; Figure 2B), again showing an age-related decline, as well as for the nocturnal period ($r = .43$, $p = .03$; Figure 2C).

Regarding diet effects, the results shown in Figure 1 would suggest that diet had no overall impact on activity; however, further analysis revealed that diet effects varied across age groups. In Figure 3A, a generally lower activity level ($\sim$20%) is observed among EXP monkeys in the J group during the diurnal period. This diet effect was confirmed by the results of a 2 (diet group) by 21 (hour) repeated measures ANOVA that revealed a significant diet effect, $F(1,12) = 5.86$, $p = .03$; hour effect, $F(20,240) = 89.5$, $p < .001$; and a significant Diet $\times$ Hour interaction, $F(20,240) = 2.09$, $p = .005$. Although a pattern of generally lower activity in the EXP group is evident across most diurnal hours, the diet effect was significant only at hour 18, $p <$

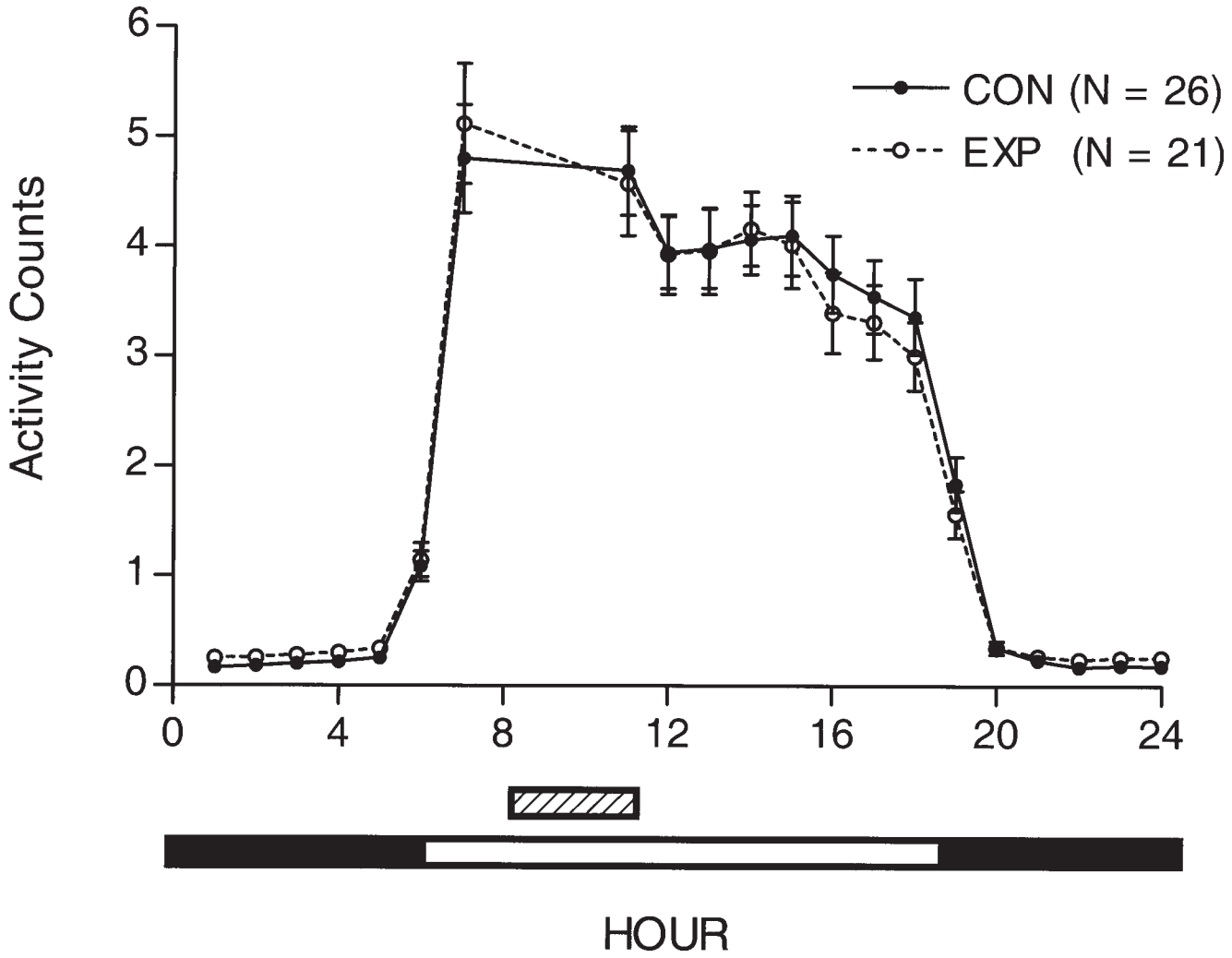

Figure 1. Mean (*SEM*) hourly activity counts over 24-hr period for female rhesus monkeys (all ages combined) on control (CON) or experimental (EXP) diets. Open bar = lights on; filled bar = lights off; striped bar = data deleted during this husbandry period.

.006, when comparisons were made at each hour using the Bonferroni adjustment for multiple *t* tests.

In the A group (Figure 3B), the diet effect appears reversed, with higher activity observed among the EXP animals; however, this apparent difference did not prove statistically significant as indicated in the results of the ANOVA. Although the effect of hour was significant, $F(20,380) = 50.1$, $p < .001$, neither the diet effect nor the Diet × Hour interaction was