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LATERALIZATION OF SPATIAL PREFERENCE IN THE FEMALE RAT

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Summary

Female rat pups were either left undisturbed in infancy and raised in lab cages or were handled in infancy and raised in enriched environments. In adulthood, animals underwent brain surgery consisting of: 1) a right neocortical ablation, 2) a left neocortical ablation, 3) a sham operation, or 4) no surgery. After recovering, they were tested for the initial direction of movement (left or right) in the open field. Nonhandled intact females were biased to move leftward indicating an asymmetrical brain organization. The intact handled-enriched group was unbiased. The right and left lesions caused the animals to move ipsilateral to the lesion, but there was no difference in the magnitude or response in either early experience group. Thus, early experience in the female rat has a different effect then in the male, and the nature of the brain organization in the two sexes is markedly different.

In a recent summary of human clinical and experimental data, McGlone (1) concluded that the female brain was functionally less asymmetrical than the male brain. The evidence, however, is oftentimes contradictory, and neither conclusive nor convincing. The resultant impasse reached after examining this literature suggests the need for an appropriate animal model to explore this phenomenon with the objective of gaining a deeper understanding. Recent research suggests that the rat may be useful for this purpose. Functional asymmetries have been discovered in rats which may be somewhat similar to those observed in humans. Denenberg et al. (2) found that male rats exposed to certain early experiences possess asymmetrical brains. When these animals were tested for activity in the open-field, right and left neocortical ablations produced differing results: in animals given extra stimulation in early life, a right ablation produced a sharp decrease in activity, while a left ablation had no effect. Since activity is a measure of emotional reactivity, with low movement indicating high emotionality, the above data suggested that the right hemisphere may be preferentially involved in emotional processing. This parallels what is found in humans (3,4,5,6).

In a later paper using male rats, neocortical ablations produced different magnitudes of effects on left-right spatial choice in the open field (7). Both right and left ablations caused turning ipsilateral to the side of lesion, but the left lesions produced a greater magnitude of ipsilateral movement. In addition, intact males handled in infancy were biased to move leftward, while nonhandled animals were unbiased. Thus, male rats can have symmetrical or asymmetrical brains, depending on their rearing history. The obvious question is: how is the brain of the female rat organized?

Evidence suggesting that the brains of male and female rats may be differently organized comes from several sources. Diamond, Dowling, and Johnson (8) found morphological differences: the right cortex was thicker than the corresponding left cortical area in male rats; in females the left cortex was thicker than the right although not

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significantly so. The right hippocampus is also thicker on the right side in male rats and thicker on the left in females (9). Ross et al. (10) found that the tails of neonatal female Sprague-Dawley pups were biased to the right while the males showed no significant bias. They also followed a group of these animals into adulthood and found that 85% had a net rotational bias in the same direction as the initial tail posture. We have recently extended these findings by showing that both male and female Wistar pups have a leftward tail bias, with the females more strongly biased than the males (11). These data also suggest that there are strain differences with respect to postural asymmetry.

Since we have previously found that nonhandled males with intact brains showed no spatial bias in our open-field test, while intact handled males were left-biased, we used the same apparatus to investigate the nature of spatial asymmetry in the female.

Methods

The data reported here were obtained from offspring of three separate breeding periods (July, 1978; January, 1979; October, 1979). Female Purdue-Wistar rats from our closed colony were mated and placed into maternity cages. At birth, litters were sexed and reduced to eight pups, with at least four females. Whole litters were then randomly assigned to the nonhandled or handled treatment. Nonhandled rats were immediately returned to their maternity cages and were not disturbed thereafter until weaning at 21 days. Pups in the handled litters were placed individually for three minutes into one gallon cans containing shavings, and then returned to their maternity cages. This procedure was repeated daily from Day 1 through Day 20.

On Day 21 the handled females were placed into enriched environments. These are large cages which contain a number of playthings and are identical in physical dimensions to the units used by the Berkeley group (12). The nonhandled females were placed by littermate pairs into standard laboratory cages. On Day 50 the rats from the enriched environment were also placed by pairs into laboratory cages. By Day 70 all animals were isolated. This provided us with two treatment groups which in past studies were different on measures of functional asymmetry: handling plus enriched environment experience and nonhandling plus laboratory cage experience.

In adulthood (age ranged from 60 to 140 days of age), the four females within a litter were randomly assigned to one of four surgical procedures: 1) left-hemisphere neocortical ablation, 2) right-hemisphere neocortical ablation, 3) a sham operation, or 4) no surgery. Surgical procedures were performed under deep Equithesin anesthesia (dosage: 2.5 ml/kg body weight). After midline incision of the scalp and retraction of the overlying muscle and connective tissue a bone defect was made, exposing one of the cerebral hemispheres. In the ablation groups, after the dura mater was cut and laid aside, the neocortex of one hemisphere was removed by gentle suction through a glass pipette. The intended area of ablation included virtually all of the neocortex from pole to pole in an anterior-posterior direction, and from the saggital to the rhinal fissures mediolaterally.

After a recovery period of 30 days, all animals were tested for three minutes in an open field (114 cm square and subdivided into 25 23-cm. squares) for four successive days. Two animals were tested at a time by one observer. The two fields were placed next to each other. L-shaped barriers were placed into the adjacent corners of the two fields, thus creating square cells into which each animal was put (7). A timer was started and, when 10 seconds had lapsed, the barriers were removed and the 3-minute observation interval started. Thus, the removal of the barriers was independent of the position of the rat in the starting square. For those animals which did move from the starting square, we recorded whether they moved along the left-hand wall, the right-hand wall, or into one of the center squares. A movement was defined as having occurred when all four feet entered the adjacent square. Since the two open fields were set orthogonally, we were able to control for possible asymmetries in room lighting, observer's position, nearness of the fields to the walls of the room, etc. Thus, if both animals moved left, or right, they would be moving at right angles to each other. As a further control, on the second test day the rats were switched and placed in the other field; they were switched on the third and fourth test days as well. Finally, the testers were blind with respect to the experimental treatments the animals had received.

