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Effects of Neonatal Forebrain Noradrenaline Depletion on Recovery from Brain Damage: Performance on a Spatial Navigation Task as a Function of Age of Surgery and Postsurgical Housing

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The experiments examined the contributions of forebrain noradrenaline and environmental enrichment to recovery of place navigation ability in rats after hemidecortication in infancy or adulthood. Noradrenaline depletion did not affect recovery from neonatal hemidecortication, although the early hemidecortications did allow sparing of function relative to adult operates. Noradrenaline depletion also failed to attenuate the positive effects of enriched housing on otherwise normal rats. Noradrenaline depletion did retard recovery of adult hemidecorticate rats housed in standard laboratory cages, but it did not retard recovery of adult hemidecorticate rats housed in enriched environments. The results suggest that noradrenaline is importantly involved in enhancing recovery from brain damage when other sources of compensation (e.g., neonatal injury, enriched environment) are absent.

The behavioral effects of very similar brain damage differ from individual to individual. Two factors that have been repeatedly shown to be important determinants of post-traumatic behavioral competencies are age at which the damage is sustained and the quality of the individual's experience. For example, in rats, neonatal damage to frontal cortex or neonatal removal of an entire cortical hemisphere has a less deleterious effect on

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some behavioral systems than comparable damage inflicted in adulthood (Kolb & Nonneman, 1978; Kolb, Sutherland, & Whishaw, 1983). Likewise, if rats with these brain lesions are placed into an "enriched" environment (involving group housing, a large space in which to move around, and many, varied objects with which to interface), there appears to be a substantially greater post-surgical behavioral recovery compared to similarly brain-damaged rats who are housed in individual, barren wire-mesh cages (Walsh, 1980; Whishaw, Zaborowski, & Kolb, 1984; Will, Rosenzweig, Bennett, Herbert, & Morimoto, 1977). The enhancement of behavioral recovery associated with very early brain damage and with enriched postsurgical experience probably does not generalize to all classes of behavioral impairment (see Kolb & Whishaw, 1981, 1985a, 1985b), and it clearly does not generalize to all loci of brain damage (Kolb & Holmes, 1983; Sutherland & Dyck, 1982), but the fact that the efficacy of these two factors can be observed following damage to many areas of the human cortex makes the study of the processes that may underly these effects interesting not only from the point of view of understanding normal brain function, but also from a more practical perspective in the treatment of many human patients with brain damage.

In the present study we take advantage of a preparation and behavioral task that have proven useful in our previous work (Kolb et al., 1983; Sutherland, Kolb, Whishaw, & Becker, 1982; Whishaw et al., 1984). A version of the place navigation task of Morris (1981) is employed in which the rat must swim to a small, invisible platform in order to escape from cool, opaque water. To perform accurately, the rat must learn to navigate using the configuration of distal cues; no useful proximal cues are provided inside the pool. Using this preparation we have found that hemidecortication performed in infancy is associated with improved acquisition of place navigation relative to hemidecortication in adulthood and that postsurgical enrichment improved performance of hemidecorticate rats undergoing surgery in adulthood but not those undergoing neonatal surgery. Presurgical enrichment did not have a major effect on performance of adult hemidecorticates, nor did enrichment greatly enhance performance of unoperated control rats. Thus, we have shown that the animal's age at the time of brain damage and its postsurgical experience both affect the degree of behavioral recovery. It is probable that reorganization and modification of connections within the remaining cortex (e.g., Diamond, 1976; Diamond, Rosenzweig, Bennett, Lindner, & Lyon, 1972; Rosenzweig & Bennett, 1976) and between the remaining cortex and ipsi- and contralateral subcortical structures (e.g., Hicks & D'Amato, 1970; 1975; Kartje-Tillotson & Castro, 1980; Neumann, Pritzel, & Huston, 1982) underlies the improved performance associated with enrichment and neonatal surgery, although these two effects do not have a detectable in-

teraction. Given the greater capacity for major anatomical reorganization in the neonatal brain it is likely that the enhanced recovery associated with neonatal surgery relies to a large extent on different mechanisms than those associated with adult enrichment (Kolb et al., 1983).

One factor that has been shown to influence the modifiability of cortical function in response to experiential factors is the availability of cortical noradrenaline (Kasamatsu & Pettigrew, 1979; Kasamatsu, Pettigrew, & Ary, 1979; Sutherland, Kolb, Whishaw, & Becker, 1982). Single neurons in the visual cortex of the kitten do not show the normal modification of ocular dominance in response to unilateral visual deprivation if cortical noradrenaline is depleted by the selective neurotoxin, 6-hydroxydopamine (6-OHDA). Chronic infusion of noradrenaline into the visual cortex restores this modifiability (Kasamatsu et al., 1979). Whereas these results have been confirmed by other work (Bear et al., 1983; Daw, Rader, Robinson, & Ariel, 1983), the effects do depend on route of 6-OHDA administration, age of treatment, and extent of noradrenaline depletion (Bear & Daniels, 1983; Bear et al., 1983; Daw, Robinson, Rader, Videen, & Coscia, 1984). Similarly, in the rat, it has been shown that depletion of cortical noradrenaline prevents behavioral and anatomical changes normally produced by environmental enrichment (Brenner, Mirmiran, Uylings, & Van Der Gugten, 1983; O'Shea, Saari, Pappas, Ings, & Stange, 1983). The availability of cortical noradrenaline also modulates the processes of cortical modifiability that underlie the enhanced recovery from cortical damage associated with neonatal surgery (Sutherland, Kolb, Whishaw, & Becker 1982). Depletion of cortical noradrenaline produced by neonatal, peripheral administration of 6-OHDA completely blocked the enhanced behavioral recovery associated with bilateral removal of frontal cortex in rats. Interestingly, a direct comparison of neonatal vs adult frontal cortex removal with neonatal vs adult hemidecortication revealed a very similar degree of behavioral recovery associated with neonatal surgery but markedly different changes in morphogenesis of remaining neocortex (Kolb et al., 1983). Neonatal frontal cortex removal produced thinning of remaining neocortex relative to normal control and adult-operated rats. In contrast, neonatal hemidecortication produced thickening of the neocortex in the intact hemisphere relative to normal control and adult-hemidecorticate rats. This dissociation implies that the enhanced recovery associated with neonatal surgery may, in these two cases, rely on different processes of neural compensation.

