

BRAIN PLASTICITY AND BEHAVIOR

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ABSTRACT

Brain plasticity refers to the brain's ability to change structure and function. Experience is a major stimulant of brain plasticity in animal species as diverse as insects and humans. It is now clear that experience produces multiple, dissociable changes in the brain including increases in dendritic length, increases (or decreases) in spine density, synapse formation, increased glial activity, and altered metabolic activity. These anatomical changes are correlated with behavioral differences between subjects with and without the changes. Experience-dependent changes in neurons are affected by various factors including aging, gonadal hormones, trophic factors, stress, and brain pathology. We discuss the important role that changes in dendritic arborization play in brain plasticity and behavior, and we consider these changes in the context of changing intrinsic circuitry of the cortex in processes such as learning.

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INTRODUCTION

One of the key principles of behavioral neuroscience is that experience can modify brain structure long after brain development is complete. Indeed, it is generally assumed that structural changes in the brain accompany memory storage (Bailey & Kandel 1993). Although the idea that experience can modify brain structure can probably be traced back to the 1890s (Ramon y Cajal 1928, Tanzi 1893), it was Hebb who made this a central feature of his neuropsychological theory (Hebb 1949). Hebb did the first experiments on the consequences of enriched rearing on the behavior of the rat (Hebb 1947). Later, the group at Berkeley began to demonstrate changes in brain weight, cortical thickness, acetylcholine levels, and dendritic structure that accompanied the behavioral changes related to experience (e.g. Diamond et al 1967, 1981; Globus et al 1973; Rosenzweig & Bennett 1978; Rosenzweig et al 1962). In the 1970s, and continuing still, William Greenough and his colleagues initiated a multidisciplinary investigation of the cellular effects of rearing animals in visually or motorically enriched environments (e.g. Greenough & Chang 1989). Perhaps the fundamental point that this group has made over the past decades is that synapses can form and dendrites can grow well beyond the period of brain development. Although this point is certainly not unique to Greenough, he and his colleagues have shown most forcefully that the adult mammalian brain (and presumably other vertebrate brains as well) can add not only dendrites and synapses in response to behavioral demands but also supportive tissue elements such as astrocytes and blood vessels.

There is now an extensive literature correlating neural and glial changes with behavioral change in species ranging from insects to humans. Because many other chapters review synaptic changes during development, our focus is on studies in which some sort of experimental manipulation has been shown to change behavior and neural structure, especially in mammals.

Assumptions

The study of brain and behavioral correlations necessarily involves assumptions about methodology, and this review chapter is no exception. In particu-

lar, we assume that changes in the structural properties of the brain will reflect changes in brain function. Furthermore, we assume that the most likely place to identify neural changes associated with behavior is at the synapse. In order to relate synaptic change to behavioral change, it also is assumed in the current review that synaptic changes can be measured by analysis of the postsynaptic structure of cells, either by light microscope or electron microscope techniques. We do not consider neurochemical or neurophysiological changes in the current review.

METHODS OF STUDY

Analysis of Behavior

Three important sets of behavioral distinctions are relevant to plastic changes in the brain. The first relates to the difference between exercise and skill acquisition. Running in a treadmill is wonderful exercise as it no doubt improves cardiovascular function, reduces body fat, and improves health in old age, all of which may contribute to brain plasticity. But running may not require much in the way of plastic changes to support it. Learning a new skill, such as playing a musical instrument, learning to type, or reading Braille requires extensive practice, and this practice is likely instrumental in changing the neuropil in relevant brain regions. This distinction is methodologically important because a group receiving exercise can be used as a control for nonspecific effects in a group receiving skill training. In most of the experiments reviewed below some form of exercise regime is administered to a control group that will subsequently be compared with a group receiving skill training.

A more subtle, and often unrecognized, distinction is that between voluntary movements and supporting reactions. Most voluntary movements, such as advancing a limb to grasp food, require concomitant supporting reactions. For example, when a quadruped, such as a rat, lifts and advances a limb to reach for food in an experimental test, it must support its weight with its remaining limbs. To do so, it usually supports and shifts its weight with the diagonal couplet of the contralateral forelimb and the ipsilateral hind limb, and it sometimes assists in balancing itself and moving by using its tail (Whishaw & Miklyaeva 1996). Whereas it is widely accepted that acquiring the act of reaching is a skill that is accompanied by morphological changes in the forelimb area of motor cortex (Greenough et al 1985), it is unclear whether balancing, weight shifting, and tail use are also skills in the same sense. This could be tested empirically, but the more important point relates to how much of the brain undergoes plastic change during the acquisition of the skill of reaching. Perhaps only the neurons controlling the reaching arm undergo change, but it is more likely

that the entire motor system will change to varying degrees as the animal acquires the reaching skill. Thus, experiments must be quite complex and include measures from the brain area of interest, adjacent brain regions, and the contralateral hemisphere as well as from appropriate control groups.