significant, $F(1,19) = 1.02$, $p > .05$ and $F(20,380) < 1.0$, respectively. Meanwhile, in the O group (Figure 3C), there is no indication of a significant diet effect on activity. Again, the effect of hour was significant, $F(23,230) = 49.7$, $p < .001$, with no significant effects of diet, $F(1,10) < 1.0$, nor significant Diet by Hour interaction, $F(23,230) < 1.0$.

A correlational analysis summarized in Table 2 was used to identify possible relationships between body weight and activity levels. When all monkeys were considered, no significant correlation between body weight and total activity counts was noted even when CON or EXP groups were analyzed separately. When this relationship was examined within age groups, again no significant correlations were found. When the relationship was examined within individual age–diet groups, only one significant correlation emerged, but a few trends were evident. Among EXP monkeys in the A group, higher activity was significantly related to higher body weight. A similar relationship appeared in both control and experimental monkeys in the O group, but none of the correlations were statistically significant because of the small sample sizes. In the J group, the opposite relationship was observed in the CON group, that is, higher activity was related to lower body weight, but the correlation was not significant.

Discussion

Applying a reliable measure of locomotor activity in the home cage, we observed clear evidence of an age-related decline in activity in this cross-sectional study of female rhesus monkeys. Activity in the oldest group of monkeys (18–26 yrs) was half that of the youngest group (6–8 yrs).

