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Sex-Dependent Behavioral Effects of Cerebral Cortical Lesions in the Developing Rhesus Monkey

Abstract. *Male rhesus monkeys with orbital prefrontal lesions were impaired on behavioral tests at 2½ months of age whereas similar deficits were not detected in females with comparable lesions until 15 to 18 months of age. The results suggest that the maturation of a cortical region in the primate brain proceeds at different tempos in males and females.*

The literature of comparative and physiological psychology contains abundant evidence of behavioral differences between the sexes, not only with regard to the more obvious reproductive activities of the species, but in such nonreproductive behaviors as food preferences, emotionality, aggression, and play (*1, 2*). Since differences between the sexes in behaviors such as aggression and play may be construed as intimately bound up with reproductive activities, it is not surprising that these, as well as the more plainly evident sexual behaviors, can be modified by gonadal hormones at critical periods in development (*1*). Further, since gonadal hormones are thought to affect behavior by influencing brain mechanisms (*3*), it would also not be surprising if neural structures subserving sex-typical behaviors were to differ in males and females. Indeed, anatomical differences between male and female rats have recently come to light in studies of the preoptic area, a region of the brain that has been implicated in reproductive function (*4*).

In addition to evidence for differences between males and females in reproductive and related activities, substantial evidence exists from studies of human aptitudes for sex differences in performance on intelligence tests (*5*). However, it is not known to what degree these differences are rooted in cultural patterns and to what degree, if any, they can be attributed to genetically determined dimorphism in neural structures subserving cognitive functions. We have discovered a sex difference in the learning performance of monkeys whose orbital prefrontal cortex had been removed in infancy. Our findings suggest that regions of the neocortex may be sexually dimorphic in nonhuman primates at certain stages of development.

The evidence emerged unexpectedly in the course of experiments concerned with the effects of early cortical and subcortical lesions on cognitive behavior (*6*). The monkeys of relevance to the present report are those that (i) had been given bilateral orbital prefrontal lesions in infancy (1 to 8 weeks) or as juveniles (18 to 24 months) or were age-equivalent unoperated controls; and (ii) had been tested at various ages on an object discrimination reversal task or on spatial delayed-response problems, tests that are interchangeable as measures of the integrity of orbital prefrontal functions (*7*).

In all cases, bilateral lesions were made in one stage under aseptic conditions. Infants were anesthetized with ether or methoxyflurane; juveniles, with sodium pentobarbital (40 mg per kilogram of body weight). The ablation involved removal of cortex on the inferior convexity of the frontal lobe and all of the cortical tissue on the ventral surface of the lobe rostral to the Sylvian fissure and lateral to the olfactory stria (Fig. 1a).

The object reversal test involved training monkeys to discriminate between two objects differing in color, size, and shape. After the animals reached criterion (two successive 30-trial sessions with 90 percent correct in each session), the reward contingencies were reversed so that the previously positive object became negative. The monkey's score for this task was the total number of errors to criterion made over six reversals. In the delayed-response task, the monkey was trained to observe the experimenter conceal a bait in the left or right of two food wells located on a test board in front of the animal. The position of the baited well on successive trials was governed by a modified random order. On any given trial, the monkey could select the baited food well only after an opaque screen had been interposed between the monkey and the test board for up to 5 seconds. In a related task, delayed alternation, the monkey was required to alternate between the left and right food wells on successive trials separated by 5-second intervals. The monkey's score for each of these tasks was the number of trials required to achieve a performance criterion of 90 correct responses in 100 consecutive trials. Detailed procedures for behavioral testing have been described (*6*).

When testing was completed, the brains of the operated monkeys were perfused and processed for histological and anatomical analysis. To date, anatomical results are available for 21 of the operated cases. The remaining monkeys are still being studied.

The first study involved eight early operated and nine unoperated monkeys of both sexes that were tested at 2½ months of age (object reversal). The results (Table 1) showed that the operated males were impaired relative to unoperated males ($P < .032$), while operated females performed as well as unoperated females.

In a second study, 33 monkeys that had been operated in infancy were tested at 12 months of age (delayed response). Eight of these animals had been tested on object reversal at 2½ months of age. Again, the results were sex-dependent: the operated males were impaired compared both to their controls ($P < .02$) and to the operated females ($P < .02$), which in turn did not differ from unoperated females (Fig. 1b). Also, the results were not influenced by prior testing experience. The difference between operated males and operated females was obtained in the monkeys that had been tested previously as well as in those that had not (Fig. 1b).

Examination of the brains by light microscopic methods has so far failed to provide evidence of more pathology in males than in females either with regard to the extent of the lesions or the retrograde degeneration in the dorsomedial nucleus of the thalamus. Thus, the different effects of orbital prefrontal lesions in males and females are probably not due to differences in the size of the lesions. Figure 1, a, c, and d, presents, respectively, reconstructions of the lesions, serial sections through these lesions, and serial sections through the thalamus of a male and female that were tested on delayed response at 12 months of age. The cortical lesions of the two animals were similar, but the retrograde changes in the dorsomedial nucleus were more extensive in the female than in the male. In spite of this, the male and not the female was impaired on delayed response (Fig. 1b).