The third distinction is between recovery and compensation following brain injury. There is a great deal of interest in how surviving brain tissue changes to contribute to recovery following brain injury (e.g. Forgie et al 1996, Jones & Schallert 1994, Prusky & Whishaw 1996). Careful analysis of the behavior of rats recovering from injury suggests that much of what appears on cursory examination to be recovery is actually a compensatory substitution of new movements for lost movements (Whishaw & Miklyaeva 1996). Thus, the recovery of behavior following injury may not be due to spared neurons assuming the functions of lost neurons but may be due to spared neurons changing their morphology to support compensatory skills. Because both recovery and compensation are potentially important avenues for therapeutics following brain injury, this distinction, though subtle, is not unimportant.

Analysis of the Brain

The analysis of neuronal change and behavior rests upon the assumption that changes will be found at the synapse when behavior changes. There are, however, two problems to solve. First, the visualization of morphology must provide similar results from animal to animal and study to study. Injections of neuronal tracers to identify axons will not satisfy this concern because visualization of axon terminals depends critically upon how many cells are actually affected by the injection. Furthermore, it is not always possible, a priori, to know where in the brain to look for experience-dependent change, so injections into focal areas are often impractical. Second, because there are so many neurons in the brain, it is essential that only a subset of cells is stained, at best randomly, throughout the brain. Golgi-type stains solve these concerns. Somewhere between 1%–4% of neurons are stained, and there is good evidence that the staining is random (e.g. Pasternak & Woolsey 1987). Furthermore, modern Golgi techniques (e.g. Golgi-Cox; see Gibb & Kolb 1997) provide reliable and extensive staining. Once the cells are stained with a Golgi procedure, the dendritic length can be measured with the aid of a light microscope. Cells are traced using either some sort of semiautomated imaging system or a camera lucida procedure in which cells are drawn with pen and ink. The length of dendritic arborization and the density of synaptic spines then can be estimated using various methods (e.g. Capowski 1989, Kolb et al 1997a). The rationale for selecting dendrites is based upon their special attributes. In particular, dendrites represent up to 95% of the receptor surface with which neurons form

connections (Schade & Baxter 1960). The dendrites grow and retract in response to various events including neuronal activity, various chemicals, and injury to adjacent neurons. This makes dendrites one of the more sensitive indicators of change within the CNS. Finally, because dendrites form a large fraction of the neuropil, they are an important indicator of the functional capacity of neural networks. Furthermore, because the majority of excitatory synapses are found on synaptic spines, measurements of spine characteristics including their density, shape, and ultrastructural characteristics also can be made to supplement the dendritic results. (Of course, dendrites do not allow quantification of the actual number of synapses; this can only be done using electron microscopic procedures.)

EXPERIENCE AND THE CHANGING BRAIN

We can now identify a large range of neural changes associated with experience. These include increases in brain size, cortical thickness, neuron size, dendritic branching, spine density, synapses per neuron, and glial numbers. The magnitude of these changes should not be underestimated. For example, in our own studies of the effects of housing rats in enriched environments, we consistently see changes in young animals in overall brain weight on the order of 7%–10% after 60 days (e.g. Kolb 1995). This increase in brain weight represents increases in glia, blood vessels, neuron soma size, dendritic elements, and synapses. It would be difficult to estimate the total number of increased synapses, but it is probably on the order of 20% in the cortex, which is an extraordinary change!

Environmental Enrichment

The logic of enrichment studies is that one group of animals is placed in laboratory cages while a second group is housed in a more stimulating environment, the extreme case being Hebb's home (Hebb 1947). Hebb's enrichment procedure was extreme because Hebb's rats roamed fully around his home, whereas most studies of this sort have placed the experimental animals in large enclosures that contain visually stimulating objects and an opportunity to interact haptically with the environment, including the objects. In many studies, the objects are changed routinely and in some studies the social housing conditions may also be manipulated. As mentioned above, it was the group of Bennett, Krech, Rosenzweig, Diamond, and their colleagues at the University of California, Berkeley that first showed large changes in various measures of cortical morphology. As important and seminal as the Berkeley experiments were, they had the weakness that they did not demonstrate changes in brain organization so much as in brain size. It was not until the early 1970s that several

groups, including the Berkeley group, began to look at dendritic fields (e.g. Globus et al 1973, Uylings et al 1978). The most thorough studies of this sort were done, however, by Greenough. Typical experiments showed that the dendritic fields of these neurons increased by about 20% relative to cage-reared animals (e.g. Greenough & Volkmar 1973; Volkmar & Greenough 1972). These effects were not restricted to the visual cortex, although other regions tended to show lesser effects and some cell types were relatively unaffected (e.g. Greenough et al 1973). A parallel set of studies has examined changes in the cerebellum of animals trained in complex motor tasks and, as might be anticipated, there are parallel changes in the Purkinje cells, which are the major output cell of the cerebellum. Furthermore, as in the studies of neocortical regions, there is evidence that neuronal changes are not inevitable consequences of experience because cerebellar granule cells do not show the same changes (e.g. Floeter & Greenough 1979).

