

Experience and Brain Development

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GREENOUGH, WILLIAM T.; BLACK, JAMES E.; and WALLACE, CHRISTOPHER S. *Experience and Brain Development*. CHILD DEVELOPMENT, 1987, 58, 539-559. This article considers how experience can influence the developing and mature brain and proposes a new categorization scheme based upon the type of information stored and the brain mechanisms that appear to be involved in storing it. In this scheme, *experience-expectant* information storage refers to incorporation of environmental information that is ubiquitous in the environment and common to all species members, such as the basic elements of pattern perception. Experience-expectant processes appear to have evolved as a neural preparation for incorporating specific information: in many sensory systems, synaptic connections between nerve cells are overproduced, and a subsequent selection process occurs in which aspects of sensory experience determine the pattern of connections that remains. *Experience-dependent* information storage refers to incorporation of environmental information that is idiosyncratic, or unique to the individual, such as learning about one's specific physical environment or vocabulary. The neural basis of experience-dependent processes appears to involve active formation of new synaptic connections in response to the events providing the information to be stored. Although these processes probably do not occur entirely independently of one another in development, the categories offer a new view more in accord with neural mechanisms than were terms like "critical" or "sensitive period."

What is the Meaning of Infancy? What is the meaning of the fact that man is born into the world more helpless than any other creature, and needs for a much longer season than any other living thing the tender care and wise counsel of his elders? [John Fiske, 1883/1909, p. 1]

The extended period of infancy reflects the importance of incorporating enormous amounts of information into the brain. It has been estimated that, even within the much smaller brain of the rat, perhaps a quarter of a million connections between nerve cells are formed each second during the first month of postnatal development (Schüz, 1978). These connections, at least those that persist, comprise the combination of intrinsic and experiential information, recorded in neural circuitry, upon which behavior is based. Although research has demonstrated substantial effects of experience on brain connections, we do not yet understand just how the infant's brain is specialized to organize and incorporate experience, or the ways in which the infant may program its own experience. However, biological research using ani-

mals has helped outline basic mechanisms whereby experience affects the brain, and has provided a new view of how the brain may adapt to different types of experience.

Such studies of animal development have suggested a fundamentally different view of what have been called "sensitive-period" or "critical-period" phenomena. The traditional concept has been likened by Bateson (1979) to the brief opening of a window, with experience influencing development only while the window is open. A window for visual development in kittens, for example, might open at the time the eyes first open, and close a few weeks later. Although the term "sensitive period" is a useful label for such a process, it does little to explain the underlying mechanisms. We propose a new classification based on the type of information that is stored and the brain mechanisms used to store it. This approach allows consideration of the evolutionary origins of a process, its adaptive value for the individual, the required timing and character of experience, and the organism's potentially active role in obtaining appropriate experience for itself.

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We propose that mammalian brain development relies upon two different categories of plasticity for the storage of environmentally originating information. The first of these probably underlies many sensitive- or critical-period phenomena. This process, which we term *experience expectant*, is designed to utilize the sort of environmental information that is ubiquitous and has been so throughout much of the evolutionary history of the species. Since the normal environment reliably provides all species members with certain experiences, such as seeing contrast borders, many mammalian species have evolved neural mechanisms that take advantage of such experiences to shape developing sensory and motor systems. An important component of the neural processes underlying experience-expectant information storage appears to be the intrinsically governed generation of an excess of synaptic connections among neurons, with experiential input subsequently determining which of them survive. The second type of plasticity, which we call *experience dependent*, is involved in the storage of information that is unique to the individual. Mammals in particular have evolved nervous systems that can take advantage of such information, as of sources of food and haven, and individual survival depends upon it to a very great extent. Since such experience will differ in both timing and character among individuals, the nervous system must be ready to incorporate the information when it becomes available. An important aspect of the mechanism underlying experience-dependent information storage appears to be the generation of new synaptic connections in response to the occurrence of a to-be-remembered event.