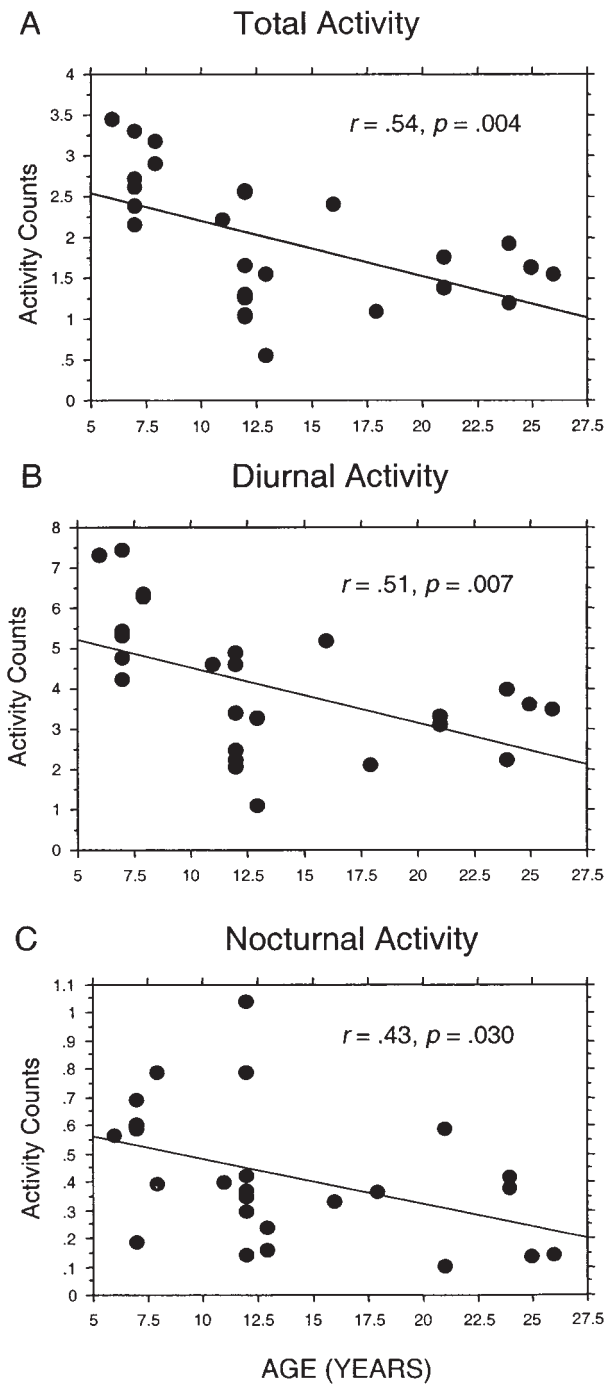

Figure 2. Regression of age on activity counts for female (CON) rhesus monkeys for (**A**) total activity; (**B**) diurnal activity; and (**C**) nocturnal activity.

The finding of an age-related decline in activity extended to a much wider age range than reported for an earlier study of male rhesus monkeys from the same study (12). Using a similar automated device to monitor home cage activity, Irwin and colleagues (28) reported a decline in activity with advancing age in squirrel monkeys. Using observational techniques, Janicke and colleagues (29) also reported an age-related decline in activity in several primate species housed outdoors in a zoological park. Thus, when considering the current results collected in a large sample of female monkeys monitored under controlled conditions, it would appear that reduced locomotor activity is a phenomenon that is generalizable to primate species. This phenomenon is also observed in a variety of other invertebrate and vertebrate species, including man (1–6).

While confirming the age-related decline in activity in this species, a major rationale for the study was to examine the effects of long-term CR on activity. With the exception of one age group of monkeys, we noted no generalized diet effects on activity of female rhesus monkeys in the current analysis. In the J group (6–8 yrs), EXP monkeys exhibited significantly less activity compared to CONs, about a 20% reduction overall; however, this difference was restricted primarily to time periods during the light hours. The general finding contrasted with the earlier observation from the same study (21), that male rhesus monkeys about 10–11 years of age showed significantly higher activity levels on the experimental diet as compared to controls. A similar diet effect did appear in the A group of female monkeys (10–19 years of age) in the current study, but the difference was not statistically significant. Moreover, Weed and colleagues (21) noted no difference in activity levels between EXP and CON groups of male monkeys about 8 years of age.

The differential effect of diet on activity across age groups should also be considered in light of differences in food intake data shown in Table 1. Food intake was clearly reduced in the EXP groups of J and A animals (70% and 73% of CON levels, respectively); however, the difference in intake was less in the O group (84% of CON). Even with the difference in food intake, CON and EXP groups differed little in body weight in the O group. These statistics were the result of attrition in the O group, in which some of the lighter EXP monkeys and some of the heavier monkeys in CON group had died, thus bringing the mean body weights closer together. Yet, despite the clear differences in body weight and food intake in the J and A groups, the activity effects of the restricted diet emerged in opposite directions.

Rodent studies have observed generally higher activity levels in CR groups compared to controls (16–20). In other studies of male rhesus monkeys using devices similar to the one used in the current study, conclusions regarding the effects of CR on activity have been variable. Kemnitz and colleagues (13) reported that activity was reduced in adult rhesus monkeys (9–10 years of age) on CR after 1 year of study; however, after 5 yrs of study, the difference between control and CR groups was no longer significant (30). DeLany and associates (31) reported higher activity in a group of old (22 yrs) rhesus monkeys on CR for 10 years, compared to controls. This diversity of findings within the monkey studies might be due to differences in diet composition, age, gender, source of animals, length of CR, health, and other factors. Regarding the results of our study, it should be noted that the monkeys were obtained from different sources, although the youngest and oldest groups came from the same source. Regarding health issues, it was clear that an age-related decline in activity was emerging among the middle-age group of monkeys (~10–12 years of

