Complex Environments: Effects on Brain Development

Many scientists have believed for some time that very early experiences are critical in intellectual and emotional development, but only within the last decade has it been demonstrated that the actual structure and chemistry of brain tissue are affected by differential rearing. If animals are reared in an environment that is more complex than the standard laboratory cage, interesting changes occur in key brain areas, accompanied by behavioral changes. Progress is now being made toward ascertaining the specific effects of rearing conditions on brain and behavior, the properties of the environment that contribute to these effects, and the developmental periods in which brain tissue is most sensitive to environmental modification.

The goal of these experiments has been to determine the effects of enrichment and impoverishment on brain development, but the definition of these conditions remains a tricky problem. No one really knows what constitutes an enriched environment for a young rat, for example. But a group of scientists at the University of California at Berkeley, headed by Mark Rosensweig, a biological psychologist, Edward Bennett, a neurochemist, and Marian Diamond, a neuroanatomist, believed that rearing rats in groups of 12 in a large cage, with playthings that were changed daily, would certainly be more complex, if not more enriching, than the experience of living alone in a standard lab cage. These definitions of enrichment and impoverishment have since been used by almost all those working with rats, with only slight modifications.

The Berkeley scientists found that, compared with "impoverished" rats, "enriched" rats had a heavier cerebral cortex, which is an area of the brain associated with intellectual functioning and information processing, and greater thickness of cortical tissue. The occipital region of the cortex, which processes mostly visual information, seems to be the area most affected by enriched rearing. A number of structural differences were also noted, such as an increase in the size of the nerve cell bodies and their nuclei, suggesting that these cells maintained a higher metabolic activity. Measures taken on brain RNA and DNA supported this hypothesis. While the amount of DNA per unit weight of brain tissue decreased, the amount of RNA remained unchanged, so that the ratio of RNA to DNA was higher for the enriched rats. This increase suggests higher metabolic activity.

Further studies revealed that there were more glial cells in rats reared in the enriched environment. These cells perform a variety of functions including transportation of materials between capillaries and nerve cells, formation of the fatty insulating sheath around the neural axons, and removal of dead neural tissue. Biochemical differences in addition to the changes in RNA and DNA included an altered activity of acetylcholinesterase, a key enzyme that breaks down a chemical involved in transmitting information from nerve cell to nerve cell. The enriched rats also showed greater activity of the less specific enzyme known as cholinesterase, which is found in the glial cells and blood capillaries that surround the nerve cells.

Impact on Memory?

The finding that enriched rearing results in measurable physical changes has led to speculation concerning the importance of the changes and their value to the rat. There is some disagreement concerning whether these changes are related to the mechanisms underlying memory storage. One hypothesis is that the changes in brain must be due to the accumulation of minute learning experiences during enriched rearing; another is that these changes might simply be related to "fine tuning" the nervous system to the environment. Evidence bearing on the debate has been gathered by a group of scientists at the University of Queensland in Australia, including Roger Walsh. They hypothesized that if enriched rearing effects are at least partly attributable to long-term memory storage, these effects should be pronounced in those areas of the brain that are known to be involved in long-term memory. Some evidence points to the hippocampus as one of these areas, and the Queensland group has been able to show particularly large increases in the size of the medial area of the hippocampus after enrichment. Whether these increases are related to memory storage is still unclear, however.

A number of scientists have been investigating the enrichment effects at the level of the nerve cell itself. Kjeld Møllgaard of the University of Copenhagen, for example, in collaboration with the Berkeley group, found that differential rearing produced differences in the size of synaptic junctions, the actual connection sites that transmit information from one cell to the next. The occipital region of enriched rats' brains had synaptic junctions that averaged much larger in cross section than those of impoverished rats. William Greenough and his colleagues at the University of Illinois have found similar, though smaller, increases in the size of synaptic junctions, and in addition more branching of nerve cells in the enriched rats, which suggests that more connection sites are being made between nerve cells. Whether these differences provide the animal with potentially superior capabilities is still unanswered.

Lynda Uphouse, of Yale University, among others, is using a different approach in studying the effects of enriched environments, which involves the hybridization of brain RNA from enriched and impoverished rats to DNA, to get an idea whether the RNA from the enriched brain has a greater number of unique base sequences. Early results from some experiments suggest a greater complexity of RNA from enriched rats; the data are not yet conclusive.

Considerable research has been devoted to identifying the behavioral changes that accompany the physical changes after enrichment; unequivocal answers are not yet available. Impoverished rats are clearly more emotionally reactive and more aggressive than enriched ones, take longer to adapt to testing situations, and generally perform rather poorly on learning tasks. Whether there are real differences in their learning abilities, however, has been very difficult to determine because emotionality is so important to an animal's performance on a learning task. Nevertheless, most investigators believe that the enriched rat does have potentially superior learning capabilities, over and above its superior ability to adapt to novel environments.