In the present study we addressed two questions: first, is the availability of cortical noradrenaline necessary for environmental enrichment to enhance the behavioral recovery of adult hemidecorticate rats, and second, is the enhanced recovery of place navigation ability associated with neonatal hemidecortication dependent upon the availability of cortical noradrenaline?

METHODS

Subjects. Long–Evans hooded rats (51 male, 52 female) served as subjects.

Surgical procedure. The central noradrenaline depletions (Clark, Laverty, & Phelan, 1972; Sachs & Jonsson, 1975; Sutherland et al., 1982b) were made with three subcutaneous injections of 6-OHDA (100 mg/kg in 0.9% saline and 0.2% ascorbic acid, sc). Since the noradrenergic projection to the forebrain develops postnatally (Coyle & Molliver, 1977; Lauder & Bloom, 1974; Levitt & Moore, 1979) and can be selectively lesioned with neonatal injections of 6-hydroxydopamine (Clark et al., 1972; Sachs & Jonsson, 1975) the depletions were made over the first 3 postnatal days whereas the cortical ablations were performed shortly thereafter or in adulthood. The first injection was given within 12 h after birth and subsequent injections were given at intervals of 24 h. Rats that were to serve in the control groups were given sc injections of saline.

Hemidecortications were produced by aspiration. The neonatal ablations were made in pups aged 7–9 days while they were under hypothermic anesthesia (Kolb et al., 1983). The skull overlying one hemisphere was reflected and the neocortex and cingulate cortex were aspirated. After the wound was sutured the pups were warmed and returned to their nests. Adult hemidecortications (Kolb et al., 1983) were made while the rats were anesthetized with sodium pentobarbital (50 mg/kg for male rats and 35 mg/kg for female rats). The frontal and parietal bones and part of the squamosal bone (after freeing and retracting the temporal muscle) were removed over one hemisphere. A narrow strip of bone was left in the midline to cover the sagittal sinus. After retracting the dura, the neocortex was removed. After hemostasis, the scalp wound was closed and sutured.

Apparatus. The rats' spatial learning ability was tested in the Morris Water Task (Morris, 1981). A circular pool was used (diam, 146 cm; height, 45 cm), which was painted white and filled to a height of 25 cm with 18°C water in which 1500 ml of instant powdered skim milk had been dissolved. A clear Plexiglas platform (11 × 12 cm) was located in the center of the northeast quadrant of the pool with its top surface 14 mm below the surface of the water. The platform was invisible to a viewer inside the pool and thus could only be located by a rat using a non-cue-learning strategy. Between trials, the rats were held in individual mesh cages, which had a mesh cover. Thus, from both the holding cages and from the pool the rats had a clear view of the abundant cues present in the room (e.g., two experimenters, metal counter, cupboards, curtained windows, refrigerator, door, ceiling light fixtures), but these cues were held constant throughout testing.

Training. A trial consisted of gently placing a rat by hand into the water, facing the wall of the pool, at one of four starting locations, north,

south, east, or west, around the pool's perimeter. Within each block of four trials, each rat started at each of the starting locations, but the sequence of locations was randomly selected.

The behavioral testing was conducted on consecutive days, with each rat receiving eight trials on each day. If, on a particular trial, a rat found the platform, it was permitted to remain on the platform for 15 s. A trial was terminated after 120 s if a rat failed to find the platform. At the end of a trial, the rat was returned to its holding cage (the cages were located beneath a heat lamp, which could be turned on to prevent the rats from becoming hypothermic), and approximately 5–8 min elapsed before the beginning of the next trial.

The swimming path for each rat on each trial was recorded on a map of the pool by an experimenter seated by the south end of the pool's edge. The latency to find the platform (escape latency) was timed by a second experimenter standing by the northwest edge of the pool. During the time that the rats were on the platform, the number of instances of rearing was recorded.

To determine whether the rats located the platform using distal visual cues, after a designated number of acquisition trials, the platform was moved from the center of the northeast quadrant of the pool to the center of the southwest quadrant.

Environmental treatments. Two environmental treatments were used. The enrichment procedure consisted of placing rats in large holding cages for 90 days. The cages were 120 × 120 × 75 cm high, were constructed of Fiberglas, and they had mesh screen coverings. The cages contained a mixture of objects including a sawdust and alfalfa substrate, which covered plastic pipes of various diameters through which the rats could crawl. On top of this were numerous pieces of wood, branches, various kinds of toys, etc., through which and over which the animals could climb. The objects in each cage were changed once or twice each week. Rat chow was placed in the cages and water was available from six metal water spouts protruding through the walls of the cages. Various objects were also placed on top of the screen roof and these were moved or changed once or twice each week. The impoverished environments consisted of single wire mesh laboratory cages 20 × 25 × 18 cm high. Lighting in the enriched environment was natural lighting through the windows of the building (enrichment took place during November to January) and lighting for the deprived group was artificial light controlled on a 12 h on and 12 h off cycle.

Data analysis. The distance that each rat swam on each trial and the error in initial heading over the first 12 cm of each swim path was calculated by means of an Apple II Plus computer connected to a magnetic Graphics tablet. Differences in escape latency, swim distance, error in initial heading over the first 12 cm, swim distance within the previously

correct quadrant of the pool after the platform had been moved, and the number of rears the animals made on the platform in 15 s were assessed by an analysis of variance procedure with repeated measures and by trend analysis with orthogonal polynomials and by follow-up Newman–Keuls' tests. In addition to these measures, an error measure was also used. An error was scored if a rat deviated from an 18-cm wide path (the most direct path it could take to reach the platform) as it swam from the start location to the platform. A maximum of one error was given on any one trial.

Anatomical procedures. At the end of testing, representative rats with neocortical ablation were sacrificed, their brains processed, embedded in celloidin, and sectioned at 20 μm. Every fifth section through the lesion was mounted and stained with cresyl violet. The lesion extent was assessed microscopically in the coronal sections and the extent of the cortical ablations were assessed at 20 coronal levels (see Whishaw, Schallert, and Kolb (1981) for photomicrographs of the representative levels) by measuring the area of residual cortex with the Graphics tablet-area program on the Apple II Plus microcomputer and converting this area to a percentage of the area of an intact cortical area at an analogous coronal plane. The remaining animals were used for catecholamine assays. The animals were killed by decapitation; the brain was rapidly removed and chilled in 0.9% saline on ice for 30 s. The extent of the lesion was sketched on prepared horizontal and saggital brain maps at this time. Three areas of the brain were then dissected for the assays performed in Experiment 1: (1) the neocortex and cingulate cortex of the intact hemisphere, or a randomly selected hemisphere of a rat that had not received a cortical ablation; (2) the hippocampus, bilaterally; and (3) the brainstem. In Experiment 2 the caudate nucleus from each hemisphere was also dissected.

