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Executive System Dysfunction in the Aged Monkey: Spatial and Object Reversal Learning

ZONA C. LAI,* MARK B. MOSS,*†‡ RONALD J. KILLIANY,* DOUGLAS L. ROSENE*‡ AND JAMES G. HERNDON‡

*Department of Anatomy and Neurobiology and †Department of Neurology, Boston University School of Medicine, Boston, MA 02118
‡Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30322

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LAI, Z. C., M. B. MOSS, R. J. KILLIANY, D. L. ROSENE AND J. G. HERNDON. *Executive system dysfunction in the aged monkey: Spatial and object reversal learning.* NEUROBIOL AGING **16**(6) 947-954, 1995.—As part of an effort to characterize age-related cognitive changes in executive system function in a nonhuman primate model of human aging, the performance of seven rhesus monkeys, 20 to 28 years of age, was compared to that of five young adult monkeys, 6 to 11 years of age, on spatial and object reversal tasks. No differences in performance were found between the two groups in the initial learning of either task. On spatial reversals, aged monkeys were impaired relative to young adults, but there was no difference in overall performance between the groups on object reversals. Central to this article, a perseverative tendency was noted in the aged group on both spatial and object reversal tasks. Changes in executive system dysfunction may represent an important aspect of age-related cognitive decline.

Aging Reversal learning Discrimination learning Hippocampus Executive function *Macacca mulatta* Monkey

EFFORTS to characterize age-related cognitive changes in humans have focused on short-term memory function and consistently yield evidence for a mild decline with normal aging (3,19). More recently, age-related disruptions have been demonstrated in executive function, a domain of cognitive abilities that include abstraction, establishment of set, and set shifting (2,3).

Like aged humans, aged rhesus monkeys exhibit a mild but significant decline in short-term, recognition memory relative to young adults (6,14,20,22). Less is known about executive function in the aged nonhuman primate. Reversal learning involves responding to a change in reinforcement contingencies by first "unlearning" or breaking the initial stimulus-reinforcement bond, and then acquiring, or "shifting" to a new one. In this way, reversal learning can be considered a measure of executive function. The few studies that have assessed executive function in aged monkeys have used pattern discrimination reversal learning paradigms (7,23). Previous findings on reversal learning in aged monkeys appear contradictory, with Bartus et al. (7) reporting severe age-related impairment but with Rapp (23) reporting no deficit in such tasks in aged monkeys. Accordingly, the aim of the present investigation was to determine the nature and extent of executive function changes that may occur in aged rhesus monkeys using spatial and object reversal learning paradigms. In further characterizing the nature of any age-related deficit in reversal tasks, apparent contradictions in earlier studies might be reconciled. This study is part of an ongoing investigation to develop a nonhuman primate model of cognitive and neurobiological changes in human aging.

METHOD

Subjects

The 12 rhesus monkeys in this sample included a group of 5 young adult monkeys (aged 6 to 11 years) and 7 aged monkeys (aged 20 to 28 years); exact birthdates, and thus age at test, were available for all animals. Sex distribution in the two groups is shown in Table 1.

[1]Requests for reprints should be addressed to Mark Moss, Ph.D., Department of Anatomy and Neurobiology, Boston University School of Medicine, 80 E. Concord Street, W701, Boston, MA 02118.

TABLE 1

SUBJECT DESCRIPTION

Group	Monkey	Sex	Age at Testing
Young adult (n = 5)	AM35	M	6
	AM22	M	7
	AM32	M	8
	AM33	M	11
	AM39	M	11
Mean			8.6
(SD)			(2.3)
Aged (n = 7)	AM38	F	20
	AM48	M	20
	AM19	F	24
	AM26	F	24
	AM30	F	25
	AM29	M	27
	AM27	M	28
Mean			24.0
(SD)			(3.1)

Monkeys are listed from youngest to oldest.

