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Cognitive Function in Aged Ovariectomized Female Rhesus Monkeys

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To determine whether ovariectomy exacerbates age-related cognitive decline, the performance of 6 aged monkeys that had been ovariectomized early in life (OVX-Aged) was compared to that of 8 age-matched controls with intact ovaries (INT-Aged) and that of 5 young controls with intact ovaries (INT-Young) in tasks of visual recognition memory, object and spatial memory, and executive function. The OVX-Aged monkeys were marginally more impaired than the INT-Aged monkeys on the delayed nonmatching-to-sample with a 600-s delay. In contrast, they performed significantly better than the INT-Aged controls on the spatial condition of the delayed recognition span test. The hypothesis that prolonged estrogenic deprivation may exaggerate the age-related decline in visual recognition memory will require additional support. However, the findings suggest that long-term ovariectomy may protect against the development with aging of spatial memory deficits.

The influence of gonadal steroid hormones on brain structures and cognitive function has been well documented. For example, early influences of gonadal hormones during development (organizational influences) and later influences during adulthood (activational influences) have been shown to affect brain organization and a variety of reproductive and nonreproductive sexually dimorphic behaviors (Collaer & Hines, 1995; Goy & McEwen, 1980; Williams & Meck, 1991). In recent years, a number of animal and human studies have focused on the activational effects of estrogen on cognition in females. For example, it has been found that women's performance on some sexually dimorphic tasks fluctuates with estrogen levels across the normal menstrual cycle. During the preovulatory and midluteal phases of the menstrual cycle, when estrogen levels are high, verbal and manual motor skills are at their peak, but spatial skills are poor; during menstruation, when estrogen levels are low, spatial skills improve and verbal and manual skills decline (Broverman et al., 1981; Hampson, 1990a, 1990b; Hampson & Kimura, 1988; Komnenich, Lane, Dickey, & Stone, 1978; Silverman & Phillips, 1993). Cyclic variation in verbal memory has also been reported, with better performance during periods in which estrogen is high (Phillips & Sherwin, 1992b).

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Because most women undergo permanent loss of ovarian function at some time in their lives, whether through ovariectomy or menopause, it is important to examine whether declining levels of estrogen affect cognitive function in women. One study (Sherwin & Tulandi, 1996) investigated the effects of complete suppression of ovarian function in young women through administration of a gonadotropin-releasing hormone agonist. Such treatment resulted in impairments in verbal memory that were later reversed in a subset of the women who were given estrogen replacement therapy (ERT), but not in those given a placebo.

If estrogen deficiency is related to declining cognitive capacity in women, one might expect menopause to exacerbate the cognitive deficits that accompany normal aging. In fact, studies comparing pre- and postmenopausal age-matched women have found impairments in at least some cognitive functions in the latter compared with the former group of women. Halbreich et al. (1995) reported, for example, that a variety of skills, including simulated automobile driving, reaction time, and some visuospatial tests were impaired in menopausal women compared with premenopausal women. Some postmenopausal cognitive deficits may be improved or even reversed by ERT. For example, numerous studies have reported improvements in verbal memory (Campbell & Whitehead, 1977; Hackman & Galbraith, 1976; Phillips & Sherwin, 1992a; Sherwin, 1988), visual memory (Resnick, Metter, & Zonderman, 1997), reaction time (Fedor-Freybergh, 1977), attention (Fedor-Freybergh, 1977; Sherwin, 1988; Vanhulle & Demol, 1976), sensorimotor speed (Hogervorst, Boshuisen, Riedel, Willeken, & Jolles, 1999), and abstract reasoning (Jacobs et al., 1998; Sherwin, 1988) in postmenopausal women undergoing estrogen therapy. Other studies, however, have failed to detect memory improvements after ERT in menopausal women (Barrett-Connor & Kritz-Silverstein, 1993; Matthews, Cauley, Yaffe, & Zmuda, 1999; Polo-Kantola et al., 1998). Nevertheless, recent reviews (Resnick et al., 1997; Sherwin, 1997) concluded that the literature, considered as a whole, suggests that (a) estrogen helps to maintain aspects of verbal and visual memory in women, and (b) cognitive changes due to estrogen deprivation are reversible.