Although most studies of environment-dependent changes in the cortex have been done with rodents, several studies have used monkeys or cats. In general, these studies have found similar results (e.g. Beaulieu & Colonnier 1987, Floeter & Greenough 1979, Stell & Riesen 1987). One curious difference between the rodent and primate studies appears to be the effects upon the visual system. Because monkeys are highly visual compared to rats, one might predict greater effects upon the visual cortex of monkeys; yet the opposite appears to be true. In fact, it appears that the effects upon the primary visual cortex of monkeys reared in enriched environments are negligible (e.g. Riesen et al 1977, Struble & Riesen 1978). One explanation is that much of the exploration of the visual world of monkeys is done without movement, and because monkeys in relatively impoverished housing can still visually explore their environment, this stimulation may be sufficient to ensure the development of visual cortical synapses. In contrast, the visual system of the rat has relatively poor acuity and is not designed for pattern vision so much as for spatial navigation. The gathering of spatial information likely requires movement in space. An alternate explanation is that because the visual areas of the primate have expanded dramatically, and because the primary visual cortex is multifunctional, then it is "higher" visual areas that show greater experience-dependent changes. In this case, one might predict that visual experiences that emphasized object exploration and recognition would lead to growth in the ventral visual pathway, whereas visual experiences that emphasized visuomotor guidance, such as in climbing or object manipulation, would lead to growth in the dorsal visual pathway (for a discussion of the two pathways, see Milner & Goodale 1995).

Most studies of dendritic change have used a Golgi-type technique to measure dendritic space, and from this there is an assumption that dendritic space is



correlated tightly with synaptic numbers. Turner & Greenough (1983, 1985) examined this hypothesis directly by calculating the number of synapses per neuron in the cortex of animals housed in enriched environments. They found an increase of about 20% in the number of synapses per neuron in the brains of enriched versus cage-reared animals. Thus, although the density of synapses in a section of cortical tissue is relatively constant in enriched and cage-reared animals, there is more dendritic space in the enriched animals and, consequently, there are more synapses per neuron. Similarly, Beaulieu & Colonnier (1988) analyzed the number and type of synapses in cats reared in laboratory cages or in enriched housing. Like Turner & Greenough, they found that synaptic changes correlated with experience. One additional finding, however, was that experience increased the number of excitatory synapses per neuron and decreased the number of inhibitory ones in the visual cortex. Thus, enrichment had modified the excitatory-inhibitory equilibrium of the visual cortex. One prediction from this observation is that neurons in the cortex of enriched animals would be more reactive to visual stimulation than those in impoverished animals.

It is reasonable to expect that if there are increases in the size of the dendritic fields of neurons, and correspondingly in the number of synapses per neuron, then these neurons will require more support both from glial cells, especially astrocytes, and from blood vessels. In one heroic series of studies, Sirevaag & Greenough (e.g. 1987, 1988, 1991) used light and electron microscope techniques to analyze 36 different aspects of cortical synaptic, cellular, and vascular morphology in rats raised in complex or in caged-housing environments. The simple conclusion was that there is a coordinated change not only in neuronal morphology but also in glial, vascular, and metabolic processes in response to differential experiences. Thus, not only are there more synapses per neuron in animals with enriched experience, there is also more astrocytic material, more blood capillaries, and a higher mitochondria volume. (Mitochondrial volume is used as a measure of metabolic activity.) It is therefore clear that when the brain changes in response to experience there are the expected neural changes but there are also adjustments in metabolic requirements of the larger neurons. One interesting implication of this conclusion is that things that influence the maintenance and adjustment of the metabolic components of the aging brain can be expected to influence the brain's capacity for neural change as well (e.g. Black et al 1987, 1989). This speaks to the importance of examining the effects of exercise and nutrition on the brain's capacity for change, especially in senescence. It is important to note in this context, however, that merely having exercise is not sufficient to induce neuronal changes. Black et al (1990) trained animals to negotiate a complex obstacle course ("acrobat rats") or placed rats in running wheels where they obtained



forced exercise. The animals in the wheels showed increased capillary formation but no change in cerebellar Purkinje cell synapses, whereas the acrobat rats showed a 30% increase in Purkinje synapses. Thus, merely increasing neuronal support does not change the neurons. The critical feature for neuronal change is presumably increased neuronal processing, which would be facilitated by a complementary increase in metabolic support.