Sensitive Periods in Sensory-System Development: Experience-expectant Information Storage

That there are sensitive periods during which experience manipulations profoundly affect sensory-system development in mammals is well known, and this will be reviewed only briefly here. For more extensive reviews, the reader is referred to Mitchell and Timney (1984) or Movshon and Van Sluyters (1981). The vast majority of data regarding experience effects on sensory development have come from studies of the visual system. However, to the extent that other modalities have been examined, relatively similar results have been obtained (Clopton & Winfield, 1976; Feng & Rogowski, 1980; Meisami, 1975). The visual manipulations range from total pattern deprivation (bilateral eyelid su-

ture or dark rearing) to selective deprivation (e.g., of certain contours or of movement). Monocular deprivation in species with binocularly overlapping visual fields and binocular depth perception is a special case that will be discussed separately. Each of these manipulations interferes with an experience that otherwise would be common to the young of the species.

Behavior

Total pattern deprivation may occasionally involve interpretational problems, since dark rearing can disturb endocrine rhythms, parental behavior, and feeding (Eayrs & Ireland, 1950; Mos, 1976) and can damage the retinae of some species (Rasch, Swift, Riesen, & Chow, 1961), and eyelid suture can lengthen the optical axis of the eye, causing nearsightedness (Wiesel & Raviola, 1977). Nonetheless, an extensive literature demonstrates that behavioral deficits resulting from total pattern deprivation arise primarily from impairment of visual information processing by the brain. In rats, for example, Tees (1979) has noted that particular aspects of visual discrimination tasks, such as the relation among elements within the stimulus, rather than task difficulty per se (measured as number of trials required for learning), are sensitive indicators of visual deprivation induced impairment. Moreover, visually deprived rats are not impaired on similarly complex tasks involving nonvisual modalities (Tees & Cartwright, 1972). A human parallel to this process is the impaired vision of the surgically corrected congenital cataract patients of Senden (1960). For at least 2 weeks, such patients could discriminate forms such as squares and triangles only by counting their corners. In general, total deprivation effects become less reversible by later visual experience with longer periods of deprivation (Crabtree & Riesen, 1979; Timney, Mitchell, & Cynader, 1980). This may result in part because deprived animals tend increasingly to rely on nonvisual cues (Fox, 1966), but it certainly reflects impairment of visual processing ability as well.

Physiology

Deficits at the neurophysiological level parallel, and presumably underlie, the behavioral impairments. The neurophysiological deficits described to date probably relate more closely to differences in acuity than to ones in complex aspects of form and pattern perception—the latter processes having not yet been understood at the neurophysiological level. What have been studied are the stimuli that best activate single neurons in the visual system, recognizing generally that such neurons

are merely components of a quite complicated circuit. In kittens at the time the eyes open, somewhat less than half of primary visual cortex neurons respond selectively to the orientation or direction of movement of a stimulus (Blakemore & Van Sluyters, 1975; Buisseret & Imbert, 1976). Over several weeks in normal light, virtually all cells gain orientation sensitivity, and there is a general tendency for cells to become much more selective to specific orientations as well. In the absence of patterned visual stimulation, visual cortex neurons gradually lose responsiveness to stimulus orientation. As with behavior, the degree to which recovery toward normal physiological responsiveness can be achieved with exposure to patterned stimulation declines as deprivation is prolonged (Cynader, Berman, & Hein, 1976). Moreover, the recovered animal, if it has binocularly overlapping vision, is quite different from the normal: about half of its neurons never recover, and the ability to orient to stimuli across the midline is lost from both eyes (Sherman, 1973, 1977).

More selective effects have been obtained with selective forms of deprivation. In the most extensively studied paradigm, animals have been reared such that their visual experience is limited to a pattern of lines at a particular (usually horizontal or vertical) orientation. Initial neurophysiological studies indicated that visual cortex neurons fired strongly when the animal saw lines at angles close to those of the rearing stimuli (Hirsch & Spinelli, 1970). Later work has qualified these findings to some extent (e.g., Gordon, Presson, Packwood, & Scheer, 1979; Leventhal & Hirsch, 1975), but the essential details remain intact. As expected, these animals were also better at resolving lines at those same angles in behavioral tasks (e.g. Blasdel, Mitchell, Muir, & Pettigrew, 1977; Corrigan & Carpenter, 1979). Similar results have been obtained for cortical neurons sensitive to direction of stimulus movement. Cynader and Chernenko (1976), for example, deprived cats of visual movement perception by rearing them in a stroboscopic environment. Because the flashes of light were very brief, these cats saw the world as a series of "still pictures" rather than one of continuous movement. In these animals, cells sensitive to movement were much less frequently found. Thus cells in visual cortex were impaired in responding to specific stimulus characteristics that were missing from the rearing environment. A behavioral parallel to this in humans has been suggested by a persistent reduction in acuity, even while wearing glasses, if astigmatism