In addition, estrogens may have a therapeutic role in ameliorating the cognitive deficits, mood disorders, and social withdrawal that occur in Alzheimer's disease (Backstrom, 1995; Fillit et al., 1986; Henderson, 1997; Henderson, Paganini-Hill, Emanuel, Dunn, & Buckwalter, 1994; Henderson, Watt, & Buckwalter, 1996; Ohkura et al., 1994). ERT may also reduce a woman's risk of dementia in advanced age (Henderson et al., 1994; Kawas et al., 1997; Mortel & Meyer, 1995; Paganini-Hill & Henderson, 1994, 1996; Tang et al., 1996).

Recent findings have suggested plausible biological mechanisms by which estrogens may influence cognition (reviewed by McEwen et al., 1997). Estrogen receptors are found in several nonreproductive brain regions, including the hippocampus, a structure known to be involved in learning and memory processes, and which may play a crucial role in mediating estrogen effects on cognition. It has been demonstrated, in cultured neurons (Brinton, Tran, Proffitt, & Montoya, 1997) and in vivo (McEwen et al., 1997), that estrogens increase the number of dendritic spines of hippocampal and cortical neurons of rats. Synaptogenesis in the CA1 subfield of the hippocampus also fluctuates with the estrous cycle in female rats (for reviews see Woolley, 1998, 1999). It has been proposed that estrogens may also act, through alterations of cholinergic neurotransmission, to modulate hippocampal function and memory (Gibbs, 1998). Neuroimaging studies have revealed that ERT affects brain activity in women: Using positron emission tomography (PET), Berman et al. (1997) found that young women temporarily treated with a gonadotropin-releasing hormone agonist did not show the normal increase in regional cerebral blood flow (rCBF) in the prefrontal cortex when performing the Wisconsin Card Sort Test. However, the normal pattern of activation in the prefrontal cortex was restored after estrogen or progesterone administration. A number of differences in brain activation patterns as detected by PET (Resnick, Maki, Golski, Kraut, & Zonderman, 1998) or functional magnetic resonance imaging (Shaywitz et al., 1999) have also been found between ERT users and nonusers in postmenopausal women confronted with verbal and nonverbal tasks. Altogether, these data show that estrogen alters brain functioning in young and aged women.

Despite the large number of studies supporting a positive link between estrogens and cognition in menopausal women, some recent reviews have pointed out that the evidence for this link is rather unconvincing, due to the lack of valid and reliable measures of cognitive performance as well as a variety of confounding factors inherent in studies on women (Barrett-Connor, 1998; Birge, 1997; Haskell, Richardson, & Horwitz, 1997; Rice, Graves, McCurry, & Larson, 1997; Yaffe, Sawaya, Lieberburg, & Grady, 1998). These limitations include difficulty in matching treatment groups of women according to lifestyle and educational level, possible biases in participant selection, and ethical limitations on the use of invasive experimental procedures. The rhesus monkey model minimizes these limitations and allows control over environmental factors such as housing condition, subject's rearing and experimental history, and experimental factors like testing schedule and ability to change the hormonal milieu. In addition, rhesus monkeys share numerous cognitive and physiological characteristics with humans. First, the time course of circulating gonadotropic hormones during the menstrual cycle of the female rhesus monkey is essentially identical to that described in women (Knobil, 1974). Second, the decline of ovarian functions in female macaques during the third decade of life parallels the menstrual and hormonal events associated with menopause in women (Gilardi, Shideler, Valverde, Roberts, & Lasley, 1997; Walker, 1995). Third, rhesus monkeys are capable of complex cognitive behaviors such as short-term memory, executive function, and spatial ability, all of which undergo an age-related decline closely resembling that observed in humans (Albert & Moss, 1996; Bachevalier et al., 1991; Bartus, Fleming, & Johnson, 1978; Herndon, Moss, Rosene, & Killiany, 1997; Lacreuse, Herndon, & Moss, 1998; Moss, Killiany, & Herndon, 1999; Rapp, 1990). Finally, the lifespan of the monkey has been well-characterized (Tigges, Gordon, McClure, Hall, & Peters, 1988), and the brain and many of its structural elements have been thoroughly studied across the lifespan (Andersen, Zhang, Zhang, Gash, & Avison, 1999; Gallagher & Rapp, 1997; Herndon, Tigges, Klumpp, & Anderson, 1998; Peters, Morrison, Rosene, & Hyman, 1998; Peters et al., 1996; Smith, Roberts, Gage, & Tuszynski, 1999).