Biochemical assays were performed using high-performance liquid chromatography with electrochemical detection (Felice, Felice, & Kissinger, 1978). Tissue was homogenized in 1 ml 0.05 *N* $HClO_4$ containing also 100 ng 3,4-dihydroxybenzylamine hydrobromide as an internal standard, 0.8 m*M* $NaHSO_4$ as a reducing agent, and 0.1 m*M* EDTA. A standard curve (tissue blank plus three standards containing known amounts of NA and DA (free base)) was run with each assay. Samples were centrifuged at 3500*g* for 45 min at 4°C. After centrifugation, all of the supernatant was transferred to conical tubes containing 20 mg acid-washed alumina and 500 μl 3 *M* Tris–HCl (pH 8.5 at 4°C). Samples were immediately vortexed for 1 min and shaken on a reciprocal shaker for 10 min. Alumina was washed twice with 1 ml 6 m*M* Tris–HCl (pH 8.6 at 4°C) and three times with 1 ml H_2O. After completely removing the H_2O, the catecholamines were extracted in 200 μl of 0.05 *N* $HClO_4$ by vortexing for 1 min. An aliquot of the supernatant was stored at −20°C until assayed.

Samples of 10 μl were assayed with a sensitivity of 10 pg/mg for NA and for DA.

EXPERIMENT 1

Experiment 1 had two purposes. The first was to determine whether neonatal noradrenaline depletion by 6-hydroxydopamine in neonatal rats impairs spatial navigation. The second purpose was to determine whether neonatal noradrenaline depletion blocks the behavioral sparing that follows neonatal hemidecortication (Kolb et al., 1983) in the same way that it blocks the sparing that follows neonatal frontal cortex lesions (Sutherland, Kolb, Whishaw, & Becker, 1982).

Procedure

Forty-five rats (22 male and 23 female) were used. Eighteen of the rats received the 6-OHDA injections as neonates and the remaining animals received saline injections. The animals were then assigned to one of five groups of 9 rats each: (1) one group of 6-OHDA-treated rats and (2) one group of saline-treated rats received hemidecortications when they were between 7 and 9 days of age, (3) one group of saline-treated rats received hemidecortications when they were 90 days of age, and (4) one group of saline-treated rats and (5) one group of 6-OHDA-treated rats served as control groups for the hemidecorticated groups. The group divisions were made in such a way that approximately one half of the rats in each group were female and one-half of the animals that received surgery had right and one-half had left hemidecortications. When the rats were 120 days of age they began testing in the water task. Before the end of training one rat in group 4 was lost to the experiment.

The rats were tested in the water task for 6 consecutive days, during which they received 12 trial blocks (a block consisted of 1 trial from each of the four starting locations) or 2 trial blocks a day. Between the 11th and 12th trial blocks the platform was moved from the northeast quadrant of the pool to the southwest quadrant of the pool.

Results

Normal rats quickly learned to swim directly to the hidden platform, reaching asymptotic performance in only a few trial blocks. In contrast hemidecorticate rats acquired the task more slowly and failed to achieve the proficiency of normal rats. Behavior was quantified in terms of latency to reach the platform, accuracy (angle) of the approach, and swim distance and is described below.

Latencies. The mean latencies to escape during each trial block are summarized in Fig. 1. It can be seen that all groups displayed a decrease in escape latencies over trials. All of the groups also mastered the place response as witnessed by their significant increase in swim latencies upon

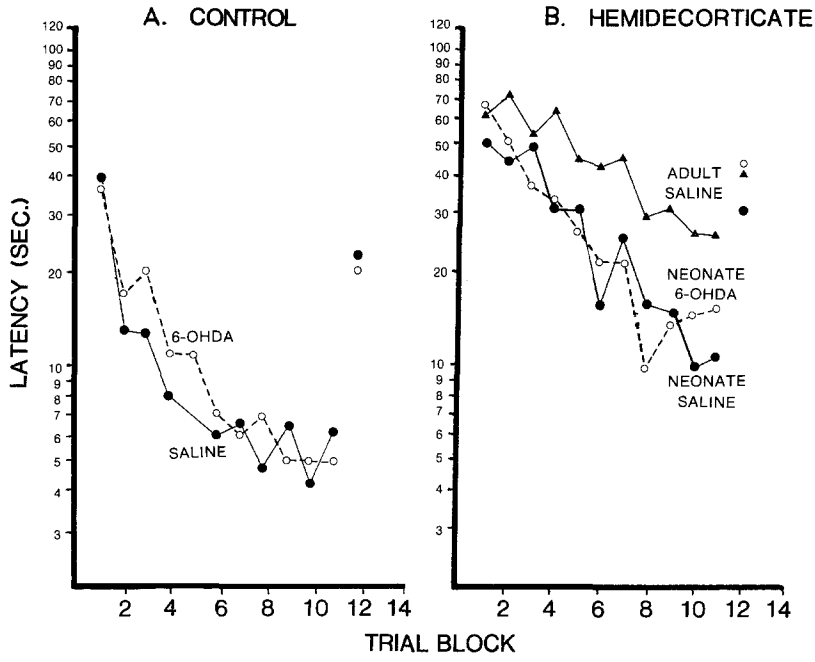

FIG. 1. Mean latencies to acquisition on the water task for (A) rats treated neonatally with 6-hydroxydopamine (6-OHDA) or saline and (B) rats treated neonatally with 6-OHDA or saline and hemidecorticated in neonatally (neonate 6-OHDA and neonate saline) or decorticated in adulthood (adult saline). Note that neonatal 6-OHDA treatment did not disrupt performance but that adult hemidecortication did disrupt performance more than did neonatal hemidecortication. On trial block 13, the hidden platform was relocated.

relocation of the platform. The control groups also showed the most rapid improvement in performance, reaching asymptotic latencies within eight trial blocks. The 6-OHDA treatment had no effect on performance when given either alone (Fig. 1A) or in combination with neonatal hemidecortications (Fig. 1B). The acquisition rates and latencies for the cortically intact saline and 6-OHDA-treated control groups were similar. They both reached asymptotic escape latencies of about 4 to 6 s.