went uncorrected in childhood (Mitchell, Freeman, Millodot, & Haegerstrom, 1973).

Morphology

Total pattern deprivation has pronounced effects on central visual structures, and particularly upon the visual cortex. Most nerve cell connections in the visual cortex occur on spines (see Fig. 1). There are fewer of these spines on dendrites of neurons in visually deprived animals (Fifkova, 1968, 1970; Rothblat & Schwartz, 1979; Valverde, 1971). This indicates that the nerve cells of visually deprived animals make fewer interconnections. While later exposure to light can reverse differences to some extent, at least in dark-reared mice (Valverde, 1971), significant differences persist (Ruiz-Marcos & Valverde, 1969). Reduction in the overall amount of dendrite has also been reported for visual cortex neurons following dark rearing in some species, again indicating fewer connections among neurons (Coleman & Riesen, 1968; Valverde, 1970). Finally, an overall measure of synaptic connectivity, the number of synapses per visual cortex nerve cell, was lower in visually deprived than in normal cats (Cragg, 1975a; Winfield, 1981). A straightforward interpretation is that the complexity of the visual cortex "wiring diagram" is reduced in animals deprived of visual experience during early post-natal sensitive periods.

While the results will not be detailed here, differences in the morphology of sub-cortical visual structures (see Fig. 1) have also been reported following visual deprivation (e.g., Fifkova, 1979; for review, see Globus, 1975). Overstimulation (constant lighting), a procedure that eventually damages the rat retina, has been reported to increase spine frequency on neurons above that seen with normal diurnal lighting in the lateral geniculate nucleus (Parnavelas, Globus, & Kaups, 1973) and also in the visual cortex (Parnavelas & Globus, 1976). These findings indicate that many brain structures may be affected simultaneously by experience.

Particularly interesting morphological results have been reported in a selective visual experience paradigm. Coleman, Flood, Whitehead, and Emerson (1981) studied the orientation of dendrites of visual cortex neurons in cats raised with their visual experience limited to either horizontal or vertical lines, as described above. They found that the outer dendrites were oriented at about 90° from each other in the two groups, a result that could correspond to the visual cortex neurons selectively modifying their dendrites such that they responded to the exposure orien-

