Environmental Stimulation Reduces Learning Deficits in Experimental Cretinism

Abstract. *Behavioral deficits in adult rats exposed perinatally to thiouracil were substantially reduced or eliminated by a 5-week period of "superenriched" postweaning rearing conditions before testing. This treatment resulted in remediation of hypothyroid rats' deficits in maze learning, maze retention, and resistance to extinction of bar-pressing; the facilitative effect persisted for more than 4 months. These behavioral results were consistent with neurohistological findings from studies of early thyroid deficiency and postweaning environmental stimulation in rats.*

Thyroid deficiency around the time of birth in rats produces enduring impairment of learning capacities (*1*) and central nervous system development (*2*); these changes parallel the permanent arrest of intellectual functioning that is the hallmark of human cretinism (*3*). Conversely, exposure to a complex, enriched environment in the early postweaning period results in both neuroanatomical changes (*4*, *5*) and enhanced behavioral performance (*6*) in normal rats. We report here that enriching the postweaning environment substantially reduces several learning deficits which early hypothyroid rats typically display after impoverished rearing conditions.

In our main experiment we induced hypothyroidism by feeding mash containing the antithyroid drug thiouracil (0.2 percent dose) to pregnant Holtzman rats from day 17 of gestation to 10 days after birth, approximately the critical period in which thyroid deficiency results in adult learning disorders in rats (*7*). Control mothers received untreated mash during the same period. During the first month after birth the drug-exposed offspring displayed retarded physical growth, delayed eye opening, reduced activity, and other characteristic hypothyroid signs. At 36 days of age, 42 thiouracil-treated and 48 normal offspring were weaned, and both treated and normal littermates were randomly assigned to enriched or impoverished housing conditions which were maintained until 70 days after birth.

The rats in the enriched condition (24 normal, 21 treated) were continuously housed in a "superenrichment" apparatus similar to that devised by Kuenzle and Knüsel (*8*). This apparatus consisted of three compartments, each 56 by 51 by 38 cm, which were interconnected by small tunnels containing swinging gates. The compartments contained play objects, shelves, ramps, sleeping boxes, and an enclosed maze. This environment differed from the enriched conditions used by Rosenzweig *et al.* (*4*) in that nearly four times as many rats were housed within an area that was about three times as large. More importantly, in our procedure features of the apparatus (such as, food and water locations, direction of swing of the tunnel gates, and presence or absence of the maze) were repeatedly changed, so that approximately every 3 days the rats had to learn a new means of obtaining food or water.

The rats in the impoverished condition were housed individually in standard 24 by 18 by 17.5 cm cages having three opaque sides and mesh fronts. Except during the rehousing at weaning, no rats in either type of housing were handled until 70 days after birth, after which all rats were housed individually in the standard rack cages. At 75 days of age, randomly selected groups of 24 thiouracil-treated and 24 normal rats were placed on a daily food deprivation schedule in which the rats were maintained at approximately 85 percent of normal free-feeding body weights.