To our knowledge, however, only two studies have examined the effects of ovarian hormones on cognitive functions in adult nonhuman primates. Voytko and Hinshaw (1996) reported deficits in a measure of visual attention after ovariectomy in cynomolgus monkeys, and Roberts, Gilardi, Lasley and Rapp (1997) showed that postmenopausal rhesus monkeys are impaired in the delayed response task compared with age-matched premenopausal females. These findings demonstrate that the hormonal state of the female monkey plays an important role in modulating some cognitive functions.

The goal of the present experiment was to examine the effects of prolonged deprivation of estrogenic stimulation on cognitive functions in aged female rhesus monkeys. We compared the performance of long-term ovariectomized female rhesus monkeys with that of age-matched females with intact ovaries on a broad battery of tasks designed to test visual recognition memory, object and spatial memory, and executive functions. To determine whether long-term ovariectomy exacerbates normal age-related cognitive decline, the aged females were also compared to a group of intact young females.

We tested two hypotheses. First, because estrogen deficiency has been found to impair memory functions both in aged women (Sherwin, 1997) and aged monkeys (Roberts et al., 1997), we expected the OVX-Aged monkeys to be more impaired than the INT-Aged monkeys, relative to the INT-Young females, in tasks of visual recognition memory. The second hypothesis was based on reports in young women (e.g., Hampson, 1990a, 1990b, 1995) and female rodents (e.g., Fugger, Cunningham, Rissman, & Foster, 1998; Galea, Kavaliers, Ossenkopp, & Hampson, 1995; Rissman, Wersinger, Fugger, & Foster, 1999) showing deleterious effects of estrogens on spatial functions. We tested the hypothesis that the OVX-Aged females would outperform the INT-Aged monkeys in tasks of spatial memory.

Method

Subjects

Six aged ovariectomized (OVX-Aged) female rhesus monkeys (*Macaca mulatta*), between the ages of 19 and 27 years (M = 21.4, SD = 3.02), 8 aged female rhesus monkeys with intact ovaries (INT-Aged) between the ages of 19 and 27 years (M = 22.9, SD = 2.8), and 5 young intact females

(INT-Young) between the ages of 4 and 7 years ($M = 5.4$, $SD = 1.12$) were used. The OVX-Aged subjects had been ovariectomized at a mean age of 9.2 years and had therefore been without ovaries for most of their adult lifetime (see Table 1). All but 1 of these subjects, however, had received ERT for brief periods of time ranging from 3 months to 1 year, but none had received ERT during a period of at least 1 year prior to this study. Data from the INT-Aged and INT-Young females were available as part of our ongoing project on normal cognitive aging in the rhesus monkey (Herndon et al., 1997). Four of the INT-Aged females did not complete the entire test battery because some tests were added after they completed the study. The hormonal status of the INT-Aged females was not known. Because of their age, however, we can assume that at least some of these monkeys, especially those above 25 years old ($n = 2$) were menopausal or perimenopausal (Gilardi et al., 1997; Walker, 1995).

Procedure

Monkeys were tested in a Wisconsin General Testing Apparatus (WGTA; Harlow, 1949) on seven cognitive tasks presented in the following order: the acquisition phase, the 120-s and the 600-s delays of the delayed nonmatching-to-sample (DNMS) task, the spatial and object conditions of the delayed recognition span test (DRST), and the spatial and object conditions of the reversal test. These tasks have been described elsewhere (Herndon et al., 1997).