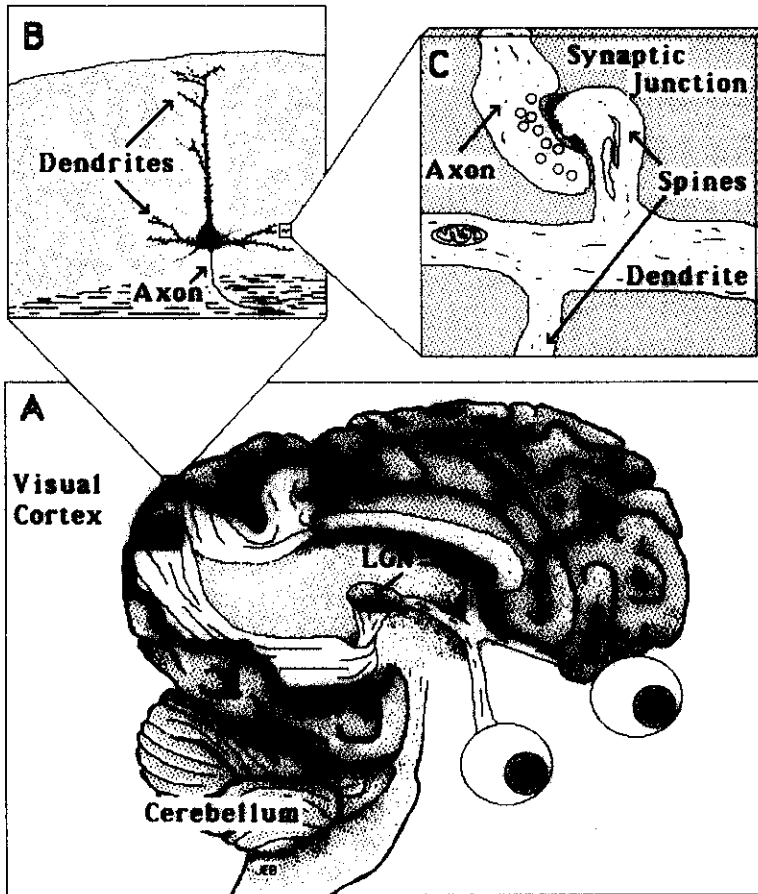


FIG. 1.—A, A human brain, with much of the right hemisphere removed and many subcortical structures omitted to reveal a simplified view of the visual system. Visual information travels from the retina to visual cortex via the lateral geniculate nucleus (*LGN*). As fibers from the retina pass back toward the *LGN*, some of them cross to the other side, reflecting the general principle that a sensory input originating on one side of the body is processed by brain structures in the hemisphere on the opposite side. Fibers from each retina which receive light from the *right* half of the visual field project to visual cortex on the *left* hemisphere. Hence, the visual cortex in the left hemisphere “sees” only the right half of the world, through both eyes. Within visual cortex, inputs from each eye are organized into adjacent bands called “ocular dominance columns.” B, A section of visual cortex showing a neuron, as would be seen through a light microscope. Visual cortex, which is approximately 2 mm thick in a 2-year-old infant, is actually much more densely packed with neurons and their interconnecting fibers than is depicted by this figure. A neuron in visual cortex might receive, depending on cell type, 10,000–30,000 synaptic inputs to its dendrites, most of which will occur on spines. At this level of magnification, spines appear as tiny dots along the dendrites. C, Detail of a portion of dendrite containing a synapse between an axon terminal (distinguished by the presence of spheres called vesicles) and a dendritic spine, a small projection from the dendrite trunk. For perspective, note that spines are somewhat less than 1/1,000 of a millimeter wide. Thus, to see a synapse requires the resolving power of an electron microscope.

tation. Tieman and Hirsch (1982) similarly reported approximately perpendicularly oriented visual cortex dendrites in vertical and horizontal stripe reared cats. These studies indicate that the pattern of connections among visual cortex neurons, not merely the number of connections, is influenced by visual experience during early development.

Expected Experience

An important question is *why* there are experience-expectant or sensitive periods in sensory development. On the surface, it may not seem to make much evolutionary sense to have designed an organism that will be forever impaired in its sensory performance if the proper sorts of experiences do not occur at

relatively specific developmental time points. The offsetting advantage appears to be that sensory systems can develop much greater performance capabilities by taking advantage of experiences that can be expected to be available in the environment of all young animals. Thus many species seem to have evolved such that the genes need only roughly outline the pattern of neural connectivity in a sensory system, leaving the more specific details to be determined through the organism's interactions with its environment.

The way in which this finer tuning of both sensory and motor systems is often accomplished has provided us with some real insight into the circumstances that may give rise to sensitive-period phenomena. Studies of a number of developing sensory systems as well as of peripheral connections in the autonomic and skeletal musculature systems have indicated that synapses are overproduced in early development (Boothe, Greenough, Lund, & Wrege, 1979; Brown, Jansen, & Van Essen, 1976; Brunjes, Schwark, & Greenough, 1982; Cragg, 1975b; Purves & Lichtman, 1980). Similar findings have been described in the human visual and frontal cortex (Huttenlocher, 1979; Huttenlocher, de Courten, Garey, & Van Der Loos, 1982). As development proceeds, the extra synapses are lost, such that the final wiring diagram consists of those synapses that remain. Two examples serve to illustrate how a refined pattern can emerge from relatively more chaotic beginnings through selective retention of synapses: synapse elimination at the neuromuscular junction and ocular dominance column (see Fig. 1 caption) formation in the visual cortex.