As can be seen in Fig. 1B, the saline- and 6-OHDA neonatally hemidecorticated rats also were not different from each other but their performance was not as good as that of the unlesioned groups (Fig. 1A). In fact, their best mean latencies of 10 to 15 s were substantially inferior to the asymptotic performance of the unlesioned groups. Nevertheless, their performance on every trial block was better than that of the adult hemidecorticate group (Fig. 1B).

Despite the differences in escape latency, rats in all of the groups appeared to use a place learning strategy to find the platform, because when the platform was repositioned between trials 11 and 12, there was

a significant increase in escape latencies, suggesting that the rats were searching the previously correct quadrant of the pool for the platform (Fig. 1).

An overall analysis of variance on the escape latencies for acquisition confirmed these observations. There was a significant trial effect, $F(11, 44) = 39.30$, $p < .0001$, demonstrating that the rats in the different groups showed significant improvement in performance as training progressed. Follow-up analyses showed that the improvement in performance in each of the individual groups was significant. There was also a significant groups effect, $F(4, 39) = 22.05$, $p < .0001$, demonstrating that there were differences in performance between the groups. There was a significant interaction, $F(44, 429) = 2.39$, $p < .0001$, confirming that there were differences in acquisition rates between the groups. Follow-up Neuman–Keuls' tests on group means ($p < .05$) confirmed that the difference between the saline and 6-OHDA groups was not significant, and they showed that the performance in both of these groups was significantly better than the performance of the two neonatally hemidecorticate groups, which also did not differ sigificantly from each other. Finally, all of these groups were significantly better than the adult hemidecorticate group. In order to measure the overall magnitude of the difference in performance between the groups the mean escape latency per trial over the entire test was computed. Mean escape latencies for the saline and 6-OHDA groups were 12 and 10.5 s, values that were more than twice as fast as those for the saline neonatal hemidecorticate group (27 s) and the 6-OHDA neonatal hemidecorticate group (29 s). The mean latency for the adult hemidecorticate group (46 s) was in turn about 16 s per trial slower than that for the neonatally ablated groups.

Swim distance and heading angles. Measures of swim distance were highly correlated with those of latency and produced identical differences to those obtained from the latency measures. Measures of heading angles that evaluated the overall accuracy of the rats' swims also produced consistent results. By the end of training, saline- and 6-OHDA-treated rats typically had heading angles of between 18 and 20° neonatally hemidecorticated rats had less accurate heading angles of between 23 and 27°, whereas the angles for the adult hemidecorticate group approximated chance values of 39°. That is, the former groups swam relatively directly to the escape platform whereas the adult hemidecorticate group's initial swim direction was random.

Biochemical Assay

Assays performed on nine saline-treated rats and six 6-OHDA-treated rats (Table 1) indicate that the treatments produced more than a 95% depletion of (NA) in the neocortex and hippocampus as well as an increase of about 40% in brainstem NA. These changes were significantly different

TABLE 1
Levels of Noradrenaline and Dopamine in Rats Treated Neonatally with Saline or 6-Hydroxydopamine

		Neocortex		Hippocampus		Brainstem	
	n	NA	DA	NA	DA	NA	DA
Saline	(9)	289 ± 19[a,*]	30 ± 3	311 ± 38*	26 ± 2	526 ± 2*	107 ± 10
6-OHDA	(6)	14 ± 7	37 ± 3	14 ± 11	26 ± 2	880 ± 31	120 ± 10

Note. NA, noradrenaline; DA, dopamine; 6-OHDA, 6-hydroxydopamine.
[a] Mean ± SD; ng/pg.
* Significantly different from 6-OHDA group; Student's *t* tests for independent samples, $p < .05$.

as shown by Student's *t* tests, $p < .05$. There were no significant differences in dopamine (DA) content in the neocortex, hippocampus, or brainstem of the saline- and 6-OHDA-treated rats.

Histological Results

Histological examination of the extent of the hemidecortications showed that typically the cingulate cortex was entirely removed in all rats and between 90 and 100% of the neocortex was removed. Any residual neocortex lay along the dorsal bank of the rhinal fissure and in the most ventral extent of the medial frontal cortex. There were no differences in the location and extent of the cortical removals. Figure 2 shows photomicrographs of representative lesions in a neonatal (A) and in an adult (B) hemidecorticate rat.

Discussion

Two findings emerged from the results of the experiment. First, neonatal noradrenaline depletion produced no impairment in the performance of otherwise intact rats. Acquisition speed, swim speed, and accuracy in acquiring the place task was identical in the control and noradrenaline-depleted rats. Second, noradrenaline depletion did not block the sparing of function obtained in neonatal operates. The neonatal hemidecorticate saline group and the neonatal hemidecorticate 6-hydroxydopamine group were not different from each other but they were inferior to the nonlesioned rats. They also performed significantly better on all measures than did the adult hemidecorticate group. The major conclusion that stems from the present findings is that the attenuation of sparing of function produced by noradrenaline depletion in animals receiving infant lesions is not invariant. Thus, the failure to attenuate sparing in the hemidecorticate rats must be due either to some difference in the lesion per se, as compared with our previous results with frontal cortex lesions (Sutherland et al.,

