Infantile Stimulation Induces Brain Lateralization in Rats

Abstract. *The hypothesis tested was that the effects of early experiences are asymmetrically distributed in the two brain hemispheres. Litters were either handled or not handled between birth and weaning, and the weanlings were reared in either laboratory cages or enriched environments between 21 and 50 days. When approximately 135 days old, animals within each of the four treatment groups had a right neocortical ablation, a left neocortical ablation, a sham operation, or no surgery. About 1 month later, all animals were given the open-field test for emotionality and exploratory behavior. Ablating either the right or left neocortex increased the activity scores of nonhandled controls, but there was no evidence of lateralization. However, the groups handled in infancy did show lateralization. Ablating the left brain did not significantly increase activity, but ablating the right brain caused extreme scores: handled rats without enrichment experience were the most active, and handled rats also placed into the enriched environment had near-zero scores in the open field.*

In several studies, different emotional responses were found to be mediated by the right and left hemispheres of humans. Perria *et al.* (*1*) and Rossi and Rosadini (*2*) pharmacologically inactivated one or the other hemisphere by injecting sodium amytal into one of the carotid arteries; they found a "depressive" reaction after injections into the left hemisphere and a "euphoric" response after injections into the right hemisphere. Comparable data were obtained by Gainotti (*3*), who reported that patients with lesions in the left hemisphere exhibited "catastrophic reactions" including anxiety, tears, swearing, refusal, and renouncement; those with lesions in the right brain had an "indifferent reaction" composed of joking, minimizing their ailments, denying illness, and being apparently indifferent toward failure. Using very different methodologies and working with normal subjects, several researchers have shown a right-hemisphere involvement for emotional material. Dimond *et al.* (*4*) obtained judgments of emotional reactions to films viewed by either the right or left hemisphere; ratings of "unpleasant" and "horrific" were significantly greater when the films were viewed by the right brain. In other studies, an increase in left lateral eye movements was observed when subjects were asked emotional questions (*5*); faster reaction times were recorded for the right hemisphere in the memory of emotional faces (*6*); and a left-ear advantage was obtained for the recognition of the emotional tone of a sentence and of emotional nonspeech sounds (*7*).

Given that the two hemispheres process emotional reactions differently, a pertinent question is, How did these differences arise? This is the question of the ontogeny of hemispheric specialization, which, as pointed out by Teuber (*8*), has "hardly been touched upon at all in the past and current work on our two hemispheres." However, even though direct evidence is scanty, two lines of evidence suggest that experiences during early life may have a strong influence upon later emotional processes in the two brains. The source of one is clinical observations on human patients. (i) Psychoanalytic theory explicitly implicates experiences during infancy as influencing affective behavior. (ii) In psychotherapy, early emotional experiences are often an important consideration; the difficulty of expressing one's emotional problems in words suggest that the nonverbal right brain is significantly involved. Galin (*9*, *10*) has pointed out compelling similarities between the kinds of conscious dissociations seen in split-brain patients and some phenomena of clinical psychiatry, and he reviewed evidence that some unconscious psychological processes are mediated by the right brain in normal adults.

The second, and complementary, line derives from animal experimentation. (i) Studies of the effects of early experiences lead to the generalization that stimulation during infancy modifies a number of adult behavioral and biological variables, including emotionality and exploratory behavior (*11*, *12*). However, these researchers have not examined laterality differences. (ii) Laterality effects, but not early experiences, have been studied in animals. Evidence of brain asymmetry in rats has been reported by Zimmerberg and her colleagues (*13*), who found that the dopaminergic nigrostriatal pathways of the two sides of the brain contained different concentrations of dopamine; in a T-maze, the animals turned in the direction contralateral to the striatum containing more dopamine. Though these findings were consistent within an animal, there was no evidence of a right-left preferential bias in their population.

These several findings, taken together, suggest the hypothesis that the effects of early experiences are asymmetrically distributed between the two hemispheres (*14*). The purpose of the following experiment was to test this hypothesis, with the rat as our experimental subject. Since all three lines of evidence focus on affective and spatial behaviors, we chose to use the open-field activity test, which measures both emotional and exploratory behavior (*12*).

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 males per litter. Our first experimental variable was handling, since it had been shown to reduce emotionality and increase exploratory behavior in adulthood (*11*, *12*). Whole litters were handled from day 1 through day 20 of life (day 0 = day of birth) by removing the pups from the maternity cage, leaving the mother in the cage, and placing each pup singly into a 1-gallon can containing shavings, where they remained for 3 minutes before being returned to the maternity cage. Control animals were not disturbed during this time. Twenty-four litters were handled and 24 were nonhandled controls. When weaned at 21 days, the males from 12 of the handled and 12 of the control litters were placed into large enriched environments, identical in dimensions to the environments used by the Berkeley group (*15*), and containing a number of "playthings." This treatment reduces emotionality and increases activity (*16*). The remaining male rats were placed, by pairs, into standard laboratory cages. When 50 days old, the rats in the enriched environment were also placed by pairs into laboratory cages. At 70 days, all rats were placed singly into standard cages.