Motor neurons in the spinal cord connect with fibers of skeletal muscle. While a specific spinal location projects to each muscle, the pattern is quite different in the newborn rat from that in the adult. Brown et al. (1976) reported an overlapping pattern in the newborn rat, such that individual motor neurons connect to several muscle fibers, and each muscle fiber receives connections from several motor neurons. During the first 2 weeks after birth, these overlapping multiple connections disappear, as all but one of the synapses on each muscle fiber drop out. Brown et al. (1976) suggest that a selection process occurs that involves competition between the various neurons innervating a muscle fiber, leaving behind a one-to-one pattern. Precisely what leads to competitive success is not known, but at least some experiments have suggested that neuronal activity is a nec-

essary part of the process (Gouze, Lasry, & Changeux, 1983; O'Brien, Ostberg, & Vrbova, 1978; Thompson, Kuffler, & Jansen, 1979). The important point is that, if the proper connections are selectively retained (or if improper ones are selectively eliminated), a highly ordered pattern can emerge from a much less organized one by the loss of synaptic connections (Changeux & Danchin, 1977).

The development of ocular dominance columns in mammals with binocularly overlapping visual systems provides an example of a similar selection process in the central nervous system. In species such as cats or monkeys, closure of one eye during a relatively brief postnatal sensitive period causes a severe visual impairment when the eye is later reopened (Wiesel & Hubel, 1963). The effect is far more pronounced and lasting than that seen with binocular deprivation (Wiesel & Hubel, 1965). At the neurophysiological level, the deprived eye loses most of its ability to control the activity of visual cortex neurons, while the open eye correspondingly gains in control. Thus it appears that the deprived eye becomes functionally disconnected from visual cortex neurons. LeVay, Wiesel, and Hubel (1980) have shown that the monocular deprivation effect involves a competitive process in which connections actually are lost in the visual cortex. In the binocular regions of normal adult monkey visual cortex, inputs from the two eyes terminate in alternating bands termed "columns" which are about 400 microns wide. In monkeys in which one eye has been closed during development, the bands are still present, but those arising from the deprived eye are much narrower than normal, and those arising from the open eye are correspondingly wider. LeVay et al. (1980), studying the development of these bands, found that axons from the two eyes initially have overlapping terminal fields (Fig. 2), such that distinct columns are not present. In normal development, the terminal fields of axons from both eyes gradually and simultaneously regress, such that the sharply defined ocular dominance bands of the adult emerge. When one eye is deprived, its terminals regress more than normally, whereas those of the open eye retain a larger part of initial dually innervated territory, thus generating the alternating pattern of narrow and wide bands. This work, along with supportive evidence (e.g., Guillery, 1972), points to the view that a competition process occurs in the visual cortex, in which inputs from experienced eyes are advantaged. Hypotheses regarding the neural bases of the advantage have proposed that actively firing synapses

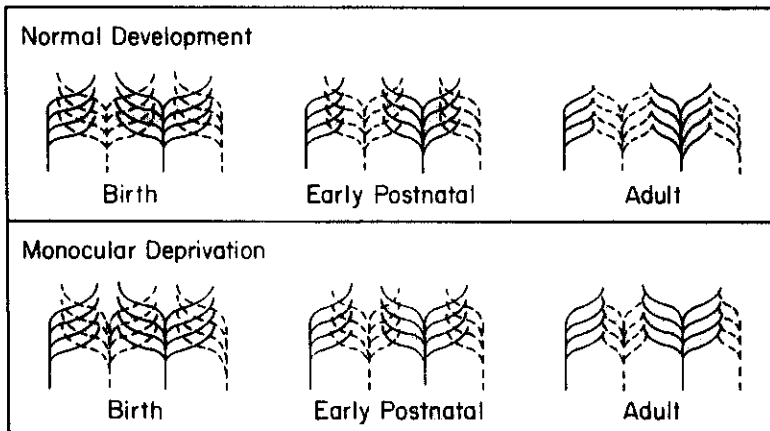


FIG. 2.—Schematic depiction of ocular dominance column development in monkeys reared normally or monocularly deprived. The left panels represent the substantial overlap of the axonal branches from the two eyes at birth. In normal development (top), the competitive interactions result in equal pruning back of axons from each eye in the adult (right panels). After monocular deprivation, however, axons from the nondeprived eye (solid lines) retain more branches, while the axons from the deprived eye (dashed lines) retain fewer branches (from Greenough & Schwark, 1984; copyright 1984 by Plenum Publishing; reprinted by permission).