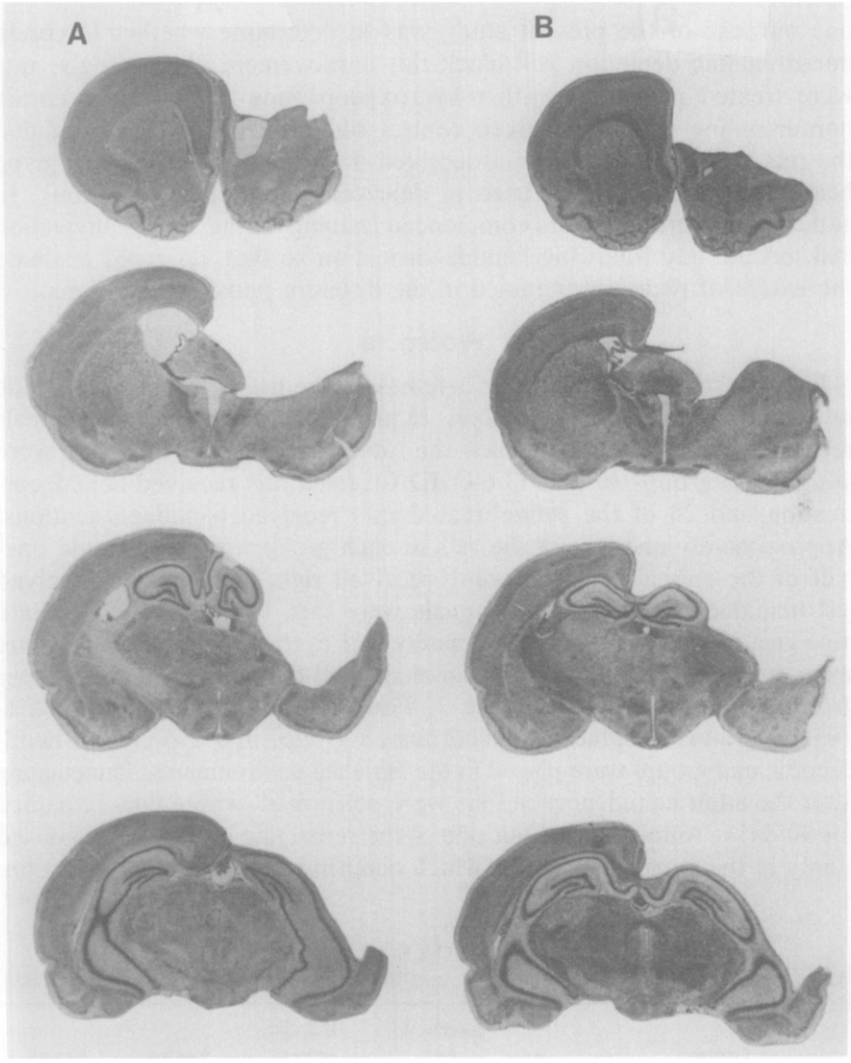

FIG. 2. Photomicrographs of representative sections from (A) a neonatal hemidecorticate rat and (B) an adult hemidecorticate rat. Cresyl violet.

1982), or to an interaction between the lesion location and some subsequent behavioral experience.

EXPERIMENT 2

O'Shea et al. (1983) have found that 6-hydroxydopamine attenuates the neural and behavioral effects of enriched rearing in the rat. Since we have found that environmental enrichment improves performance in rats that receive hemidecortications in adulthood (Whishaw et al., 1984),

one purpose of the present study was to determine whether forebrain noradrenaline depletion will block this improvement. Accordingly, rats were treated neonatally with 6-hydroxydopamine to deplete forebrain noradrenaline or they received control saline injections. When adults, the rats were housed either in deprived or enriched conditions or given hemidecortications and housed in deprived or enriched conditions. In addition, one group of rats commenced training on the spatial navigation task on the day following hemidecortication so that we could evaluate the extent of recovery obtained in the different housing conditions.

Procedure

Fifty-eight rats (29 male and 29 female) were used. Twenty-five of the rats received the 6-OHDA injections as neonates and the remaining animals received saline injections. When the rats were 120 days old, they were assigned to groups so that 13 6-OHDA-treated rats received hemidecortication and 20 of the saline-treated rats received hemidecortications. Approximately one-half of the rats in each group were female and one-half of the animals in each group received right and one-half received left hemidecortications. The animals were then further subdivided into nine groups of 6–8 rats (approximately half of the animals in each group were male); the actual group assignments and the number of animals per group are summarized in Table 2. Four groups (a saline group, a 6-OHDA group, a saline-hemidecorticated group, and a 6-OHDA-hemidecorticated group) were placed in the enriched environments, immediately after the adult hemidecortications were performed, where they remained for 90 days. Animals in all but one of the remaining groups were housed singly in the wire mesh cages, which comprised the deprived condition.

TABLE 2
Measures of Latency, Distance, Angles, and Errors on Acquisition of the Water Task

Group	*n*	Latency (s)	Distance (cm)	Angles	Errors
Control enriched	(6)	5.8 ± 0.3[a]	285 ± 11	10.9 ± 2	1.5 ± 0.4
6-OHDA enriched	(6)	6.0 ± 3	244 ± 298	19.9 ± 3	1.9 ± 0.4
Control deprived	(7)	7.9 ± 2	308 ± 97	15.5 ± 5	2.4 ± 0.6
6-OHDA deprived	(6)	6.7 ± 1.2	268 ± 27	15.9 ± 4	2.8 ± 0.6
C-Hemi enriched	(6)	12.5 ± 4	430 ± 94	20.2 ± 7	4.1 ± 0.9
6-OHDA-Hemi enriched	(6)	17.1 ± 5.7	598 ± 191	26.2 ± 4	5.2 ± 0.6
C-Hemi deprived	(8)	21.4 ± 7.5	766 ± 765	29.2 ± 5	6.2 ± 0.9
6-OHDA-Hemi deprived	(7)	53.2 ± 28.5	1268 ± 611	42.5 ± 11	7.0 ± 0.7
Imm Hemi	(6)	58.4 ± 20	1308 ± 528	41.3 ± 10	7.1 ± 0.13

Note. Hemi, hemidecorticate; Imm, tested day following adult hemidecortication.
[a] Mean ± SD per trial.

Animals in the remaining group, which were all hemidecorticated, began training in the water task on the day following hemidecortication. At the end of the 90-day enriching or lab-housing period, rats in all of the other groups were tested in the water task.

The rats were tested for 10 consecutive days, during which they received 20 trial blocks (a block consisted of 1 trial from each of the four starting locations), or 2 trial blocks per day. Between the 15th and 16th trial blocks, the platform was repositioned from the northeast quadrant of the pool to the southwest quadrant of the pool.

Results

Overall analyses of performance on the different behavioral measures (latency, distance, angles, and errors) showed (1) superior performance of the rats without cortical lesions in comparison to those with hemidecortications and (2) an interaction of experience and 6-OHDA treatment upon this difference. Since the overall variability across different groups was high, separate analyses were done on the performance of rats without cortical lesions and on the performance of the hemidecorticate rats. These results are given below. The analysis on rearing showed no significant group effect but there was a significant trials effect, $F(12, 686) = 14.3$, $p = .001$, and group by trials interaction, $F(112, 686) = 3.1$, $p < .001$. In the absence of the group effect further analyses were not done, but it is noteworthy that the interaction was due to the fact that the non-decorticated groups reared more frequently in early trials and the hemidecorticates reared more in later trials. The delay in rearing in the latter group was due to the fatigue from long swims on early trials.

Effect of 6-OHDA Treatment and Enrichment on Intact Rats

The major finding obtained from the comparison the effects of noradrenaline depletion on environmental enrichment of the rats without cortical lesions was that enrichment improved spatial navigation performance but there was no effect of 6-OHDA treatment. This result was obtained in the analysis of escape latency and heading errors but no significant differences were found for distance swam.