Training in Specific Tasks

Although it is tempting to conclude that the synaptic changes observed in animals housed in complex environments reflect changes in learning about the environment, there is little direct evidence of this. One way to approach this issue is to train animals in specific tasks and then to demonstrate specific changes in dendritic fields of neurons in regions suspected of being involved in the performance of such tasks. Perhaps the most convincing studies of this sort were done by Chang & Greenough (1982). These studies took advantage of the fact that the visual pathways of the laboratory rat are about 90% crossed. That is, about 90% of the cortical projections from the left eye project via the right lateral geniculate nucleus to the right hemisphere. Chang & Greenough placed occluders on one eye of rats and then trained the animals in a visual maze. Comparison of the neurons in the two hemispheres revealed that those in the trained hemisphere had larger dendritic fields. This experiment is compelling because the rest of the two hemispheres (e.g. auditory, somatosensory, or olfactory regions) would still have interacted with the maze, and both hemispheres would be required for the motor demands. It was only the visual cortex contralateral to the open eye that could process and/or store the task-specific visual information, however; and this was reflected by the specific dendritic changes in that hemisphere.

Another experiment is relevant here. Although they did not train animals in a visual learning task, Tieman & Hirsch (1982) raised cats with lenses that restricted visual exposure to lines oriented vertically or horizontally. Many previous studies had shown that cells in the visual cortex of cats with such restricted experience show a marked change in their tuning characteristics. Hence, neurons in cats with selective exposure to lines of vertical orientation are most excitable when presented with lines of the same orientation. The new wrinkle in the Tieman & Hirsch study was that they examined the morphology of visual cortical neurons from cats with selective horizontal or vertical visual experience. Cats raised in a normal environment showed a random distribution of orientation of dendritic fields, but cats raised with selective experiences showed a change in the orientation of the dendritic fields. These changes were specific, too, because they occurred in pyramidal cells in visual cortex and not in the adjacent stellate cells.

A second set of experiments has taken advantage of the fact that rats are very talented at using their forepaws to retrieve food from tubes, through bars, and so on. Because the cortical control of the forelimbs is largely crossed, it is possible to train one limb to reach for food and to compare the layer V neurons in the forelimb region of motor cortex, many of which form the cortical spinal tract, in the trained and untrained hemispheres. Several studies have shown dendritic changes in the expected neurons (Greenough et al 1985, Kolb et al 1997a, Withers & Greenough 1989).

The changes in dendritic fields seen in the studies of visual and motor learning are strikingly reminiscent of the changes seen in studies of enriched rearing, which have been taken as evidence that the observed changes in synaptic connectivity in animals in enriched environments are somehow involved in memory and learning (Greenough & Chang 1989). While this is a reasonable conclusion, there may be important differences in details of dendritic change in the enrichment and learning studies. **It is generally found that enrichment not only increases dendritic length but also increases the density of synaptic spines on the dendrites.** In contrast, animals trained in specific tasks show changes in dendritic length but not in spine density (Kolb et al 1996). Thus, it appears that although there are marked similarities between the effects of enriched rearing and specific training on dendritic fields, there may be differences in other measures of dendritic morphology, especially spine density.

Olfactory Experience in Rodents

Rodents have a keen sense of smell so it is reasonable to suppose that experience would have significant effects upon the structure of the olfactory system. In fact, the general finding is that olfactory deprivation leads to restricted morphological development of the olfactory system, whereas olfactory training or olfactory "enrichment" leads to enhanced development (e.g. Doving & Pinching 1973, Pinching & Doving 1974, Rehn & Breipohl 1986, Rehn et al 1986) (see also the extensive studies by Leon and colleagues, e.g. Leon 1992a,b). **One surprising finding is that olfactory experience not only changes the morphology of existing neurons, but it also alters the number of neurons. For example, odor deprivation results in reductions in neuronal number** (e.g. Brunjes & Frazier 1986, Meisami & Safari 1981, Skeen et al 1986), **whereas enriched odor exposure leads to increased neuron numbers** (Rosselli-Austin & Williams 1990). **This neuronal increase is not trivial, being in the order of 35-40%! Evidence of increased neuron numbers in the olfactory system is especially intriguing because it has not been seen in analyses of neocortical or cerebellar cortex.** One important difference between the olfactory system and neocortical and cerebellar regions is that olfactory neurons are generated throughout the lifetime of rodents (e.g. Lois & Alvarez-Buylla 1994). Thus, it is likely that en-

hanced olfactory experience influences neuronal growth in the olfactory bulb throughout life. One possible reason for this could be that the addition and deletion of olfactory neurons throughout life allow a mechanism for the nervous system to form new olfactory memories and to modify existing ones. It is noteworthy that the other forebrain structure that generates neurons throughout adulthood is the dentate gyrus of the hippocampus, and this area has been implicated in certain types of learning and memory.

Plasticity in the Avian Brain

Three general types of studies look at brain plasticity and behavior in birds. These include studies of bird song, imprinting, and one-trial learning. Studies of bird song have been reviewed extensively elsewhere (e.g. Bottjer & Arnold 1997) and largely have focused on the development of neurons and their connectivity. Our emphasis here therefore is on imprinting and one-trial learning.

