Effect of training and environment on brain morphology and behavior

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Schrott L. Effect of training and environment on brain morphology and behavior. Acta Pædiatr 1997; Suppl 422: 45–7. Stockholm. ISSN 0803–5326

Using defined rearing or training paradigms, environmental stimulation has been found to increase brain weight (especially forebrain), cortical thickness, the number of glial cells, the glia to neuron ratio, neuronal cell body and nucleus size, and to alter synaptic profiles by increasing dendritic branching, dendritic spine density and the number of discontinuous synapses. Examples will be given from both animal and human studies that document these profound changes. Controversy exists as to whether enriched environments and/or training can compensate for neural deficits produced earlier in life. Examples will be given from animal studies with induced cortical lesions and prenatal genetic neural anomalies that support a role for environmental manipulations ameliorating earlier central nervous system damage. □ *Cortical ectopia, cortical lesions, environmental enrichment, plasticity, synaptic profiles*

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For the past 50 years researchers have investigated how the environmental surroundings of an organism influence its behavior. Much of this work has focused on the physical changes that the environment and training can elicit in the central nervous system (CNS), including alterations in brain morphology, biochemistry and physiology. This research has primarily been conducted in animals with two basic paradigms. The first is comparisons among animals with defined rearing environments: enriched—group-housed subjects in a large complex environment with toys and/or other aspects of visual, motor or cognitive stimulation; standard cage—group-housed subjects reared in a standard laboratory cage; and impoverished—isolation-reared subjects in a small cage, sometimes with less than normal amounts of visual stimulation. The second commonly used paradigm involves repeated training of a subject on a learning task. These subjects are then compared to matched subjects who did not receive training for evidence of altered CNS function. Training paradigms can also be used to examine differences among subjects who have different rates of acquisition to see if there is a structural or physiological basis to the difference. The training paradigms have also been used in humans to examine neural plasticity (reviewed in Refs. 1–3).

Using the above paradigms, numerous researchers have documented changes in gross morphology following environmental stimulation. One of the first parameters examined was brain weight. Increases in brain weight (especially dry weight) are thought to reflect increases in the synthesis of proteins. Although some studies reported that rodents reared in enriched environments had increased total brain weights (4, 5), the majority of studies found increases specific to the forebrain (6, 7) or cortex (8, 9). For example, Rosenzweig and Bennett (8) found increased cortical weight and cortical/subcortical weight ratio in rats, mice and gerbils that were reared in an enriched environment as compared to those reared in an impoverished environment. The dimensions of the brain such as thickness, height, length and width, can also be altered by environmental conditions. However, these changes appear to be more dependent on the duration of and the time at which environmental manipulations are applied, implying that there are critical periods for altering these parameters (reviewed in Refs. 1 and 2).

Structural changes in specific regions of the brain have been documented by Diamond and her colleagues. Rats reared in enriched environments had thicker occipital cortices (layers II, III and IV) than those reared in impoverished environs (10–12). This increased thickness was not due to increased neuron numbers because Diamond et al. actually found a decreased number of neurons in the occipital cortex of enriched rats. Rather, it appeared to be due to larger distances between neurons as dendritic arborization increased (see discussion below). In addition, the size of the cell body and nucleus also increased by about 20% in the upper cortical layers (11). An important contribution to the increased cortical thickness is alterations in the glial cells, which anchor and support the neurons. Diamond demonstrated increased numbers of glial cells, including oligodendrocytes, and a 16% increase in the glia/neuron ratio (2, 12). Other research groups have found similar increases in glial cells following environmental manipulations. Walsh et al. (13) and Szeligo and Leblond (14) found an increased density of glia cells and an increased glia/neuron ratio.

Some of the most exciting results involve changes in the synaptic profiles of neurons. Exposure to an enriched environment very early in life (prior to weaning) has

been shown to increase the number and length of the dendritic segments of pyramidal neurons in the occipital cortex (15). In a series of studies, Greenough and colleagues have demonstrated alterations in dendritic branching patterns following rearing in complex environments (16, 17), maze training (18), and training in a reaching task (19). These environmental manipulations lead to corresponding increases in dendritic branching, with a pronounced increase in the higher order branches. In addition, Greenough (20) has reported increased postsynaptic thickening and subsynaptic perforations in the occipital cortex of rats reared in complex environments, suggesting an increase in the discontinuous or mature type of synapse. Alterations in the synaptic profiles of neurons provide a mechanism by which the environment can alter complex behaviors such as learning.