One of the important questions still to be answered is what specific properties of the enriched environment are responsible for the brain changes. Reasoning that visual stimulation must be a significant component since the brain changes are concentrated in the visual cortex, the Berkeley group studied blinded rats reared in enriched environments. They found that in spite of the total absence of visual stimulation, brain changes still occurred and were still concentrated in the occipital region, visual stimulation being thereby ruled out as a necessary component of enrichment. Since many people believe that olfactory information about the environment is more important to a rat than visual information, it would be of interest to know what role olfactory stimulation plays in the development of the brain changes. While this question has not been systematically investigated yet, the Berkeley group has found that rats that are exposed to the smells of an enriched environment, as well as to its sights and sounds, but that do not actively participate in it, do not develop the brain changes typical of the enriched rats.

The investigators have also explored the question of what constitutes an enriched environment from the standpoint of social versus nonsocial influences. Simply rearing rats in social groups, without the constant change of toys, was not sufficient to produce the typical enriched brain, although it did produce smaller changes. Nor did rats reared by themselves in physically enriched environments show the typical brain changes. Apparently, neither social grouping nor varied stimulation alone provides the appropriate characteristics of enrichment. However, rats that were allowed daily access to a physically enriched environment while under the influence of a stimulant or during the dark part of their cycle (when rats are normally more active) did have the brain changes associated with enrichment. In consequence, the Berkeley group is convinced that at least one of the relevant features of enrichment is the highly active exploration of a varied physical environment, which can be the result of drugs, darkness, or social grouping.

Are there even more enriching environments for the rat which can produce even greater brain changes? The Berkeley group reared rats in a seminatural outdoor environment, and found that they have even heavier cortexes than the rats reared in the lab's enriched environment. Other investigators have found that even laboratory environments can be made more enriching in terms of their effects on brain development. Just where the limits to these enrichment effects may lie has been the subject of no little speculation.

Enrichment and impoverishment effects on brain development have been observed in rodents other than rats, but no one has yet attempted to study these effects in higher mammals, such as monkeys. William McKinney, at the University of Wisconsin, however, has evidence that another type of social stress during development, separation from the mother, has measurable effects on brain chemistry. McKinney has now launched a major project, involving several universities, which will determine whether long-term differential rearing results in altered brain development in the monkey. A great deal of interdisciplinary cooperation will be necessary to examine these effects in monkeys, but it is now widely agreed that the importance of studying the phenomenon in a species more closely related to man makes the effort well worth the cost.

Behavioral Studies with Monkeys

The lack of data on the effects of differential rearing on brain development in monkeys is in contrast to the large body of literature which deals with the effects of rearing conditions on their later behavior. Most of these studies are not strictly comparable to the rat experiments because enrichment is defined differently for the monkey and because differential rearing environments begin right after birth rather than after weaning, but a number of parallels can be noted. For example, Harry Harlow and his associates at the University of Wisconsin have found that impoverished monkeys, like impoverished rats, tend to be more emotionally reactive and more aggressive as adults, and more fearful in novel environments, than normal animals. Because studies of learning abilities in monkeys, as in rats, are complicated by the effects of emotionality in a test situation, it has been very difficult to determine whether differential rearing produces any real differences in intellectual abilities, although there is some evidence of differences at least on complex learning tasks.

Another parallel has emerged from Gene Sackett's work at the Regional Primate Center in Seattle. He noted that female monkeys seemed to be less vulnerable than males to the harshest effects of impoverishment on social behavior. The Berkeley group has recently gone over the data on brain measures that it collected on female rats, and has found indications that female rats are less vulnerable to isolation than are males in terms of brain effects. Sackett interprets his findings by pointing to the generally more rapid developmental rate of females, which would put them at a more mature stage when they are exposed to the impoverishment.

Patricia Goldman, of the National Institute of Mental Health, however, has evidence that a certain part of the brain, specifically the orbital prefrontal cortex, develops more slowly in the female monkey, and believes that Sackett's findings might be interpreted in another way. Before enriched or impoverished rearing conditions can have an effect, it might be necessary for specific parts of the animal's brain to reach a certain stage of development. If the animals were removed from their different rearing conditions before the brains of the females had developed to this point, the enriched and impoverished females would show fewer differences and would appear to be less vulnerable than the males. Both of these hypotheses emphasize the notion that the magnitude of the effects of rearing conditions is at least in part dependent upon the developmental stage at which the differential rearing occurs.

While most investigators tend to agree with this notion, they also firmly deny that it is a critical-period effect which is strictly limited to early life, and cite evidence that brain structure and chemistry can be modified by enrichment even in "elderly" rats. In addition, the Berkeley group has shown that if rats reared in enriched conditions are later transferred to an impoverished environment, many of the brain changes produced by the enrichment gradually diminish. The brain apparently maintains a great deal of plasticity well beyond the early developmental period.

Greenough has reviewed research on the time course of enrichment effects on brain and behavior, and suggests that some brain structures, particularly those involved in the control of emotion, may show more susceptibility to enrichment effects during the early period and much less during later life, while others, such as the cortex, may benefit from enrichment throughout the animal's life.