Imprinting is a process whereby an organism learns, during a sensitive period in development, to restrict its social preferences to a specific class of objects (e.g. Bateson 1966). Imprinting is especially common in precocial birds such as chickens or geese. Within hours of hatching, a young bird will approach and follow a moving object, which may or may not resemble an adult female of the same species. Horn and his colleagues (for reviews, see Dudai 1989, Horn 1985) have identified a specific neural region (region IMHV) in the chick brain that changes morphologically during imprinting. For example, there is increased metabolic activity and genetic (RNA) activity in IMHV during imprinting. Morphological studies have emphasized ultrastructure where it has been shown that imprinting is correlated with an increase in the length of the postsynaptic density (PSD) of spine synapses in the IMHV, but only in the left hemisphere (Horn et al 1985). The PSD is the active receptor-dense region of the postsynaptic cell. Thus, as the PSD lengthens, the number of receptors for neurotransmitters increases (Matus et al 1981). Horn (1985) noted that small changes in the length of the postsynaptic density provide an effective way for presynaptic cells to control the firing of postsynaptic cells, or to control local synaptic interactions. Significantly, there does not seem to be an increase in synapse number in the IMHV during imprinting.

Several studies have taken advantage of the observation that one-day-old chicks peck spontaneously at a small bright chrome bead. For instance, Patel & Stewart (1988) coated the bead with either a substance with an aversive taste or nonaversive water. Chicks presented with the aversive taste learn in one trial to avoid the bead, whereas those presented with the nonaversive bead continue to peck (for a review, see Rose 1985). Various regions of the chick brain, such as the hyperstriatum, show enhanced activity following training as revealed both by electrophysiological investigations and studies of glucose accumulation.

Patel & Stewart used a Golgi technique to impregnate chick brains 25 h after training and found a twofold increase in spine density in the neurons in a region of the hyperstriatum (intermediate medial hyperstriatum ventrale) in the “trained” chicks. They concluded that this represented an increase in synapses that reflected the learning. This interpretation was supported by a second study in which Patel et al (1988) trained chicks on the passive avoidance task described above but, in their experiment, half of the trained chicks were given a subconvulsive transcranial electroshock 5 min after training. This procedure rendered about half of the trained animals amnesic for the experience. The spine density was found to be higher in the chicks that remembered the aversive nature of the training stimulus than in the chicks rendered amnesic. This finding argues strongly in favor of a specific role for dendritic spines in experience-dependent memory formation in the chick.

There is one additional study that suggests that their conclusion may not be quite correct, however. Wallhauser & Scheich (1987) presented newly hatched chicks with either a hen or an acoustic stimulus, with the goal of imprinting the chicks to the visual or auditory stimulus. The neurons in different regions of the hyperstriatum of the imprinted chicks were compared with those of isolated chicks. There was a decrease in spine density. Thus, in the first study, there was an increase 25 h after training, whereas in the latter study there was a decrease 7 days after training. The simplest conclusion from the chick studies is that the novel stimulation may cause an initial rapid increase in spine density, followed by a pruning. The critical experiment here would be to examine the neurons in the brains of animals killed at different times in the training.

The Invertebrate Nervous System

There is a burgeoning literature on the effects of experience on the morphology of neurons of invertebrates, both during metamorphosis (e.g. Jacobs & Weeks 1990, Kent & Levine 1993) and in response to experience (e.g. Hoy et al 1985). Two studies on *Drosophila* are especially intriguing. In one, Technau (1984) showed that the complexity of neurons in *Drosophila melanogaster* depends upon the flies' living conditions. Flies were housed for 3 weeks either singly in small plastic vials or in groups of 200 in larger enclosures with colored visual patterns on the walls, various odor sources, and plants. Analysis of the Kenyon cell fibers in the mushroom bodies (cells in the “brain” of the fly) showed about 15% more fibers in the enriched versus impoverished flies. A subsequent study by Heisenberg et al (1995) showed that most regions of the *Drosophila* brain were continuously reorganized throughout life in response to specific living conditions. In particular, social and sexual activity was associated with increased brain size, as was the volume of space available. These experience-dependent changes in *Drosophila* are remarkable and leave little

doubt that experience is a major force in shaping the nervous system of all animals. Furthermore, changes in insect brains are not only seen in artificial lab experiments but can also be seen in ecologically valid settings. For example, Withers et al (1993) examined the changes in the brain of the honey bee in relation to the division of labor in adult worker bees. Adult worker bees spend about the first 3 weeks of their 4–7-week life performing a variety of tasks within the hive, including caring for the queen and brood (“nursing”). They then make a dramatic transition in behavior and begin to forage outside for food. Food foraging is a complex behavior that requires that the animal learn the location of both the hive and the food and the nature of different foods, as well as learn to recognize and use species-typical signals about food sources from other bees. Withers et al (1993) found not only that the behavioral change is associated with striking changes in brain structure, but that these changes are dependent not on the age of the animal but on its foraging experience. This honey bee model offers a new entry into the cellular mechanisms of neural and behavioral plasticity.