Although the majority of studies examining the effects of training and environmental enrichment have occurred in animals, both *in vivo* imaging techniques and postmortem analysis have revealed that training and environmental variables affect the human brain. A recent report by Elbert et al. (21) using magnetic source imaging revealed that violinists and other musicians who play stringed instruments have increased representation in the primary somatosensory cortex of the digits on their left hand (the hand used for fingering) as compared to non-musician controls. This study demonstrated that specific peripheral inputs can affect corresponding central structures in humans. More diffuse inputs in the central nervous system can also affect brain morphology, as is seen in animals. A postmortem analysis of male and female brains from neurologically normal right-handed subjects by Jacobs et al. (22) revealed a positive correlation between education and dendritic branching in Wernicke's area, a region of the temporal lobes involved in processing verbal information. As level of education increased, the total length of all dendrites combined the average length of each dendrite and the total number of dendritic segments increased. This was particularly true when comparing high-school versus college-educated subjects and was found for both males and females. Of course it is impossible to know if there were initial differences (prior to schooling) in the brains of these subjects that ultimately led some, but not others, to pursue further education. These differences could have been genetic in origin or due to prenatal/early developmental factors that affected brain morphology. Animal studies, especially those using genetically identical animals with only manipulations in certain aspects of the environment at defined times, have provided converging evidence and provide support for the hypothesis that increased intellectual challenge alters brain anatomy.

Although there is much converging evidence from many groups of researchers about the kinds of brain parameters affected, there is considerable debate as to the degree of change elicited, the time periods in which these changes can occur and whether they can compensate for neural deficits produced earlier in life. This latter controversy encompasses research involving both global insults to the developing organism, such as under- or malnutrition (23, 24) (reviewed in Ref. 1), as well as focal insults such as induced cortical lesions and genetic neural anomalies. Numerous researchers have used the induced lesion paradigm to explore the property of nervous system plasticity. Lesions to the cerebral cortex during the early postnatal period result in abnormal brain organization, including alterations in cytoarchitecture and neurochemical pathways. Performance deficits in learning tasks are also present following these early lesions. Researchers have found that environmental stimulation can ameliorate some of the negative consequences of early brain damage. For example, Kolb and Elliot (25) demonstrated that cortical thinning associated with early frontal cortex lesions could be attenuated by rearing rats in an enriched environment. Rats lesioned on day 5 of life who received environmental enrichment had a 16% increase in the thickness of their overall cortex as compared to rats reared in standard cages. Improvements in learning tasks are an additional benefit of environmental stimulation in animals with lesion-induced brain alterations. Interestingly, these behavioral enhancements can be found even if there is no or little measurable change in brain parameters following the environmental stimulation (26, 27). Cortically lesioned rats reared in enriched environments have better Morris water maze (26, 28) and Hebb-Williams maze (27–29) performance than those reared in standard cages.

The above studies were performed on rodents with lesions induced during the postnatal period, after the brain has completed much of its development, including neuronal migration, terminal differentiation, axon sprouting and synaptogenesis. Lesions that occur during the prenatal period as the brain is undergoing rapid development may also affect brain organization and behavior. For example the human developmental learning disorder dyslexia is accompanied by the presence of large numbers of cortical ectopias (nests of neurons that have migrated to an improper location in the brain) in the perisylvian region of the left hemisphere (31). Cortical ectopias are also found in approximately 40–50% of mice in certain autoimmune inbred strains and these mice have been used as an animal model of the dyslexia neuroanatomical anomalies (32, 33). These ectopias develop during the prenatal period in both humans and mice (34). In mice they are found in the frontal and somatosensory cortices (32, 33) and are genetic in origin (35). Although an ectopia appears as a focal disruption, there is widespread alteration in the underlying cortex, including radially oriented fiber bundles below the ectopia that can extend into the corpus callosum (36) and an increase in the number of neurons staining positive for the neuropeptide VIP (37). In the NZB inbred mouse strain, cortical ectopias lead to specific deficits in discrimination and spatial learning tasks. However, rearing these mice in an enriched environment can compensate for the ectopia-induced learning deficit, bringing the performance of the mice with ectopias up to the levels of their non-ectopic littermates (38). Thus, rearing mice in an enriched

environment can ameliorate the learning deficits that are the consequence of a genetically induced prenatal brain insult.

As more and more genes are isolated that influence behavior, it is important to remember that the environment can have a profound effect on sculpting the behavioral output of an organism. An enriched environment can, in some cases, compensate for deleterious genes, while an impoverished environment can dampen the effect of a beneficial genotype.

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