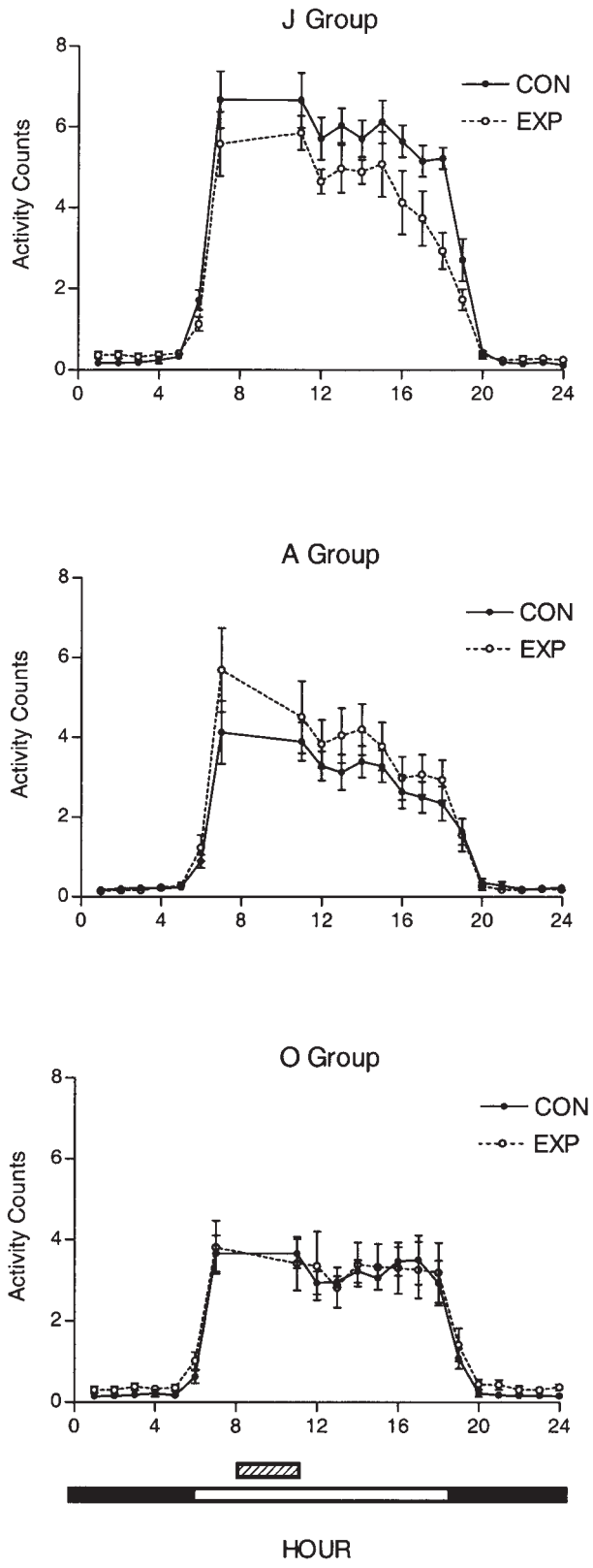

Figure 3. Mean (*SEM*) hourly activity counts over 24-hr period for female rhesus monkeys in three different age groups (J = 6–8 years; A = 10–19 years; O = 18–26 years) in control (CON) or experimental (EXP) groups. Open bar = lights on; filled bar = lights off; striped bar = data deleted during this husbandry period.

Table 2. Correlations (*n*) Between Total Activity Counts and Body Weight for Control (CON) and Experimental (EXP) Groups of Female Rhesus Monkeys of Different Ages

Age Group	All	CON	EXP
All	0.05 (47)	–0.01(26)	0.16 (21)
J	–0.21 (14)	–0.67 (8)	–0.04 (6)
A	0.15 (21)	0.14 (12)	0.78 (9)*
O	0.43 (12)	0.66 (6)	0.43 (6)

Notes: J = juvenile; A = adult; O = old.
*$p < .05$, Pearson product-moment correlations.

age), which would be well before the emergence of health problems in these animals.