To administer tests in the WGTA, the experimenter sits behind a one-way screen facing a tray containing three 1-cm-deep food wells that can be baited with desirable food, such as raisins or cereals. The central well is directly in front of the monkey; the two lateral wells are 14 cm to either side. The stimulus objects are of such a size that each completely covers one well. Between trials, the tray is concealed from the monkey by an opaque screen.

DNMS

The DNMS tests visual recognition memory by requiring the subject to discriminate a novel stimulus from a familiar stimulus after a specific delay. Objects are randomly drawn from a pool of 600 junk objects. During the acquisition phase of the DNMS, a sample object is first presented over the baited central well of the tray described above. The monkey must displace the object to obtain the reward. The experimenter then closes the opaque screen and, 20 s later, lifts the screen to reveal the sample object plus a new object in one of the lateral food wells. The position of the objects is determined randomly. The reward is placed under the novel object, and the monkey must displace the novel object to obtain the reward. Twenty trials (20 pairs of objects) per day are given until the monkey reaches a learning criterion of 90 correct responses in 100 consecutive trials. The number of trials to reach criterion and the number of errors are the dependent variables. After the monkey reaches this criterion, a delay of 120 s is introduced between the presentation of the sample and the recognition phase. Ten trials a day for 10 days are given, followed by another 100 trials with a 600-s delay. The percentage of correct responses for each delay is the dependent variable.

DRST

The DRST requires subjects to identify a new stimulus among an increasing set of familiar, serially presented stimuli.

Spatial condition. For this task, the test tray consisted of 18 food wells arranged in a 3 × 6 matrix. The stimuli were identical brown disks (4 cm in diameter). On the first trial of the first chain of trials, one well was baited with a food reward and covered by one of the disks. Once the monkey had displaced the disk and obtained the food reward, the well was again covered but not rebaited. Ten seconds later, a second well was baited and covered with another disk. The tray with the two disks was presented to the monkey, which was required to choose the disk in the new position to obtain the food reward. Similarly, each successive correct response was followed by the addition of a single new disk until the monkey made an error. Ten such chains of trials were presented each day for 10 days. The location of the disks was randomly determined. The mean number of stimuli correctly identified before an error was made was the dependent variable, and is referred to as *spatial memory span.*

Object condition. The stimuli for the object condition were different objects instead of identical disks. On each trial, the position of the previously correct stimulus was changed in a predetermined random fashion so that the monkey was able to identify the new stimulus on the basis of visual, rather than spatial, cues. The stimuli for the object condition were drawn from a pool of 600 junk objects.

Reversal Task

The reversal task assesses the monkey's capacity to change a response pattern with changing reinforcement contingencies.

Spatial reversals. Testing on spatial reversals used a three-well test tray. The stimuli consisted of two identical plastic plaques. Either the left or the right side was designated as the positive side for initial learning. The monkey obtained a reward by displacing the plaque covering the side designated as positive. Twenty seconds later, the next trial was begun by again baiting the positive lateral well. Thirty trials per day were given until the monkey reached a criterion of 18 correct responses in the first 20 consecutive trials in one session. Once the monkey had reached criterion, the first reversal was introdnced in the same session: Without any indication to the monkey, the previously unrewarded location was rewarded and the previously rewarded location was no longer rewarded. Twenty addi-

Table 1
Designation, Age (Years), Age at the Time of Ovariectomy (Years), Duration of Estrogen Deficiency (Years), and Approximate Duration of Estrogen Replacement Therapy (ERT) for Each OVX-Aged Monkey

Designation	Age at the time of the experiment (years)	Age at the time of ovariectomy (years)	Duration of estrogen deficiency (years)	ERT history
REr	18.8	10.0	8.8	1 year
OPE367	19.8	6.9	13.0	1 month
OPE361	19.9	7.6	12.3	Never treated
RKn	20.9	7.3	13.6	1 year
RQl	21.9	14.3	7.6	1 year
28	27.2	9.3	17.9	6 months
M	21.4	9.2	12.2	9 months

tional trials of this reversed condition were given (40 trials total on criterion days). Testing continued for 30 trials per day until the monkey once again reached a criterion of 18 correct responses in the first 20 consecutive trials in one session. A total of three reversals were given. The dependent variables were the number of trials required to reach criterion and the number of errors made for all three reversals.