The fact that no one has been able

to define a critical developmental stage, during which enrichment must be present if the brain changes are to occur, is particularly intriguing to those concerned with child development, and may offer hope to those children who were severely deprived in early life. While some workers in the area of child development have found that culturally impoverished children develop more slowly than more enriched children, others have pointed to cases where some of the detrimental effects of early impoverishment have been reversible after subsequent enrichment. Nevertheless, James Prescott, of the National Institute of Child Health and Human Development, believes that in light of the rapidly accumulating evidence on the effects of rearing environments on brain development in animals the possibility of such effects in children must be seriously considered. He believes that the studies in which brain differences are found between rats reared in social groups and those reared in social groups with frequently changed toys are particularly striking, and unnerving to anyone currently assuming that only very severe impoverishment might affect brain development in children.

Whatever effects an enriched environment may have on an individual, these effects clearly interact with other factors, such as the individual's sex, genetic makeup, and nutrition. For example, those working with rats assign some members of each litter to each of the rearing conditions in order to control at least partially for the effects of genetic variation on brain development, which always interact with the effects of rearing conditions. In addition, evidence exists that an enriched environment is able to overcome in part the detrimental effects on behavior produced by brain lesions, malnutrition, or hypothyroidism in rats. Sackett points out that some monkeys raised in impoverished conditions do not show very much abnormal behavior, which suggests that some unknown factor is interacting with the animal's rearing conditions and somehow providing him with a degree of insulation. The investigation of these unknown factors should provide clues about how impoverishment effects can be minimized and how enrichment effects can be potentiated.

While it is clear that enrichment has a definite effect on the brain, the significance of these effects remains obscure. Do these "super-rats" have superior capabilities by virtue of having more neural connections and a generally more complex brain? Most investigators tacitly agree that the changes in brain after enrichment must somehow be beneficial to the organism, but the research on behavioral differences has been slow and contradictory, and it is still not even certain that the brain changes are responsible for the behavioral differences which have been noted. A number of scientists favor putting off the question of the significance of the brain changes, in order to concentrate on specifying what the changes are, what features of the environment produced them, and in what developmental periods the brain is most susceptible to environmental modification. A great deal more about how the brain functions will have to be discovered before anyone can say just why enrichment has effects on the brain, and what these effects may mean to the animal, but that there is a connection between brain development and the richness of the environment in which an animal lives now seems inescapable.

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Metrology: A More Accurate Value for Avogadro's Number

Scientists at the National Bureau of Standards (NBS), Gaithersburg, Maryland, have measured a value for Avogadro's number with an uncertainty that is reduced by a factor of 30 as compared with previous direct determinations. A variety of new metrological techniques and high quality silicon single crystals have been used to obtain this value. Since the new value of Avogadro's number ($6.022\,094\,3 \times 10^{23}$ per mole $\pm 6.3 \times 10^{17}$) is not greatly different from that previously known for the constant, the immediate impact of the NBS work is likely to be felt in the application of the separate methods developed for measurements of the abundance of the isotopes of silicon, the density of the silicon, and the lattice spacing of the crystalline silicon in various standards procedures.

In the future, however, with further refinements of these techniques, it may be possible to redefine the kilogram in terms of the product of the Avogadro constant and 1/12 the mass of a carbon-12 atom. This definition would remove the last remaining artifact standard (the kilogram is still the mass of a cylinder made from platinum and iridium which is kept at the International Bureau for Weights and Measures in Sevres, France).

Avogadro's number is the ratio of the mass of 1 mole of an element (the atomic weight) to the mass of one atom of the element. For a crystalline material with cubic symmetry, the mass of one atom can be found as $\rho a_0^3/n$, where ρ is the density of the material, a_0 is the lattice spacing of the cubic unit cell from which the crystal lattice is built up, and n is the number of atoms in the unit cell. The problem is to accurately measure the atomic weight, the density, and the lattice spacing. Each of these measurements constituted a separate project for the NBS team, whose efforts were coordinated by R. D. Deslattes.

Silicon was the material chosen to be measured mainly because of the large effort on the part of the electronics industry over the last 15 years to make very pure and very uniform single crystals with well-defined properties. Silicon also has a resistant oxide coating that protects it from the environment; it contains a single principal isotope (silicon-28); and it is transparent to the x-rays used in the lattice spacing measurement. Three high quality silicon single crystals with different histories were selected for the experiments.

Although silicon consists primarily of the isotope silicon-28 (about 92 percent), it also contains lesser amounts of silicon-29 (about 5 percent) and silicon-30 (about 3 percent). Thus, in order to ascertain the average atomic weight of a silicon sample accurately, it is necessary to know the absolute abundance of each of these isotopes in the sample. This task was accomplished by a group headed by I. L. Barnes through the use of quantitative chemistry techniques that were accurate to 1 part in 10,000 and a mass spectrometer