Thus, the picture of diet effects will likely be resolved only with additional longitudinal analysis. As an example, in a longitudinal study of rats on an every day or every-other-day feeding regimen, Goodrick and colleagues (32) reported that wheel-running activity was generally less in the diet-restricted groups early in life, but ultimately greater later in life after the control groups (fed every day) had exhibited a marked age-related decline in activity.

In their study of male rhesus monkeys, DeLany and colleagues (31) suggested that the higher activity observed in the CR group was related to lower body weight. When compared to younger monkeys matched on body weight to the older CR group, no differences in cage activity were noted. In addition, there was no difference in activity between CR and age-matched controls when the activity measure was multiplied by body weight. Such comparisons in the current study were considered inappropriate. When we examined the correlation between body weight and activity, which was not reported in their study (31), we found no overall significant relationships. If anything, the opposite pattern predicted by the DeLany results prevailed. Specifically, in the O group of monkeys (18–26 yrs) and in the experimental group of A monkeys (11–19 yrs), higher activity was related to higher body weight, although only the latter correlation was significant. The prediction of higher weight with lower activity was observed only among controls in the J group (6–8 yrs), but the correlation was not significant. Moreover, even if this relationship held, the J group of heavier control monkeys had significantly higher activity levels than the lighter CR monkeys, again opposite to the prediction of DeLany and colleagues (31).

The major finding in the current study is that home cage activity can be measured reliably in female rhesus monkeys and that a marked age-related decline in activity can be demonstrated. This conclusion permits further assessment of activity as a behavioral biomarker of aging consistent with a past strategy developed for this study (33–35) as well as its relevance for use in other studies investigating interventions that purport to alter the rate of aging. Regarding the effects of CR on activity, several conflicting results in monkey studies have now been produced indicating increased, decreased, or no differences in activity (12,13,30,31). Although these discrepant results might be due to various differences in experimental factors, we noted the same diversity of conclusions in the current study in monkeys under identical experimental conditions. Only in the youngest group of monkeys

did we see a significant reduction in activity. If this conclusion remains accurate after further testing, it would, in fact, benefit the generation of other conclusions regarding the effects of CR on other biological parameters indicating retardation of aging; for instance, conclusions regarding beneficial diet effects on various parameters of aging would not be confounded by the anti-aging effects of increased exercise in CR groups. However, additional conclusions regarding age and diet effects will best be assessed in a longitudinal analysis consistent with the goals of our long-term study.

In addition, the current results might also be interpreted in the future regarding possible neurobiological mechanisms underlying the age-related decline in activity. Major hypotheses regarding this phenomenon have focused upon the ascending dopamine system (1). Consistent with our observations, Emborg and colleagues (36) reported an age-related decline in home cage activity in a small group (n = 11) of male and female rhesus monkeys. Post-mortem anatomical analysis found an age-related decline in dopamine neurons in the substantia nigra, with the number of neurons correlated with the level of activity that had been recorded. Investigating a small group (n = 21) of female squirrel monkeys, Irwin and colleagues (28) found no age-related decline in the number of nigral dopamine neurons, but did note an age-related decline in dopamine content of the substantia nigra (70%) and putamen (30%), but not in the caudate nucleus. In a recent study using positron emission tomography (PET) to examine NIA male monkeys, Morris and associates (37) observed an age-related decline in dopamine D_2 receptor binding potential in the caudate–putamen. Additionally, Morris (37) and Matochik (38) and colleagues found a marked age-related decline in striatal volume in the same monkeys. Further imaging analysis of our monkeys could provide the opportunity for correlating age-related declines in locomotor activity with specific neurobiological parameters. Post-mortem analyses of striatal D_2 receptor binding in male rats have found that the age-related decline in this neurobiological parameter can be retarded by CR (39,40). Thus, using the methodology validated in the current effort, additional longitudinal analyses of locomotor activity in both female and male rhesus monkeys and male squirrel monkeys are planned as part of this long-term study.

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