Latency. A summary of escape latencies of the groups is given in Fig. 3 and mean trial performance is given in Table 2. All of the groups mastered the place task as indicated by improved latencies over trials and significant increases in latencies when the platform was repositioned. The analysis of variance on latency showed that the enriched rats performed better than the control rats, particularly in the early training trials, but there was no effect of 6-OHDA treatment (environment, $F(1, 21) = 4.23$, $p = .052$; 6-OHDA treatment, $F(1, 21) = .92$, $p = .34$; environment by trials, $F(14, 294) = 1.91$, $p = .02$).

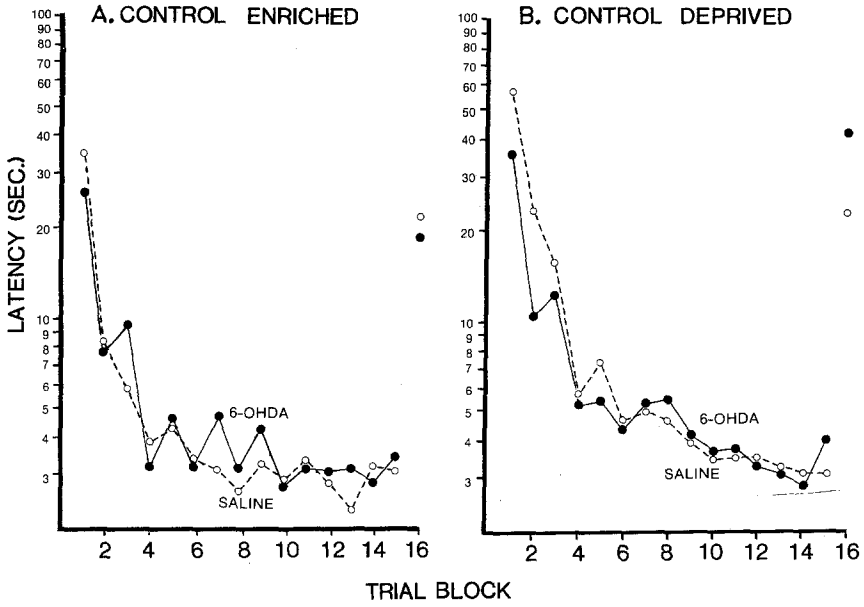

FIG. 3. Mean latencies to acquisition on the water task for (A) rats treated neonatally with 6-hydroxydopamine (6-OHDA) or saline and housed in enriched environments and (B) rats treated neonatally with 6-OHDA or saline, hemidecorticated in adulthood, and then raised in an enriched environment. Note that the 6-OHDA groups were not seriously impaired with respect to the saline-treated groups. On trial block 16, the hidden platform was relocated.

Heading angles and heading errors. The analyses of variance on heading angles and errors were almost identical and showed a significant effect of environment, no significant effect of 6-OHDA treatment, and a significant trials by environment interaction (environment, $F(1, 21) > 16$, $p < .0005$; 6-OHDA treatment, $F(14, 294) < 3.58$, $p > .07$; trials $F(14, 294) > 20$, $p < .001$; and environment by trials, $F(14, 294) < 2.40$, $p < .003$). Thus, the enriched groups were more accurate in their swims in terms of both heading angle and errors but there was no effect of 6-OHDA treatment.

Swim distance. The analysis on swim distance gave a significant trials effect, $F(14, 294) = 23.5$, $p < .001$, but no other differences.

Effects of 6-OHDA Treatment on Performance of Hemidecorticate Rats

The major result of the analysis was that hemidecorticate rats raised in the enriched environment were superior to those raised in the impoverished environment. Noradrenaline depletion did not attenuate the improvement produced by enrichment but it did block the improvement expected in the impoverished environment.

Latency. A summary of the effects of environment treatment on the performance of the hemidecorticate rats is given in Fig. 4. Figure 4A illustrates the escape latencies displayed by the hemidecorticates that were given saline or 6-OHDA treatments when neonates and placed in the enriched environment. Figure 4B shows the performance of equivalent groups raised in the deprived condition. All of the groups demonstrated an ability to acquire the task as evidenced by a decline in escape latencies with training and by subsequent increases in latency in response to relocation of the platform. However, the groups housed in the enriched environment had faster acquisition latencies than the groups raised in the deprived environment. Furthermore the overall performance of the 6-OHDA-treated groups was inferior to that of the saline-treated groups, particularly for the comparison made for the deprived condition. The analysis of variance on latency showed that the main effects of environment ($F(1, 22) = 11.19$, $p < .003$), 6-OHDA treatment ($F(1, 22) = 6.41$, $p <$

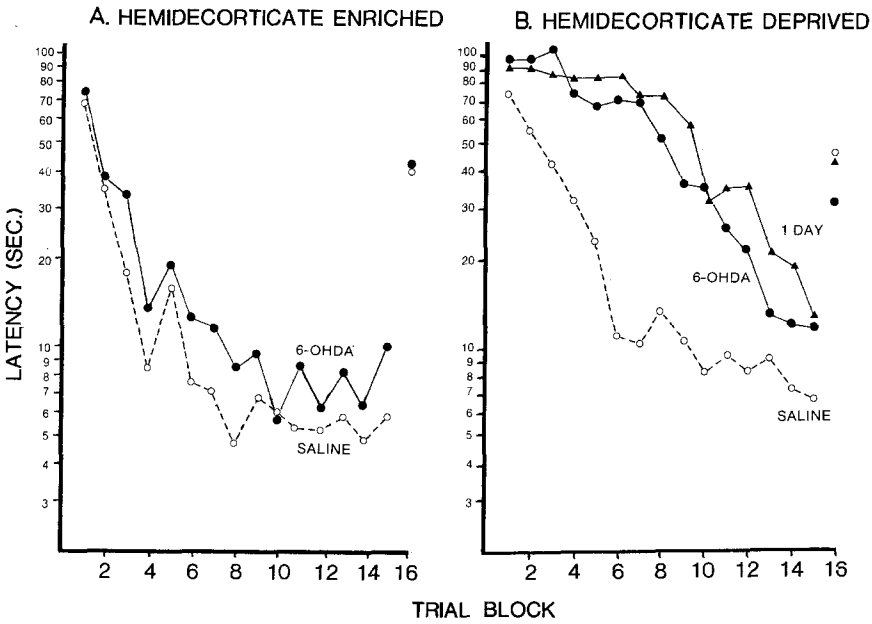

FIG. 4. Mean latencies of acquisition on the water task for (A) rats treated with 6-hydroxydopamine (6-OHDA) or saline and housed singly in standard laboratory cages (deprived) and (B) rats treated neonatally with 6-OHDA or saline and hemidecorticated in adulthood and then tested after a recovery period in which they were housed in deprived conditions (saline and 6-OHDA) or tested beginning 1 day after surgery. Note that the 6-OHDA-hemidecorticate group raised in the deprived condition was impaired compared to the saline–hemidecorticate group and further that the performance of this group was not better than the group for which no recovery was permitted. On trial block 16, the hidden platform was relocated.