Object reversals. The stimuli consisted of a single pair of objects. The objects were presented at predetermined pseudorandom locations on the test tray so that the monkey had to identify the rewarded stimulus on the basis of visual, rather than spatial, cues. In a balanced design, one object in the pair was selected as the original positively rewarded object for initial learning. Testing took place for a total of 3 reversals.

Analysis

Performance of the three groups of monkeys (OVX-Aged, INT-Aged, and INT-Young) on the acquisition and delay conditions of the DNMS, on the spatial and object conditions of the DRST, and on the spatial and object conditions of the reversals were analyzed by means of analyses of variance (ANOVAs). Tukey's honestly significant difference (HSD) was used as a post hoc test. Because the number of subjects was uneven across the two delay conditions of the DNMS, performance on each delay was first analyzed separately. In addition, we also used a repeated measure ANOVA (Ovarian Status × Delay) to analyze the performance of the smaller number of aged monkeys that completed both delays of the DNMS.

Regression analyses were used to examine the effect of the duration of estrogen deficiency and age at the time of ovariectomy on cognitive performance among the OVX females. An alpha value of .05 (two-tailed) was adopted for all analyses.

Results

Age Effects

Performance on all tests of cognitive function is summarized in Table 2. As expected, the INT-Young females performed significantly better than the INT-Aged females on the 120-s delay of the DNMS, the spatial and object conditions of the DRST, and the number of errors on the spatial reversals. On the 600-s delay of the DNMS, however, the INT-Aged monkeys did not show significant impairments relative to their young counterparts. The number of subjects involved in this test may have been too small to detect reliable differences between the young (n = 5) and older (n = 5) intact females, such as those reported in a previous study (Rapp & Amaral, 1989).

Effects of Ovarian Status

On the DNMS, a repeated measures ANOVA revealed that the performance of all three groups of monkeys differed significantly, $F(2, 13) = 10.77$, $p < .01$. Additionally, the monkeys achieved generally lower scores in the 600-s delay condition than in the 120-s delay condition, $F(1, 13) = 14.80$, $p < .01$. Post hoc analyses (Tukey's HSD) indicated that both the OVX-Aged and the INT-Aged monkeys were impaired relative to the INT-Young monkeys on the 120-s condition of the DNMS (see Figure 1a). On the 600-s delay condition of the DNMS, however, only the OVX-Aged monkeys were significantly impaired relative to the INT-Young monkeys ($p < .01$). Their performance showed a tendency

Table 2
Mean (±SEM) Performance, Number of Monkeys (n), and Post Hoc Test Results for Each Cognitive Task

Group	DNMS Trials to criterion	DNMS Errors to criterion	DNMS 120 s (% correct)	DNMS 600 s (% correct)	DRST Spatial (Span)	DRST Object (Span)	Spatial Rev Trials to criterion	Spatial Rev Errors to criterion	Object Rev Trials to criterion	Object Rev Errors to criterion
INT-Aged										
M	672.62	182.00	78.63	74.20	1.98	2.97	305.00	106.83	203.33	74.83
SEM	202.90	56.63	2.41	2.75	0.08	0.42	41.37	13.21	42.95	14.36
n	8	8	8	5	7	4	6	6	6	6
OVX-Aged										
M	542.17	123.67	78.67	65.00	2.22	3.27	238.33	80.50	220.00	80.67
SEM	106.57	23.66	3.12	3.12	0.04	0.06	23.72	10.54	36.05	10.17
n	6	6	6	6	6	6	6	6	6	6
INT-Young										
M	272.00	60.20	88.20	83.40	2.27	4.47	210.00	66.60	142.00	43.40
SEM	71.51	14.46	1.16	2.93	0.07	0.31	16.43	5.12	20.59	4.14
n	5	5	5	5	5	5	5	5	5	5
Total										
M	526.00	131.53	81.16	73.63	2.14	3.59	253.53	85.70	191.18	67.65
SEM	97.40	26.86	1.69	2.53	0.05	0.22	19.21	7.11	21.07	7.15
n	19	19	19	16	18	15	17	17	17	17
				Results of Tukey's HSD tests						
INT-Young vs. INT-Aged	*ns*	*ns*	$p < .05$	*ns*	$p < .02$	$p < .01$	*ns*	$p = .05$	*ns*	*ns*
INT-Young vs. OVX-Aged	*ns*	*ns*	$p = .06$	$p < .01$	*ns*	$p < .02$	*ns*	*ns*	*ns*	$p < .10$
INT-Aged vs. OVX-Aged	*ns*	*ns*	*ns*	$p = .10$	$p < .05$	*ns*	*ns*	*ns*	*ns*	*ns*