At approximately 135 days, the four males within a litter were randomly assigned to one of four surgical procedures: (i) left-hemisphere neocortical ablation, (ii) right-hemisphere neocortical ablation, (iii) a sham operation, or (iv) no surgery (*17*).

When about 165 days of age, all animals were tested for 3 minutes in an open field (114 cm square and subdivided into 25 13-cm squares) for four successive days, and their activity was recorded. Higher activity reflects a less emotional and more exploratory animal (*12*). When approximately 225 days old, the rats were tested for mouse killing (*18*). The animals were then killed, and their brains were removed and evaluated histologically.

During the course of the study, 19 of the 192 rats died. The deaths were randomly distributed among the treatment conditions. A preliminary statistical test determined that there were no significant litter effects, and thus this variable was dropped from our analysis of variance (*19*). As there were no significant differences between the sham and the no-surgery control groups ($F < 1.0$), their data were pooled. Table 1 shows the open-field activity scores of the four early-experience groups as a function of brain ablation.

Table 1. Mean activity score in the open field for the four early-experience groups classified by surgery. The number in parentheses is the number of subjects in each group.

Days 1 to 20	Days 21 to 50	Control + sham	Ablation	
			Left brain	Right brain
Nonhandled	Laboratory cage	8.90 (20)	27.64 (11)	22.33 (12)
Nonhandled	Enriched environment	9.91 (22)	27.08 (12)	32.89 (9)
Handled	Laboratory cage	12.51 (23)	17.91 (11)	36.27 (11)
Handled	Enriched environment	17.52 (20)	20.42 (12)	3.00 (10)

Rats with right- or left-brain ablations were significantly more active in the open field than control animals [$F(1, 157) = 5.11$ and 4.79, respectively; $P < .05$]. Of greater importance than these main effects were the findings that the handling and the enriched-environment variables interacted significantly with the right brain versus control contrast [$F(1, 157) = 5.65$, $P < .05$] and also with the right versus left contrast [$F(1, 157) = 4.06$, $P < .05$].

Ablating either the right or left neocortex of the two nonhandled groups resulted in approximately the same increase in activity. Thus, there is no evidence of hemispheric lateralization. However, ablating the left brains of either handled group resulted in no increase in activity, but ablating the right brains caused extreme scores. Handled rats without enrichment experience were the most active, and handled rats from the enriched environment were the least active. The right brain effect (Table 1, columns 3 and 5) shows that the ablation produced a marked increase in activity in three of the four early-experience groups, but ablating the right brains of those animals who were handled in infancy and then reared in an enriched environment reduced their activity to nearly zero. Finally, the differential effects of lesions of the right and left brain are seen in columns 4 and 5 (Table 1). The lesions have approximately the same effect on nonhandled rats, but differing effects on animals previously handled.

The histological analysis revealed the extent and location of the lesions to be equivalent in the two hemispheres and for the four combinations of early-experience treatments.

The results show lateralization of a behavioral function in lower mammals and confirm the hypothesis that the effects of early experiences are asymmetrically distributed in the brain. The right brain is the repository for the interactive effects of handling and environmental enrichment, at least as far as open-field activity is concerned. The decrement in activity following ablation of the right brain is particularly impressive since bilateral damage to telencephalic systems has typically been associated with increases in locomotor activity (*20*). We also found increases in the seven other ablation groups in our experiment.

Since the right hemisphere was the locus of the interactive effects of the early experiences, the phenomenon is present at a population level. If it had been present only at the individual level, the effect would have been randomly distributed, with some subjects having involvement of the right brain and others of the left, as appears to be the situation for the relationship between dopamine and spatial preferences in standard laboratory rats (*13*). To our knowledge, our study represents the first report of a "major organismic asymmetry" (*21*), in which psychological functions appear to be unequally represented between the two hemispheres within a population of laboratory rodents. Functional asymmetries related to paw preferences have been found in both the rat (*13*) and cat (*22*), but no one has reported that the left or right hemisphere dominated over its opposite member more often than one would expect by chance for the entire sample of subjects.

The asymmetry favoring the right brain raises the question of the adaptive function served by this specialization. Webster (*23*) has speculated that the biological significance of brain laterality may be related to problems of spatial position and territoriality, so that an animal with an asymmetrical brain would be better able to analyze and remember its spatial location. This should aid the animal in defending its territory and in finding a mate. We have found the right brain to be involved in the rat's locomotor activity behavior in the open field; and open-field activity reflects at least two behavioral processes, emotional reactivity and exploration (*12*), both of which are important for a territorial animal. These findings are in essential agreement with Webster's hypotheses concerning laterality and territoriality.