Dendrites and Behavior in Humans

On the basis of studies in laboratory animals it is reasonable to expect correlations between neuronal structure and behavior in humans. One way to approach this would be to look for a relationship between cell structure and education. Jacobs et al (1993) did, in fact, consider this question and found a relationship between extent of dendritic arborization in a cortical language area (Wernicke’s area) and amount of education. Hence, the cortical neurons from the brains of deceased people with university education had more dendritic arbor than those from people with high school education who, in turn, had more dendritic material than those with less than high school education. Of course, it may have been that people with larger dendritic fields were more likely to go to university, but that is not easy to test.

Another way to look at the relationship between human brain structure and behavior is to consider the functional abilities of people and to correlate them with neuronal structure. For example, one might expect to find differences in language-related areas between people with high and low verbal abilities. This experiment is difficult to do, however, because it presupposes behavioral measures before death, and this is not normally done. However, Jacobs et al (1993) considered this possibility by taking advantage of the now well-documented observation that females have verbal abilities that are superior to those of males (for a review, see Kolb & Whishaw 1996). Thus, when they examined the structure of neurons in Wernicke’s area, they found that females have more extensive dendritic arbors than males. Furthermore, in a subsequent study, Jacobs et al (1993) found that this sex difference was present as early as

age 9, suggesting that such sex differences emerge within the first decade. These sex differences in cortical architecture in humans are parallel to those reported in other studies showing sex differences in cerebral blood flow and glucose metabolism, with females having a level about 15% higher than that of males (e.g. Baxter et al 1987).

Scheibel et al (1990) approached the matter in a slightly different way. They began with two hypotheses. First, they suggested that there is a relationship between the complexity of dendritic arbor and the nature of the computational tasks performed by a brain area. To test this hypothesis, they examined the dendritic structure of neurons in different cortical regions that they proposed to have functions that varied in computational complexity. For example, when they compared the structure of neurons corresponding to the somatosensory representation of the trunk versus those for the fingers, they found the latter to have more complex cells. They reasoned that the somesthetic inputs from receptive fields on the chest wall would constitute less of an integrative and interpretive challenge to cortical neurons than those from the fingers and thus that neurons representing the chest were less complex. Similarly, when they compared the cells in the finger area to those in the supramarginal gyrus (SMG), a region that is associated with higher cognitive processes, they found the SMG neurons to be more complex. The second hypothesis was that dendritic trees in all regions are subject to experience-dependent change. As a result, they hypothesized that predominant life experiences (e.g. occupation) should be reflected in the structure of dendritic trees. Although they did not test this hypothesis directly, they did have an interesting observation. In their study comparing cells in the trunk area, finger area, and the SMG, they found curious individual differences. For example, especially large differences in trunk and finger neurons were found in the brains of people who were typists, machine operators, and appliance repairmen. In each of these, a high level of finger dexterity maintained over long periods of time may be assumed. In contrast, one case with no trunk-finger difference was a salesman in whom one would not expect a good deal of specialized finger use. These results are suggestive although we would agree with Scheibel et al's caution that "a larger sample size and far more detailed life, occupation, leisure, and retirement histories are necessary" (p. 101). The preliminary findings in this study do suggest that such an investigation would be fruitful.

Finally, one can look at pathological development and see if there is a neural correlate of abnormal behavior. In one such study, Purpura (1974) examined the dendritic structure of neurons from the brains of retarded versus average intelligence children. He did not quantify the dendritic length, but he did find marked differences in dendritic structure. The retarded children had spindly dendrites that had a very much reduced spine density. This abnormal spine

density is intriguing because it is reminiscent of the low spine density that we have consistently observed in rats with cortical injury in what would be equivalent to the third trimester of human development. Like retarded children, these rats have severe behavioral deficits that render them unable to learn cognitive tasks that are solved easily by animals with similar brain injuries later in life (e.g. Kolb & Gibb 1991a). More recently, there have been several studies of children with trisomic chromosomal states, such as Down's syndrome and trisomy 13 (e.g. Becker et al 1986, Jay et al 1990, Marin-Padilla 1974), the general observation being that there is anomalous spine morphology, decreased spine density, and small dendritic fields in many types of retardation.

MODULATION OF EXPERIENCE-DEPENDENT CHANGE

The demonstration that dendritic and/or synaptic change is related to experience is intriguing, but it is not proof of a relationship. The critical experiments are those in which an experimental manipulation alters the behavior and the morphology changes in a meaningful manner. Various manipulations fit this requirement, including especially age, sex hormones, neurotrophins, stress, and injury.