Note. DNMS = delayed non-matching-to-sample; DRST = delayed recognition span test; Rev = reversals; OVX = ovariectomized; INT = intact.

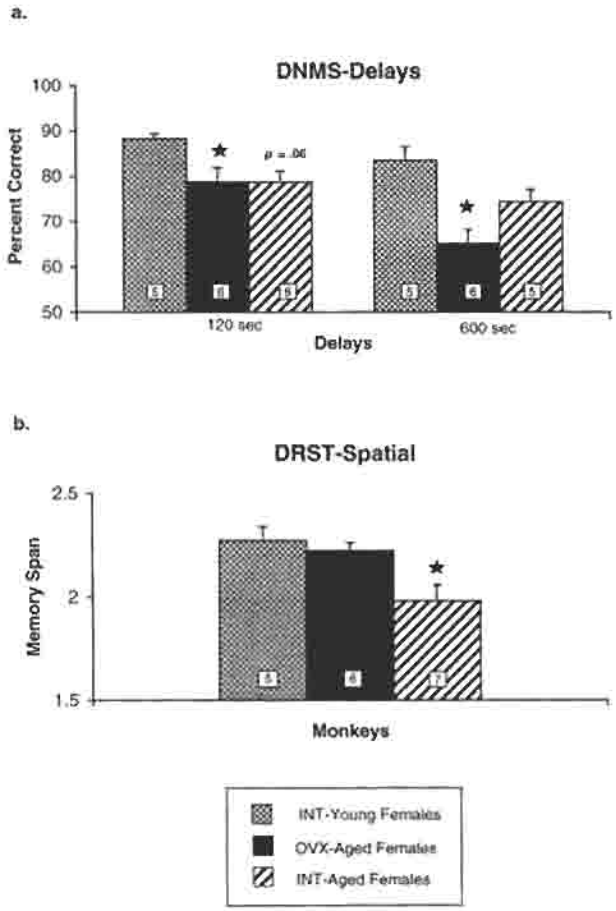


Figure 1. Representation of the performance (M + SEM) of the intact young (INT-Young) female monkeys, the ovariectomized aged (OVX-Aged) females, and the intact aged (INT-Aged) females (a) on the 120-s and 600-sec delay conditions of the delayed nonmatching-to-sample test (DNMS) and (b) on the spatial condition of the delayed recognition span test (DRST). The number of females in each group is given inside each bar. The OVX-Aged females tended to differ from the INT-Aged females on the 600-s delay of the DNMS and differed significantly from the INT-Aged females on the spatial condition of the DRST. * Differences from the INT-Young monkeys, $p < .05$.

of borderline significance to be lower than that of the INT-Aged monkeys ($p = .10$). The interaction between ovarian status (OVX, INT) and delay among the old monkeys was only of borderline significance, $F(1, 9) = 3.30$, $p = .10$.

The OVX-Aged, INT-Aged, and INT-Young monkeys differed significantly on the spatial condition of the DRST, $F(2, 15) = 5.86$, $p < .02$. Post hoc analyses revealed that the INT-Aged females were impaired compared with the INT-Young females on this test ($p < .02$). They were also outperformed by the OVX-Aged group ($p < .05$) which achieved a level of performance equivalent to that of the INT-Young (Figure 1b).