Location and extent of neocortical ablation was determined for the brains of animals from two of the three breeding periods (January, 1979, N = 35; October, 1979, N = 23). Drawings were first made of the lesions on standard Lashley diagrams. Next the location of spared cortex within predetermined frontal, parietal, lateral, occipital and temporal areas was measured on the diagrams. A two-way analysis of variance was performed with left or right side of lesion and the five locations of sparing as factors.

Results

Some rats did not move on all four days of open field testing. Because of this variation among animals, it was necessary to use a descriptive statistic which would adjust for these differences. We chose the formula used to determine ear advantage in the dichotic listening test (13). The numerator of this formula is the number of right-wall responses minus the number of responses in which the animal moved along the left wall, and the denominator is the square root of the total number of responses made. In short, the directionality score (DS) = (R - L) / (R + L). This statistic has a possible range from +2 to -2; a score of 0 indicates that the animal has no directionality bias.

A preliminary statistical test determined that there was no significant litter effect and this variable was dropped from any further analysis. There was no significant difference between the sham and no-surgery control groups (F 1.0) and their data were pooled. These groups will be referred to as intact controls. Table 1 shows the mean directionality scores and the N's for the six groups in the experiment.

TABLE I

Directionality of Female Rats in the Open Field
For the Two Early Experience Groups by Surgery

Early Experiences		Ablation		
Days 1-20	21-50	Intact	Right	Left
Nonhandled	Lab Cage	-.508 (52)*	.716 (33)	-.785 (32)
Handled	Enriched	-.166 (49)	.946 (31)	-1.055 (29)

*Number of subjects in each group

Intact Groups

The mean directionality score of the handled-enriched nonablated group was -.166, which does not differ significantly from zero (t = 1.26, df = 220). In contrast, the mean score for the nonhandled nonablated rats was -.508, which is significantly different from zero (t = 3.97, df = 220, p .001). The difference between the handled-enriched group with intact brains and the nonhandled intact group approached significance (t = 1.86, df = 220, p .07).

Ablation Groups

The groups with right or left neocortical ablations turned in a direction ipsilateral to the side of lesion, as expected. In the handled-enriched treatment a right ablation produced a mean directionality score of .946 while a left ablation produced a mean score of -1.055. The absolute values of these scores are not significantly different from each other (t = .45, df = 220). Similarly, no difference between right and left ablations was seen in the nonhandled lab cage group (t = .30, df = 220). A right lesion in this group produced a mean directionality score of .716 while a left lesion produced a mean score of -.785.

Histology

The amounts of cortex ablated in the left and right hemispheres were nearly identical, amounting to 76.97% and 75.64% respectively. Analysis of variance for the sparing data was confirmative, with side of lesion (F = 0.15, df = 1,48) and interaction between side of lesion and location of sparing (F = 0.30, df = 4,48) both not statistically significant. Location of sparing was a significant factor (F = 9.88, df = 4,48) with most sparing occurring in the anterior 4 mm of the hemisphere designated "frontal." Thus, the symmetry of right and left lesions parallels the absence of asymmetries in the behavioral data.

Discussion

Intact Purdue-Wistar females, left undisturbed in infancy and reared in laboratory cages thereafter, were significantly biased to initially move leftward in the open field. Robinson and his associates have recently obtained virtually the same result: they found that nonhandled Holtzman Sprague-Dawley females had a directionality score of -.510, in comparison to our value of -.508 (14,15). They also found that handled Holtzman males are left-biased, thus confirming our finding with handled Purdue-Wistar males (7).

The asymmetry seen in intact nonhandled females is to be contrasted to the lack of bias seen in the handled-enriched group with intact brains. It is of interest to note that nonhandled males with intact brains, tested under comparable conditions as the females in this study, did not show any spatial bias (7). However, nonhandled males with a left lesion had a significantly greater directionality score than did the right-lesion group. For females in the present study the right and left ablation means did not differ for either early experience group. Thus, both male and female nonhandled rats have an asymmetrical brain organization for left-right spatial preferences, but the nature of the organization is different in the two sexes.

These findings indicate that different brain models are needed to characterize the two experimental groups (16). Since intact nonhandled females showed a significant leftward bias, while the two lesion groups did not differ, this can be described by a model in which there is no activation difference in the two hemispheres; instead the right hemisphere inhibits the left (for detailed explanation of this hypothesis see 16). This may be compared to the handled enriched treatment which shows no evidence of laterality. These models imply that the combined effects of handling and enrichment were to remove the right hemisphere's inhibitory control over the left. An experimental test of this hypothesis can be carried out by a split-brain study.The possibility of asymmetric connections of the cortex with subcortical systems must also be considered.

The documentation of sex differences in the functional organization of the rat brain suggests that this species could serve as an animal model to help understand human sex differences. Confusion in the human realm may be reduced by the exploitation of this animal model. The rat also presents a starting point for exploring factors that may affect lateralization which are difficult to study in the human (e.g., gonadal hormones).

Reprints

Reprint requests should be mailed to Dr. Sherman, Neurological Unit, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

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