Aging

Despite nearly a century of effort by scores of investigators, many of the basic questions concerning changes in the aging brain are swirling in controversy (Coleman & Flood 1987). Buell & Coleman (1979) first noted that the aged brain showed an increase in dendritic growth that was hypothesized to compensate for the loss of neurons with age. That is, their general idea is that the number of synapses in the cortex is maintained by adding synapses to the dendrites of the adjacent neurons in the cortex. This growth would seem to be in accord with the general observation that most middle-aged people can be presumed to have suffered neuronal loss but do not appear demented. Furthermore, Buell & Coleman (1985) have shown that there is a failure of dendritic growth in the demented brain. As intriguing as the relationship between aging, dementia, and dendritic growth appears, we must caution that there nonetheless remains some controversy because not all brain regions appear to suffer cell death with age (e.g. Coleman & Flood 1987).

Sex Hormones

There is accumulating evidence that the male brain and the female brain differ in their structure and respond differently to experience. Specifically, Juraska and her colleagues (e.g. Juraska 1984, 1986, 1990; Juraska et al 1985, 1989)

were the first to report that **the visual cortex is more sensitive to experience in males than it is in females**. This is not a general increased sensitivity of males, however, because they have also reported that **the hippocampus is more sensitive to experience in females than in males**. These differences are related to the circulating gonadal hormone and therefore can be manipulated with hormone injections. Evidence of sex differences in cortical structure has now been shown to occur in the prefrontal cortical regions of lab-reared rats (e.g. Kolb & Stewart 1991, 1995), and recently it has been shown that injury to these morphologically dimorphic areas produces sexually dimorphic differences in functional recovery (Kolb & Cioe 1996).

The importance of sex hormones is not restricted to development. Stewart & Kolb (1994) have shown that ovariectomized or gonadectomized adult rats show significant change in cortical structure, especially in the females. Thus, the brains of ovariectomized rats not only grew heavier, but **the cortical neurons showed a 25% increase in dendritic arbor and a 10% increase in spine density**. This result implies that **cortical morphology is hormone-dependent throughout the life of the animal**. Because experience has sexually dimorphic effects, it seems reasonable to suppose that changes in hormonal state, especially in postmenopausal women, will alter the brain's response to experience.

Neurotrophins

Neurotrophins, which are chemicals known to have growth-enhancing properties in the nervous system, influence dendritic structure and also interact with experience. **It is known, for instance, that administration of nerve growth factor during adulthood increases both dendritic branching and spine density throughout the cortex** (e.g. Kolb et al 1997b). Furthermore, experience differentially modulates the levels of different neurotrophins such as nerve growth factor which, in turn, stimulates growth (e.g. Schoups et al 1995). Thus, it is possible that one route of action of experience on the brain is to stimulate (or inhibit?) the production of neurotrophins, and these, in turn, alter neuronal structure. This promises to be an area of intense study in the near future.

Stress

Stress has effects on the neuroendocrine system and this, in turn, has been shown to affect cell morphology (e.g. Sapolsky 1987, Sirevaag et al 1991, Stewart & Kolb 1988). Most studies to date have focused on the hippocampal formation, but there is reason to suspect that **cortical neurons are also vulnerable to the effects of stress** (Stewart & Kolb 1988). There is no specific evidence about whether stress interacts with experience-dependent changes in the brain, but it seems likely.

Injury

When the cortex is damaged there are changes in the remaining cortex that are correlated with functional outcome. For example, when Kolb & Gibb (1991b) removed the frontal cortex in adult rats there was an initial drop in dendritic arborization near the injury. This atrophy slowly resolved and four months later there was a significant increase in dendritic morphology, which was correlated with partial restitution of function. In contrast, large sensorimotor cortex lesions lead only to neuronal atrophy and no evidence of functional recovery (Kolb et al 1997b).

These results are reminiscent of those seen in the aging and demented brain: **When there is evidence of dendritic growth it leads to functional recovery, whereas when there is no dendritic growth there is no recovery.** This principle can be seen even more clearly in the developing brain. One of our consistent findings over the past decade has been that when the cortex of the developing rat is damaged in the first few days of life, which corresponds to a time just after neural proliferation is complete but neural migration and differentiation is still ongoing, there is a marked generalized atrophy of dendritic arborization and a decrease in spine density in neurons throughout the cortical mantle (for a review, see Kolb 1995). This result is correlated with a miserable functional outcome and is reminiscent of the marked abnormalities in the brains of retarded children (Purpura 1974). In contrast, when the cortical mantle of rats is damaged in the second week of life, which corresponds to the period of rapid dendritic growth and synaptic formation, there is a generalized enhancement of dendritic arborization and/or spine density throughout the remaining cortex (Kolb & Gibb 1991a). This enhanced dendritic response is correlated with dramatic functional recovery. Thus, **we see that if the injury in the cortex leads to increased dendritic space, there is a good functional outcome, whereas if the injury leads to a retarded development of dendritic material, there is a poor functional outcome.** Furthermore, we have shown that with treatments that reverse the dendritic atrophy, such as administration of neurotrophins or housing in enriched environments, there is functional improvement.