Performance on the acquisition of the DNMS, the object DRST, and the spatial and object reversals did not differ between the OVX-Aged and the INT-Aged females.

Regression analyses indicated that the performance of the OVX-Aged females on the 600-s delay of the DNMS and on the spatial condition of the DRST was not significantly related to the duration of estrogen deficiency ($r = -0.56$, *ns*, and $r = -0.58$, *ns*, respectively) or to the age at which the ovariectomy was performed ($r = 0.008$, *ns*, and $r = 0.057$, *ns*, respectively).

Discussion

Earlier reports on cognitive aging in the monkey, including our own studies, have disregarded the potential effects of endocrine status on age-related cognitive decline. The comparison of the INT-Young and the INT-Aged females replicates some of these earlier findings (Bachevalier et al., 1991; Bartus et al., 1978; Herndon et al., 1997; Rapp, 1990) by showing that aged females are impaired on several cognitive tests relative to young females. The effect of age among the intact females was not significant for the 600-s delay of the DNMS, however, probably due to the small number of INT-Aged subjects ($n = 5$) tested on that task.

The comparison of the OVX-Aged and INT-Aged females suggests that endocrine status may influence the patterns of age-related cognitive decline in this species. First, there was a borderline trend for the OVX-Aged females to be more impaired than the INT-Aged females on the 600-s delay of the DNMS, a task of visual recognition memory. Second, the OVX-Aged monkeys showed better performance than the INT-Aged monkeys on a spatial memory task, the spatial condition of the DRST. None of the other tests yielded significant differences between the OVX-Aged and the INT-Aged females.

The OVX-Aged and INT-Aged monkeys achieved a similar level of performance, lower than that of the INT-Young monkeys, on the 120-s delay of the DNMS. On the 600-s delay of the DNMS, however, only the OVX-Aged females were significantly impaired relative to the INT-Young females. They also tended to differ from the INT-Aged females ($p = .10$). Because the trend was of borderline significance, we must interpret these results with caution. If such a trend exists, it may be explained by a tendency of estrogenic deprivation to exaggerate age-related decline in visual recognition memory in female rhesus monkeys, especially when long delays are implemented. This would be congruent with a previous study (Roberts et al., 1997) that demonstrated greater memory deficits in postmenopausal rhesus monkeys compared with age-matched premenopausal females in a task dependent on frontal function, the delayed response task. Whether the deficits of menopausal rhesus monkeys extend to visual recognition memory, as measured by the DNMS is a question that should be investigated.

A more compelling finding of our study was that the OVX-Aged females obtained greater memory span than the INT-Aged monkeys and achieved a level of performance similar to that of the INT-Young females in the spatial condition of the DRST. This test requires the ability to identify the new position of a stimulus among an increasing set of identical, serially presented stimuli. Performance on the spatial DRST is disrupted by hippocampal lesions (Beason-Held, Rosene, Killiany, & Moss, 1999), is sensitive to aging in a combined group of males and females (Herndon et al., 1997; Moss, Killiany, Lai, Rosene, & Herndon, 1997), and appears to be influenced by sex hormones, as young males present an advantage over young females in this task (Lacreuse, Herndon, Killiany, Rosene, & Moss, 1999). Furthermore, the present results suggest that the absence of estrogenic stimulation in aged female