It is unlikely that this sex-dependent effect of neocortical lesions reflects a permanent difference in the functions of the orbital prefrontal cortex in males and females. All of the monkeys tested at 12 months of age on one of the measures of orbital function (delayed response) were subsequently tested at approximately 15 and 18 months of age on the other measures (delayed alternation and object reversal, respectively). At 15 months of age, more than half of the operated females began to exhibit deficits as severe as those displayed by operated males, and the two groups were not significantly different (Table 1). Nevertheless, it was still the case that only the operated males differed significantly from their unoperated controls ($P < .05$). By 18 months of age, however, the operated females not only performed as poorly as the operated males, but both groups were impaired similarly relative to controls ($P < .05$ in both cases). The results of these longitudinal investigations are consistent with those of two further studies involving independent groups of older monkeys. In one study, monkeys given prefrontal lesions as juveniles and unoperated age-equivalent controls were first tested on object reversal at approximately 24 months of age. In another study, monkeys given orbital prefrontal lesions either in infancy or as juveniles

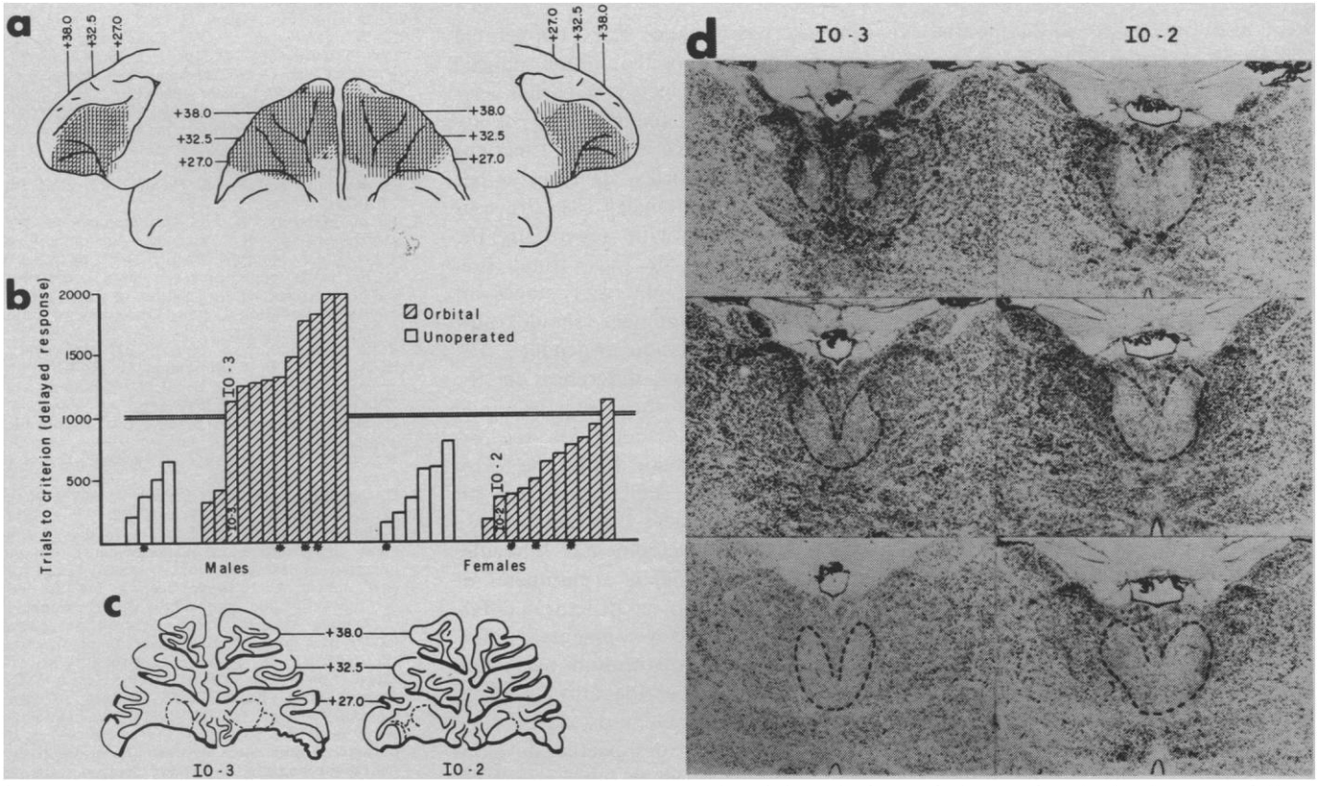

Fig. 1. (a) Examples of two lesions reconstructed on standard ventral and lateral views of the monkey brain. Interrupted lines denote the lesion of IO-2; uninterrupted lines, lesion of IO-3. (b) Performance of 12-month-old monkeys on delayed response. Asterisks indicate monkeys that had previously been tested on object reversal at 2½ months of age. IO-2 and IO-3 are the monkeys whose anatomical data are presented in (a), (c), and (d). (c) Cross sections through the brains of IO-2 and IO-3. Lesions are indicated by heavy lines. (d) Photomicrographs of thalamic degeneration in the brains of IO-2 and IO-3 at 0.5-mm intervals through the anterior portion of the dorsomedial nucleus. The boundaries of the degeneration have been marked by interrupted lines (× 13).