.02), and trials ($F(14, 308) = 43.2$, $p < .001$) were all significant. The environment by 6-OHDA treatment interaction did not quite reach significance, $F(1, 22) = 3.46$, $p = .076$, but the trials by environment and trials by 6-OHDA treatment interactions were significant, $F(14, 308) > 2.44$, $p < .002$. The third order interaction was not significant.

Heading angles and heading errors. Analysis of heading angles and errors gave results similar to those obtained for latency. The main effects for environment, 6-OHDA treatment, and trials were all significant ($p < .01$) as was the environment by 6-OHDA treatment interaction. That is, all groups displayed improvement in accuracy over training trials, but the performance of the animals treated with enriched housing was better than that of the animals housed in the impoverished environment and the performance of the animals treated with saline was better than that of the animals treated with 6-OHDA. Furthermore the animals treated with 6-OHDA and housed in deprived conditions were extremely impaired with respect to all of the other groups.

Swim distance. Analysis of swim distance gave significant main effects for environment, 6-OHDA treatment, and trials as well as significant second order interactions ($p < .001$). That is, all groups showed improvement in swimming distance with training trials, but the improvement by enriched groups was better than that of deprived groups, and distances were shorter for animals treated with saline than for those treated with 6-OHDA. Finally, animals treated with 6-OHDA and deprived were extremely impaired with respect to all other groups.

Post hoc comparisons. Follow-up Newman–Keuls comparisons (see also Table 2) were made of the performance of the groups. For the rats receiving enrichment, there were no differences between the 6-OHDA and saline groups in latency, distance, heading angles, and rearing, but the saline-treated group obtained significantly better error scores than the 6-OHDA-treated group. For the groups raised in the deprived condition there were significant differences in latency and distance ($p < .05$). There were no differences in accuracy (the heading angles of both groups were at chance and errors were made on virtually all trials) nor were there differences in rears.

Postsurgical Recovery in Hemidecorticate Rats

To evaluate the extent of recovery shown by hemidecorticated rats, one group of rats commenced training in the spatial navigation task on the day following surgery. The latency results for this group are also illustrated in Fig. 4B. The overall performance of this group was significantly inferior to all other groups, $p < .01$ on measures of latency, and distance (Table 2), with the exception of the 6-OHDA-deprived hemidecorticate group, with which their performance overlapped. (Fig. 4B). The heading

accuracy for this group was also at chance and errors were made on all trials.

Biochemical Assay

A summary of the results of the assays is given in Table 3. There were no significant differences in NA or DA concentrations between groups that received cortical ablations and those that did not, so the results from the nonlesioned and hemidecorticate groups were pooled. The 6-OHDA treatments produced a significant depletion of NA in the cortex and hippocampus. In fact, only two animals had detectable amounts of NA in the cortex, and they had 1.8 and 2.6 pg/mg, respectively. Therefore, N.D. (nondetectable) is shown for the groups in Table 3. The assays on the brainstem showed that as a result of the 6-OHDA treatments there was a significant increase in DA in the noncortically ablated rats, $t(21) = 11.9$, $p < .001$, and a significant increase in NA, $t(21) = 2.13$, $p = .04$. In the hemidecorticated 6-OHDA-treated rats there was a significant increase in NA, $t(23) = 12.3$, $p < .001$, but there was no increase in DA, $t(23) = 1.1$, $p = .24$. A comparison was also made of DA content in the caudate ipsilateral to the hemidecortications and contralateral to the hemidecortications. Concentrations were higher ipsilateral to the hemidecortications in both the saline-treated rats, $t(11) = 3.1$, $p = .009$, and the 6-OHDA-treated rats, $t(11) = 2.38$, $p = .035$.

Histological Results

Examinations of the extent of the cortical lesions were made visually when the brains were removed for assay. All of the lesions were complete and there were no obvious differences between the different hemide-

TABLE 3
Levels of Noradrenaline, and Dopamine in Brain Areas of Rats Treated Neonatally with Saline or 6-Hydroxydopamine

		Cortex		Hippocampus		Brainstem	
Group	*n*	NA	DA	NA	DA	NA	DA
Control							
Saline	(13)	418 ± 89[a]	41 ± 13	429 ± 104*	23 ± 8	611 ± 97*	78 ± 26*
6-OHDA	(13)	N.D.	50 ± 17	N.D.	31 ± 17	1612 ± 143	114 ± 53
Hemidecorticate							
Saline	(12)	504 ± 111*	35 ± 20	448 ± 56*	24 ± 10	673 ± 106*	72 ± 18
6-OHDA	(11)	N.D.	41 ± 16	N.D.	25 ± 12	1274 ± 138	80 ± 18

Note. NA, noradrenaline; DA, dopamine; 6-OHDA, 6-hydroxydopamine; N.D., not detectable.

[a] Mean ± SD; pg/mg.

* Significantly different from 6-OHDA treated group; Student's *t* tests for independent samples, $p < .05$.

corticated groups. In all cases the lesions were similar in extent to those described in detail in Experiment 1.

Discussion

One of the novel conclusions from the results is that rats depleted of cortical noradrenaline as neonates exhibit a diminished capacity for behavioral recovery from the effects of adult hemidecortication only if they were placed in the impoverished environment postoperatively. This can be seen in two results. First, on a number of measures of place navigation, NA-depleted rats maintained in the impoverished environment for 90 days did not differ from rats tested 24 h after hemidecortication in their ability to learn to navigate to a place in space. Second, the performance of NA-depleted hemidecorticate rats placed in an enriched environment was superior to that of those placed in an impoverished one.