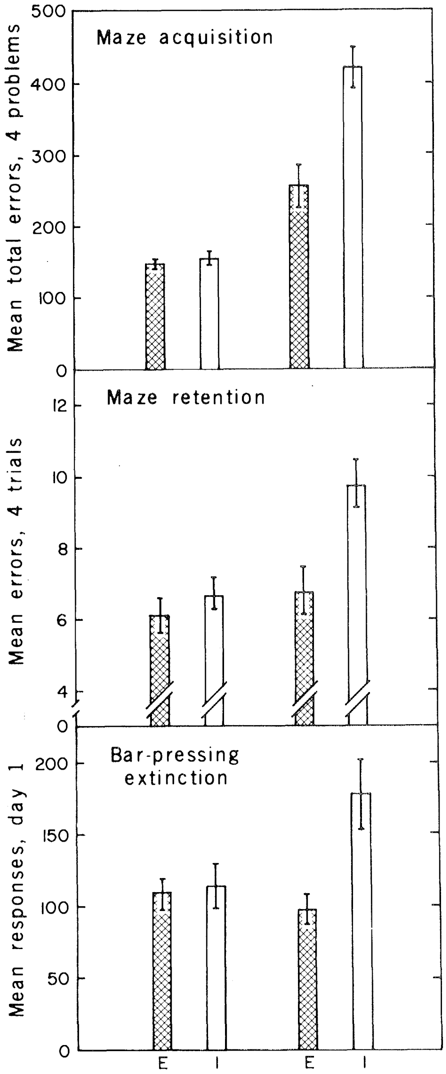

Fig. 1. Means and standard errors of scores on three behavioral tasks by normal and hypothyroid rats following enriched (*E*) or impoverished (*I*) rearing conditions. The upper panel shows total errors to criterion on problems T-6, T-9, T-10, and T-12 of the symmetrical maze series. The center panel gives mean errors in four-trial retention tests on maze problems T-9, T-10, and T-12. The bottom panel shows total bar-pressing responses in the first session of extinction.

On days 80 to 132, the rats were presented with four practice and four test problems in a symmetrical maze apparatus (*9*). In the test problems, each rat was trained in a single session until it attained criterion. Two to four days after each of the last three problems, a four-trial retention test was given. Testing continued with a passive avoidance task under conditions of free access to food on days 148 to 152. The animals were then tested on bar-pressing tasks with the deprivation schedule reinstituted, on days 157 to 183. These tests consisted of five continuously reinforced acquisition sessions and three 15-minute extinction sessions. The females were returned to the symmetrical maze for two final problems at 200 to 210 days of age.

In line with previous studies, the impoverished hypothyroid rats displayed behavioral deficits in maze acquisition, maze retention, and extinction of bar-pressing (Fig. 1). These deficits were sharply reduced in the hypothyroid rats that were exposed to the postweaning superenrichment conditions. In maze acquisition, the mean difference in error scores between the enriched and impoverished hypothyroids ($P < .001$) represented a 62 percent reduction of the performance deficit, defined as the difference between the isolated hypothyroids and the two normal groups. The deficits in maze retention and bar-pressing extinction were essentially abolished ($P < .01$) in the enriched hypothyroids (*10*). The hypothyroid groups also showed significant ($P < .005$) deficits in passive avoidance tests, but with this task no effect of enrichment appeared in either the hypothyroids or normals (*11*).

The final maze tests of females on days 200 to 210 showed durable effects of the enriched and impoverished treatments. Deficit reductions in these tests amounted to 54 percent in acquisition and 86 percent in retention, relatively small declines from the corresponding reductions of 77 and 100 percent for female hypothyroids in their initial maze testing.

The maze learning results were confirmed in two additional experiments (*6*). In one of these, with 54 normal and thiouracil-treated rats, maze learning deficits were reduced 33 percent by 1 month of postweaning enrichment of the standard type used by Rosenzweig *et al.* (*4*). In the other study, maze learning in severely deficient (propylthiouracil-treated) rats was significantly facilitated by superenrichment treatment on days 71 to 103.

Under the conditions of our studies, there was no significant facilitation of performance by enriched or superenriched experience in normal rats (*12*). This makes unlikely the possibility that our hypothyroid rats' performance was facilitated by transfer of specific associations from the enrichment settings to the criterion tasks. It also argues against the possibility that the facilitations were mediated by differences in exploratory tendencies, gross activity levels, emotionality, or other motivational functions that might have been induced by the two housing treatments. Some forms of transfer—either specific associations from the enriched environment or a generalized resistance to new learning stemming from the impoverished experience—could nonetheless have accounted for part of the differences between the performance of enriched and impoverished hypothyroid rats in maze acquisition. Our maze retention and bar-pressing extinction tasks would seem less subject to such influences, however. In both these cases, transfer mechanisms would tend to be overshadowed, in terms of their effects on long-term memory or resistance to extinction, by the training experience in the acquisition phases of these tasks and the fact that the various groups were trained to approximately equal levels of mastery (all groups were trained to the common criterion of learning in each maze problem and to virtually identical asymptotic levels in bar-pressing acquisition).