Table 1. Summary of behavioral results. Scores are given as errors to criterion for object reversal and as trials to criterion for delayed alternation; *N*, number of animals. A one-tailed Mann-Whitney U test was used to evaluate differences between operated groups and controls of the same sex; all other comparisons were two-tailed. There were no significant differences between unoperated groups at any age. Operated males were significantly impaired ($P < .05$) relative to unoperated males at all ages, whereas operated females were not impaired ($P < .05$) relative to unoperated females (and unoperated males) until 18 months of age or later. In addition, operated males performed significantly worse than operated females at 12 months of age ($U = 20$, $P < .02$). Estimates of absolute performance levels at different chronological ages are valid only for comparisons between independent groups given comparable test experience at different ages. Animals tested on object reversal at 2½ months versus 24 months or later: animals tested on delayed response at 12 months versus 24 months or later; and those tested on delayed alternation at 15 months versus 27 months or later.

Age at testing (months)	Test	Unoperated			Operated		
		Mean	Range	*N*	Mean	Range	*N*
				Males			
2½	Object reversal	168	120– 236	5	277	192 –360	4
12	Delayed response	430	200– 640	4	1334	310–2000	12
15	Delayed alternation	570	120– 950	4	1487	450–2000	12
18	Object reversal	97	57– 132	4	139	71– 221	12
24+	Object reversal	84	45– 120	3	337	263– 458	3
24+	Delayed response	420	300– 540	4	825	470–1240	4
27+	Delayed alternation	367.5	50– 560	4	1895	1160–2000	8
				Females			
2½	Object reversal	219	163– 244	4	202	131– 261	4
12	Delayed response	455	150– 810	6	619	360–1140	11
15	Delayed alternation	682	60–1380	6	1178	200–2000	11
18	Object reversal	91	54– 145	6	131	82– 221	11
24+	Object reversal	68	51– 91	5	161	89– 301	4
24+	Delayed response	425	120– 760	4	1098	980–1220	4
27+	Delayed alternation	292.5	10– 530	4	2000	2000–2000	4

were also first tested at 24 months of age or older but on delayed response. Animals from both studies were then trained on delayed alternation when they were nearly 27 months of age at the youngest. No significant sex differences emerged on any of these measures (Table 1). Further, both operated females and operated males were markedly impaired relative to controls ($P < .01$ in all instances where statistical tests were necessary). The negative findings in older monkeys are in accord with the lack of evidence in the literature for sex differences in the learning abilities of brain-damaged monkeys.

The present results suggest that, up to about 1 year of age, orbital prefrontal lesions result in impairments on object reversal or delayed response in males compared to females, whereas at later ages, 15 to 18 months and beyond, the lesions induce deficits in both sexes to the same degree. The variety of conditions under which behavioral determinations have been made indicate that neither the age of the animal at surgery, the particular test given, nor interactions between tests are critical factors in these results. Rather, what is important is the sex of the animal and the age at testing. In spite of the similar performance of unoperated groups, the finding that lesion-induced deficits can be detected at earlier ages in males than in females may be regarded as evidence that the functions of the orbital cortex develop earlier in males than in females (*8*). Previous conclusions (*6*) with regard to the functional status of the orbital prefrontal cortex at different stages of ontogenetic development should now be qualified in relation to gender.

A sex-dependent difference in the development of cortical regions could have major implications for the organization of behavior during the formative years and quite possibly for behavioral differences that outlast those years. If so, developmental schedules could be as significant a parameter of sexual dimorphism as structural differentiation itself. Developmental differences in neural maturation may conceivably have a bearing also on many central nervous system disorders, such as cerebral palsy or specific developmental dyslexia, which appear to have a higher incidence in boys than in girls (*9*). To the extent that perinatal injuries are implicated in some forms of these disorders, such injuries may exact consequences with higher probabilities in males than in females because of regional differences in brain growth at the time of insult. Finally, the present findings raise the possibility that developmental disparities between the sexes will be found for other brain regions as well, although the direction of the differences may vary with the behavioral functions involved. However, it is also possible that only structures like the orbital region become functionally mature according to different timetables in males and females because of especially intimate connections with the limbic system and hypothalamus.

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8. Although there was no evidence in the present study of a difference in performance of unoperated males and females at any stage of development, there have been a few reports in intact juvenile and adult rhesus monkeys of female superiority on delayed responses [A. J. Blomquist, thesis, University of Wisconsin (1960), No. 60-5717, University Microfilms (Ann Arbor, Mich., 1960); A. A. McDowell, W. L. Brown, A. C. McTee, *J. Comp. Physiol. Psychol.* **53**, 429 (1960)]. Such findings leave open the possibility that there are more permanent differences between the sexes in the neural mechanisms underlying delayed response than the present study indicates, or that slower development of the orbital cortex ultimately confers a functional advantage on females.
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