The results also clearly confirm four basic findings from previous studies. First, hemidecortication causes an impairment in the acquisition of a spatial navigation task (Kolb et al., 1983). Second, hemidecortication in the neonatal period is associated with reliably less behavioral impairment in the place navigation task than a similar lesion in adulthood (Kolb et al., 1983). Third, postsurgical environmental enrichment experience for 90 days facilitates recovery of place navigation following adult hemidecortication (Whishaw et al., 1984). Fourth, depletion of cortical noradrenaline in otherwise intact rats does not have any detectable effect upon acquisition of a spatial navigation task (Sutherland, Kolb, Whishaw, & Becker, 1982). Finally, the results fail to confirm the report of O'Shea et al. (1983) that neonatal noradrenaline depletion attenuates performance improvements accorded by enrichment on spatial navigation tasks in normal rats. On one measure of performance, errors, noradrenaline treatment did produce a slight performance attenuation in enriched hemidecorticated rats.

GENERAL DISCUSSION

The results of these studies demonstrate that there are some limitations on the effects that neonatal noradrenaline depletion has in attenuating the savings expected from neonatal lesions or the improvements expected from enriched housing. Nevertheless, they also demonstrate that noradrenaline does have a role in facilitating recovery from brain damage. Depleted rats subject to standard laboratory housing displayed none of the recovery observed in saline-treated hemidecorticated rats maintained in laboratory housing or depleted- or saline-treated hemidecorticates maintained in enriched housing.

These results are consistent with a notion that the presence of noradrenaline facilitates adaptive modification of cortical mechanisms in response to brain damage and in response to experience. According to such a view noradrenaline increases the impact that sensory and/or motor

events have upon plastic cortical processes, while playing no direct role in the mechanisms of plasticity themselves. There are three lines of research which are also consistent with such a role for noradrenaline. Feeney, Gonzales, and Law (1982), using cats, have found that postsurgical recovery of limb coordination after unilateral damage to motor cortex is markedly enhanced if the cats are treated soon after surgery with amphetamine and only if they are given some practice in the coordination task while under the influence of the amphetamine. The results of Kasamatsu et al. (1979) demonstrate that removal of noradrenaline from kitten visual cortex blocks the shift in ocular dominance normally produced by blocking vision in one eye during the critical period for visual development. Chronic infusion of noradrenaline into a circumscribed region of visual cortex restores relatively normal plasticity. Finally, Bliss, Goddard, and Riives (1983) have demonstrated that altering the postsynaptic availability of noradrenaline in the hippocampus significantly alters the generation of long-term potentiation of the dentate gyrus response to perforant pathway stimulation.

Given the state of current information it is not possible to specify with any degree of confidence which processes noradrenaline may modulate. Two plausible processes that could underlie the effects observed in recovery from cortical damage produced by enrichment include a modulation of compensatory synaptic enhancement in remaining cortex, similar or identical to long-term potentiation, and modulation of processes of presynaptic competition for postsynaptic space. In a study most relevant to the present paradigm, Amaral et al. (1980) have reported that neonatal noradrenaline depletion is followed by enhanced sprouting of commissural fibers in the dentate gyrus following entorhinal lesions. Similarly, Dunnett, Whishaw, Bunch, and Fine (1986) have observed enhanced sprouting of cholinergic-rich grafts in the forebrain of rats that had been treated neonatally with 6-OHDA followed, in adulthood, by denervation of cortical cholinergic input by nucleus basalis lesions. If similar enhanced sprouting follows adult hemidecortication, behavioral enrichment may be required to sculpture or functionally validate the new connections. In the absence of appropriate experience the new connections may not be adaptive, or as appears to have been the case in the present experiment, they may even impair the development of postsurgical recovery. Since the neonatal lesions in 6-OHDA-treated rats were not followed by impairments like those following the adult lesions, experiential factors associated with maturation prior to weaning (group housing, play, small size relative to cage size, etc.) may have had an effect that was equivalent to adult enrichment.

It is noteworthy that the neonatal 6-OHDA treatments resulted in increased brainstem NA in both enriched and deprived groups. There

were also increases in brainstem DA in some neonatal 6-OHDA treatment groups and increases in dopamine levels in the caudate ipsilateral to the cortical ablations. Thus, we can not rule out the possibility that some of the observed effects in the study were due to these changes. However, given substantial evidence that enrichment has its major effects on cortical processes and that spatial navigation is dependent upon cortical mechanisms, we favor the view that the observed behavioral effects were due to alterations in cortical processes or functions.

We were not able to completely confirm in our results the finding by O'Shea et al. (1983) of a reduction by noradrenaline depletion on the behavioral effect of environmental enrichment on non-brain-damaged rats. There were no differences between the enriched control and enriched 6-OHDA-treated rats on measures of latency, distance, or heading angles, but the control rats did make fewer errors. The failure to observe such a major effect may be due to task differences; for example, the radial arm maze has a greater working memory component than does the water task. However, it must also be noted that consistent anatomical/behavioral changes have not been observed following neonatal 6-OHDA treatment. Following electrolytic lesions of neonatal locus coeruleus, increases in dendritic branching in neocortex have been reported (Maeda, Tohyama, & Shimizu, 1974; Wedlandt, Crow, & Sterling, 1977). Subsequent studies using perinatal 6-OHDA have reported increased density of cortical dendrites and of synaptic contacts on pyramidal dendrites (Blue & Parnavelas, 1982; Parnavelas & Blue, 1982), whereas others have reported no changes (Lidov & Molliver, 1982) or even changes in the opposite direction, toward reduced dendritic branching and numbers of dendritic spines (Felten, Hallman, & Jonsson, 1982). In studies on the effects of 6-OHDA on behavior, Sutherland, Kolb, Whishaw, & Becker (1982) have reported absence of recovery following 6-OHDA and neonatal frontal cortex lesions, whereas in the present study the combined treatments did not produce greater impairments than were observed following only the neonatal hemidecortications. Taken together, these studies suggest that the effects of perinatal 6-OHDA treatment and its interaction with subsequent brain damage are dependent upon a number of factors that have not been fully deliniated. Nevertheless, the results of the present work suggest that the behavioral consequences of 6-OHDA treatment and its interaction with subsequent brain damage are importantly dependent upon the type of brain damage, its locus, as well as upon the environmental housing conditions.

Finally, we have demonstrated that the hemidecorticate rat preparation and the place navigation task provide a potentially very useful model system for identifying important processes that underlie behavioral and cognitive recovery from neonatal and adult cortical damage in humans (St. James-Roberts, 1981).

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