Our preferred interpretation of these results, therefore, is that postweaning enrichment resulted in enhancement of learning and memory capacities in the hypothyroid rats that was relatively generalized and enduring. In general, our data suggest that the reduced synaptogenesis and associated hypoplasia of the cortical neuropil which result from perinatal thyroid deficiency (*2*) may be in part reversed directly by growth-promoting effects of environmental stimulation in the central nervous system. In particular, the neurohistological changes which have been demonstrated in studies of enriched experience (*5*), including increased lengthening and branching of cortical dendrites, increased density of dendritic spines, and increased size of synaptic junctions, seem likely to be involved in such reversal. Our data are also consistent with results (*13*) showing persistence of brain changes for many weeks after rats are shifted from enriched to impoverished conditions (as in our studies) and demonstrations of larger neuroanatomical changes from superenriched than from standard enriched conditions (*8, 13*). It remains to be demonstrated that the effects of environmental experience and early thyroid deficiency interact at the neurohistological level suggested here.

Elsewhere (*6*) we have compared our findings with analogous results showing reductions of behavioral abnormalities by postweaning enrichment in malnourished rats (*14*) and rats with brain lesions (*15*). The significant remediation shown in all of these studies offers encouragement to those attempting to devise effective environmental therapies for certain human brain dysfunctions (*16*).

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9. The symmetrical maze has been described in detail [J. W. Davenport, W. W. Hagquist, G. R. Rankin, *Behav. Res. Methods Instrum.* **2**, 112 (1970)].
10. In analyses of variance, drug-by-environment interaction effects were significant for maze acquisition errors ($F = 12.61$; d.f. = 1, 37; $P < .005$) and bar-pressing extinction responses ($F = 4.62$; d.f. = 1, 37; $P < .05$), but not for maze retention errors ($F = 3.34$; d.f. = 1, 37; $P < .10$); for the latter task the main effect of enriched versus impoverished environment was significant ($F = 8.01$; d.f. = 1, 37; $P < .01$). The effects of enriched versus impoverished rearing in the thiouracil-treated groups reported in the text were evaluated by conservative t-tests with the normal groups' scores excluded from the error variance because of differences in variability of normal and thiouracil-treated groups. No significant differences or interactions involving the sex variable occurred in the maze or extinction tasks.
11. The passive avoidance deficit in the hypothyroid rats probably does not represent a learning or memory deficit but rather a persistent form of hyperactivity which rats treated perinatally with thiouracil display in adulthood [J. W. Davenport (*6*); ——— and R. S. Hennies, *Dev. Psychobiol.*, in press].
12. See J. W. Davenport (*6*) for a discussion of the discrepancies between the results in our normal group and the many studies showing enrichment-facilitated learning in normal rats. Some of the latter suggest that the absence of environment effects in our normal rats may be attributed to our use of moderately severe hunger conditions and extensive adaptation of the animals.
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Binocular Interaction in Strabismic Kittens Deprived of Vision

Abstract. *Artificial strabismus in kittens decreases the proportion of binocularly driven units in area 17 of the cortex. This change in the binocular interaction of cortical cells also takes place if the kittens are deprived of vision from the day in which the strabismus is surgically produced to the day of the electrophysiological recording. Thus, altered motility of the eyes per se is sufficient to affect binocular interaction in the neurons of area 17 of the cortex.*

Hubel and Wiesel (*1*) have shown that artificial strabismus in kittens decreases the number of binocularly driven neurons in area 17 of the cortex. This is usually ascribed to asymmetry in the two visual inputs to the binocular neurons of the cortex. In that case, binocular interaction should not be decreased if strabismic kittens have no visual experience. The obvious alteration which remains in strabismic kittens reared in darkness is asymmetry of eye movements.

We tested the hypothesis that the altered motility of the eyes per se is sufficient to decrease the proportion of binocularly driven cells in the striate cortex. We induced surgical strabismus in kittens during their critical period (*2*) and simultaneously prevented them from seeing until the day of the electrophysiological recording (third month of life or later). The results supported the hypothesis.

Experiments were performed on eight kittens. In six of them, under halothane