rhesus monkeys may also modulate performance on this task and protect against normal age-related decline in certain aspects of spatial memory. A number of findings in women and in female rodents support the hypothesis that estrogens may have deleterious effects on spatial performance. For example, high estrogen levels during the menstrual cycle are associated with impaired spatial performance in young women (Hampson, 1990a, 1990b, 1995). A similar negative association between high estrogen levels and visuospatial performance has recently been found in aged women (Drake et al., 2000). Some, but not all, rodent studies indicate impairments of spatial memory in females when estrogen levels are high (Frye, 1995; Fugger et al., 1998; Galea et al., 1995; McEwen et al., 1997; Rissman et al., 1999; Warren & Juraska, 1997; but see Berry, McMahan, & Gallagher, 1997; Luine, Richards, Wu, & Beck, 1998; Packard & Teather, 1997). Because estrogens induce synapse formation in the hippocampus (Woolley, 1998, 1999), one might expect estrogens to improve hippocampal-dependent memory functioning. However, the evidence so far suggests that estrogens might have facilitative or deleterious effects depending on the cognitive domain involved. Thus, McEwen et al. (1997) proposed that estrogen-induced synapse formation in the hippocampus may enhance verbal memory in humans and working memory in rats, while impairing spatial memory (see also, Desmond & Levy, 1997).

It is worth noting that differences between the performance of OVX-Aged and INT-Aged females were specific to the spatial condition of the DRST, whereas no significant differences were found for the other spatial task of our cognitive battery, the spatial reversals. It is quite remarkable that sex differences favoring young male rhesus monkeys are also restricted to the spatial condition of the DRST and are not observed for the spatial reversals (Lacreuse et al., 1999). Altogether, these findings suggest that the capacity for increasing spatial memory load, as measured by the spatial DRST, is particularly sensitive to sex hormone influences. Because performance on the spatial DRST is dependent on hippocampal function in the rhesus monkey (Beason-Held et al., 1999) and because estrogen deprivation has a well-documented effect on hippocampal morphology and physiology at least in female rodents (e.g., Woolley, 1998, 1999), we may speculate that the lack of estrogenic stimulation in the OVX-Aged females helps to prevent age-related decline in spatial memory by affecting hippocampal organization.

Finally, we failed to find a significant relationship between the age at surgery or the duration of estrogen deficiency and the cognitive performance of the OVX-Aged females. The absence of a significant relationship among these variables is not surprising considering that only 6 OVX-Aged females were involved in the study. Nappi et al. (1999) found, however, that both the age at the time of ovariectomy and the duration of estrogen deficiency correlated significantly with verbal memory scores in ovariectomized women, with earlier surgery corresponding to lower scores. We may speculate that a similar relationship would emerge in female rhesus monkeys with a greater number of subjects.

In conclusion, aged ovariectomized female monkeys and age-matched controls differed significantly in only one of the seven cognitive measures we examined and tended to differ on another test. Specifically, the OVX-Aged females were slightly more impaired than the INT-Aged females on the 600-s delay of the DNMS, but the effect did not reach significance. The hypothesis that estrogen deficiency may exaggerate the age-related cognitive decline in visual recognition memory will require additional support. In addition, the OVX-Aged females showed greater memory spans than the INT-Aged controls in the spatial condition of the DRST. It remains to be investigated whether this advantage is restricted to spatial memory or extends to other aspects of spatial cognition, such as visuospatial perception.

Because this study has a number of limitations, these results must be interpreted with caution. First, we did not obtain hormonal data from our subjects, and some of the intact females might have been menopausal. Second, we did not selectively manipulate estrogen levels, and other factors beside estrogen deficiency might have played a role in the OVX-Aged females' cognitive performance. In addition, the confounding between the duration of ovariectomy and the age of our monkeys prevents us from determining whether the pattern of performance of the OVX-Aged females was due to the long-term deprivation of estrogenic stimulation or to other factors associated with the removal of the ovaries. Despite these limitations, the results suggest that the prolonged absence of the ovaries and their secretions may prevent or lessen age-related decline in certain aspects of spatial memory. Although our study does not identify which effect of ovariectomy is responsible for these ameliorative effects, one might speculate that the normal pattern of estrogen secretion in the intact females helps to mediate the decline in spatial memory. This possibility has potentially important implications for the design of hormonal replacement therapies for postmenopausal women. Future studies should therefore examine whether estrogen deficiency has beneficial effects on some aspects of spatial cognition and whether estrogen treatments reverse some or all of the influences of long-term ovariectomy. Researchers should also seek to elucidate the neural mechanisms of estrogenic effects on cognition.

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