The following exclusionary criteria were applied in subject selection: history of chronic illness, neurological disease, chronic drug administration, participation in drug studies, exposure to radiation, and splenectomy or thymectomy. During the study, monkeys were maintained in individual primate cages at the Boston University School of Medicine or the Yerkes Regional Primate Center, both AALAC accredited institutions. Monkeys were routinely fed dry food biscuits each morning and given fresh fruit each afternoon. On test days, feeding was delayed until after testing. Water was always available in home cages. All animals were visually inspected on a daily basis by animal care personnel and research technicians, and received biannual medical examinations that included serum chemistry, hematology, urine and fecal analysis, and annual fundoscopy. Prior to the study, each monkey was assessed on a series of two-choice discrimination and visual recognition memory tasks, the latter of which included delayed nonmatching to sample and spatial and nonspatial delayed recognition span tests (15).

Behavioral Testing

Efforts to standardize test administration at the two sites included identical experimenter training protocols, extensive test supervision with videotaped monitoring, and comparison of normative data acquired from young adult monkeys at both sites, which consistently yield no significant differences for our aging study test protocol. Half the monkeys, 3 young adult (AM35, AM22, and AM32) and 3 aged (AM38, AM48, AM19) were tested at the Boston University School of Medicine and the remaining half were tested at the Yerkes Regional Primate Center.

Testing was conducted in a darkened room in the presence of white noise. Monkeys were trained on both spatial and object reversal tasks in a Wisconsin General Testing Apparatus (10). In both tests, the stimulus tray was concealed from the monkey by an opaque screen. Raisins, cereal, or uniformly small pieces of fruit were used as bait. The experimenter baited and covered the appropriate well on the stimulus tray, according to the test protocol. The opaque screen was then removed and the monkey's response was observed through a one-way vision panel. A noncorrection procedure was used throughout so that an incorrect response terminated the trial without reward.

Spatial reversal task. A stimulus tray board containing three identical, equally spaced wells was used for testing. According to random selection, either the left or right well was designated the positive baited side during initial learning. This positive side was baited and covered with a plastic plaque. An identical plaque covered the other lateral well. The middle well was never baited or covered. The monkey could obtain the reward by displacing the plaque on the appropriate side. During a 20-s intertrial interval (ITI), the screen separating the monkey from the experimenter was lowered and the same side was baited for the next trial. Thirty trials were given per day for the initial learning phase.

When the monkey attained a criterion of 90% correct responses in 30 consecutive trials, a series of three reversals began with the correct side changing in each reversal. The first reversal began the day after initial learning criterion was reached. In each reversal, the monkey was only rewarded when it chose the side that had not been rewarded in the previous learning phase. The first reversal was continued for 30 trials/day until a criterion of 90% correct in the first 20 trials of the day was reached. On that same day, the second reversal began for another 20 trials. Thereafter, 30 trials/day were given baiting the new side until a criterion of 18 of 20 trials was reached in the first 20 trials administered that day. In that session, the third and final reversal began, in which the opposite position was baited for an another 20 trials. Testing continued for 30 trials/day until the final criterion was reached. Thus, during reversal learning, a minimum of 30 trials/day and a maximum of 40 trials/day (on the day criterion was reached) were administered over a total of three reversals; the first between sessions and the last two within sessions.

Object reversal task. The object reversal task was administered after the spatial reversals were completed and was similar to the spatial reversal with two differences. First, two objects were used to cover the extreme wells and one of the two (rather than a position) was randomly chosen as the initial baited. Second, the location of the two objects (left or right) was varied from trial to trial according to the pseudorandom sequence of Gellerman (8) so that location did not serve as a relevant cue.

Analyses

A Wilcoxon Signed Ranks test was used to compare difficulty level between spatial and object reversal tests. Performances of the two groups were compared on errors made and trials required during initial learning as well as for total errors and trials combined across reversals. The Mann–Whitney U test was conducted to examine the statistical significance of between group differences.

A learning stage analysis was conducted by examining 10-trial blocks to evaluate patterns of reversal acquisition (12). This allowed group comparison of blocks concentrated in a specific learning stage (or stages) from reversal through criterion. Criterion blocks were excluded from analyses. Stage I was defined as performance in which 7 to 10 errors are made within a 10-trial block; Stage II was defined as performance in which 4 to 6 errors are made within a 10-trial block; Stage III was defined as performance in which 0 to 3 errors are made within a 10-trial block. This procedure is similar to that used in an earlier study (12) to assess performance of spatial and object reversal learning for monkeys that underwent surgical ablation of various limbic regions. An important modification from the earlier study consisted of using 10-trial blocks instead of 30-trial blocks for two