Our data relating early environmental events to later lateralization may cast some light upon the unusual findings of Tsunoda and Oka (*24*). They have reported that all their Japanese patients showed the "euphoric-maniacal" reaction when the left brain was temporarily anesthetized, whereas only 5 of 44 patients expressed a "depressive" reaction, and those all occurred when the right brain was anesthetized. These findings differ sharply from the reports of others (*1–3*) that "euphoria" or "indifference" reactions are seen after inactivation of the right brain, while "depressive" or "catastrophic" responses occur after immobilizing the left brain. Tsunoda and Oka interpret these disparities as reflecting cultural differences between Western and Japanese environments. In so far as differential early experiences may be viewed as analogous to cultural differences, our data lend general support to their interpretation.

More generally, these data suggest that lateralization for spatial and affective processes may be phylogenetically older than lateralization for cognitive processes and may also be more developmentally plastic.

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Parthenogenetic Lizards

Cuellar's article (*1*) on animal parthenogenesis cites some data that I published (*2*) on *Cnemidophorus lemniscatus*. The quotation is not entirely faithful, and the implications seem to me relevant. The issue is the distribution of bisexual and all-female populations of the lizard along the main course of the Amazonas.

Cuellar says that according to me "only unisexual populations occur along the river. . . ." In reality, I stated (*3*) clearly that bisexual populations existed at Santarém and Alter do Chão, respectively, at the mouth of the Tapajós and 50 km upstream; I further cited male specimens from Parintins (56°44′W) in an old collection. In 1974, Peccinini-Seale and Frota-Pessoa (*4*), not cited by Cuellar, listed five localities on the main course where bisexual populations occurred, the three previously noted in my 1970 paper, plus Terra Santa and Urucurituba, located by myself during a survey. The picture at present is: (i) *C. lemniscatus* occurs along the main course of the Amazonas from the coast to Urucurituba (57°40′W), no farther west; (ii) all-female populations predominate, but disjunct bisexual ones are found in the Tapajós and at the westernmost localities, Parintins and Urucurituba; and (iii) there are at least five chromosomal arrangements (*4*), and their geographical distribution is complex. This mosaic distribution seems to me to be the dominant feature of the problem, indicating, as it does, repeated shift to parthenogenesis in situ. This is made more probable by the shift actually observed in the Obidos population (*2*). A probable mosaic has also been found in the microteiid *Gymnophthalmus underwoodi* (*3*).

In addition, I called attention to the striking preference of *C. lemniscatus* for sizable villages and towns. Cuellar says that "While its distribution along the main course of the Amazonas has not been well studied . . . adequate sampling will probably reveal a uniform riparian distribution from which adjacent towns draw their unisexual populations."

"Adequate sampling" as meant by Cuellar is probably defined by its results, but I shall briefly describe what we ("Expedição Permanente da Amazônia") did about the problem. We traveled several times between Belém and Manaus in our boats *Lindolpho R. Guimarães* and *Garbe*, stopping at all villages and at numerous settlements and estates, working inland and along the rivers, doing general collecting but stressing the collection of *C. lemniscatus*. Of the latter we obtained 7332 specimens at 30 localities among several hundred visited. No specimens were seen in natural habitats; in that many other lizards were obtained at such places, I take it that the sampling was not entirely inadequate. Of the 30 localities, 24 were villages (with definite streets) or towns, and accounted for 7226 (98.6 percent) specimens. Of all towns visited between Belém and Urucurituba only one (Jurutí) failed to produce *Cnemidophorus*. The remaining six localities were sizable estates; they afforded 106 specimens. This disparity in numbers is actually an underestimate because, in places where the lizard was rare, special pains were taken to obtain it; but in towns we usually stopped buying it from the children on the second day, as many as 300 specimens a day being sometimes collected.

I think that it is inescapable that this lizard is traveling with man and settling at places of maximum disturbance. That these places are riparian is probably due to the fact that all Amazonian settlements are riparian. I have enough experience in the field not to be too dogmatic about the absence of "a uniform riparian distribution," but I think the probability of its existence is at best remote.

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In his effort to develop a new evolutionary-ecological model for parthenogenesis in animals, Cuellar (*1*, p. 837) stated, "Here, I attempt to elucidate the evolutionary ecology of parthenogenesis in light of what is known in all parthenogenetic animals." A model based on such an analysis would indeed be new and welcome, but Cuellar failed to accomplish his stated intention. His model suffers most critically from the lack of consideration of the evolutionary implications of readily available information on the genotypes of parthenogenetic animals. This omission is most pronounced in the case of the vertebrates emphasized in his discussions. Cuellar placed the greatest emphasis on two parthenogenetic species of the genus *Cnemidophorus*—*C. neomexicanus* and *C. tesselatus*—for which he related ecological observations and presented maps of the respective geographical distributions. In terms of genetic data, these are the two species of the genus about which the most has been published. For example, in their analysis of the chromosomes of *C. neomexicanus*, Lowe and Wright (*2*) found that the karyotype consisted of two quite distinct haploid complements, between which there was little, if any, morphological homology. They concluded that *C. neomexicanus* was an allodiploid that resulted from hybridization between the