CONCLUSIONS

One of the most intriguing questions in behavioral neuroscience concerns the manner in which the brain, and especially the neocortex, can modify its function throughout one's lifetime. Taken all together, **the evidence discussed above makes a strong case for a relationship between brain plasticity and behavioral change. Indeed, it is now clear that experience alters the synaptic organization of the brain in species as diverse as fruit flies and humans.** Evidence that these changes are functionally meaningful is more difficult to collect, but

there is little doubt that changes in synaptic organization are correlated with changes in behavior. Thus, animals with extensive dendritic growth, relative to untreated animals, show facilitated performance on many types of behavioral measures. In contrast, animals with atrophy in dendritic arborization show a decline in behavioral capacity. Similarly, factors that enhance dendritic growth (e.g. nerve growth factor) facilitate behavioral outcome, whereas factors that block dendritic growth (e.g. brain injury at birth in rats) retard functional outcomes. We should emphasize that although we have stressed changes in dendritic morphology, there are multiple, and likely dissociable, changes in the neuron morphology that correlate with behavioral change. These include increases in dendritic length, dendritic branching pattern, spine density, synapse number, synapse size, glial size and number, and metabolic activity.

The critical question that remains is how dendritic and synaptic change is related to behavioral change. The current evidence clearly shows that dendrites in the cortex may show a net proliferation, regression, or stability depending upon various factors that affect behavior. It seems likely that a net proliferation of dendrites is a response to an increased availability of afferent supply. In contrast, the net reduction in dendrites, which is seen in response to injury, for example, is likely to reflect a decline in the afferent supply to a cell. In this view, dendrites are hypothesized to be in a state in which they are constantly ready to expand or retract their territory, limited largely by the availability of afferent nourishment and by the metabolic capacities of the cell. Because changes in the dendritic length are presumed to reflect changes in synaptic connectivity, it follows that increased dendritic arbor reflects increased synapse formation, whereas decreased dendritic arbor reflects decreased synapse formation.

The putative increase (or decrease) in afferent supply to a neuron leads to the question of where these afferents arise. There is scant evidence that the adult or even the infant brain is capable of growing new projections over long distances. Thus, it seems most likely that changes in afferent supply reflect changes in axonal arborizations of relatively nearby neighbors. A recent analysis by Nicoll & Blakemore (1993) is instructive. They examined the patterns of connections of pyramidal cells, which are the almost exclusive outputs of the neocortex. The axons of pyramidal cells make long-range connections to other cortical regions or subcortical structures, but they also have axon collaterals that form extensive arborizations with nearby cells. In fact, the most common target of pyramidal cells is other cortical pyramidal cells. Nicoll & Blakemore estimated that roughly 70% of the excitatory synapses on any layer II/III pyramidal cell are derived from pyramidal cells in the near vicinity. One way for the functioning of an intrinsic circuit to change is for the field of influence of a neuron to change. For example, the diameter of a cell's dendritic field

could expand, allowing the cell to interact with a larger number of neurons. Alternatively, the axon terminal could redistribute to enlarge the field of influence, too. The fact that neurons can expand their field of influence means that if neurons die, remaining ones could enlarge their field to make up for some of the lost processing power.

It is assumed in our model that increasing the connectivity of pyramidal cells will increase their functional capacity. But why should this be? Hebb (1949) proposed the idea of cell assemblies in which networks of cortical neurons were seen as being responsible for mental activity. A key component of this model is that individual neurons have little role in behavioral control, but rather behavior is dependent upon networks of neurons. Furthermore, Hebb noted that a given neuron could participate in multiple networks, each with a different function. Calvin (1996) likened this to the person who is on multiple committees, each with a different function. Thus, if neurons have more connections, they are hypothesized to have more influence on the observed behavior.

A critical feature of this view is that afferent supply influences neuronal function. We are now left with the question of what controls afferent supply. Various factors, such as neurotrophins, can influence this supply, but they must do it through some clear mechanism. One likely candidate is gene expression. There is ample evidence that the expression of genes in the mature brain is influenced by environmental and behavioral events (e.g. Dudai 1989). Gene expression thus provides a mechanism whereby cells can synthesize new proteins needed to form more synapses. Studies in various species, especially *Aplysia*, have shown that blockade of protein synthesis blocks long-lasting changes in both synapses and behavior (Bailey & Kandel 1993). The most likely mechanism for increased gene activity is neuronal activity, which is stimulated by behavior and experience. Activity initiated by experience or behavior could therefore increase the activity of genetic mechanisms responsible for dendritic and synaptic growth and, ultimately, behavioral change.



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