are more likely to be preserved, or that synchronous firing of the presynaptic terminal and the postsynaptic neuron may stabilize the synapse (see, e.g. Singer, 1986), a process similar to that proposed by Hebb (1949).

These two examples illustrate a major point. In both cases, during a relatively restricted period, an *expected experience* (motor activity or visual stimulation) participates in the organization of a detailed neural pattern. The neural manifestation of expectation or sensitivity appears to be the production of an excess number of synapses, a subset of which will be selectively preserved by experience-generated neural activity. If the normal pattern of experience occurs, a normal pattern of neural organization results. If an abnormal pattern of experience occurs, an abnormal neural organization pattern will occur. We do not, of course, know that similar processes underlie all phenomena proposed to involve sensitive periods, and we shall see below that other factors may be involved in the determination of sensitive periods. Nonetheless, it seems clear that the production of more synapses than can eventually survive, combined with an experience-based selection process, is a central aspect of the sensitive-period phenomena that have been most extensively studied. Because the developing mammal's experience has been predictable throughout the evolutionary history of the species, the species has come to count on or expect its occurrence in the developmental process. We refer to this as *experience-expectant information storage*.

Schüz (1978), comparing altricial (born underdeveloped) with precocial species, has similarly noted that the overproduction of synapses might be an indication of readiness for expected experience. With its eyes open and able to move about, the precocial guinea pig's cerebral cortex shows many more dendritic spines at birth than that of the newborn mouse, which is born in a relatively altricial state. However, at the time the mouse's eyes open, about 2 weeks after birth, its cortical neurons have developed a density of spines comparable to that of the newborn guinea pig. Thus spines matured at the time the animal became able to actively explore the environment.

Control of Experience-expectant Processes

The character or quality of expected experiences may also play a role in determining the length of time that the developing nervous system remains sensitive to their effects. For example, since success in competition and consequent elimination of alternative neural patterns is promoted by experience-based neural activity, a relative reduction in that activity may prolong the competition process. Cynader and Mitchell (1980) found that kittens dark reared until 6, 8, or 10 months remained highly sensitive to monocular deprivation effects. This is in contrast to light-reared kittens, in which peak sensitivity to monocular deprivation normally occurs within the first 2 months of life, and negligible effects of monocular deprivation are seen in kittens reared normally if deprivation begins after 3 or 4 months (Hubel & Wiesel,

1970; Olson & Freeman, 1978). Relatively small amounts of normal visual experience appear to set in motion processes that can protect the organism against later deprivation (Mower, Christen, & Caplan, 1983).

The character of experience may not be the only factor regulating the temporal aspects of sensitive periods. Kasamatsu and Pettigrew (1976) initially proposed that the chemical neurotransmitter norepinephrine regulated sensitivity to monocular deprivation. They found that treatment with 6-hydroxydopamine, which reduces brain norepinephrine, prevented the shift in control of visual cortex neurons from the deprived eye in cats that were monocularly deprived during the sensitive period. If norepinephrine was replaced by local administration into visual cortex, however, the ocular dominance shift did occur in 6-hydroxydopamine-treated cats (Pettigrew & Kasamatsu, 1978). More recent work (Bear & Singer, 1986) has suggested that two neurotransmitters, norepinephrine and acetylcholine, may be involved in regulating developmental sensitivity of the visual cortex. There have also been some reports that drugs that interfere with norepinephrine action reduce or prevent the brain and behavioral effects of environmental complexity that are discussed in a later section of this article (Mirmiran & Uylings, 1983; O'Shea, Saari, Pappas, Ings, & Stange, 1983; Pearlman, 1983). These results suggest that neurotransmitters such as norepinephrine and acetylcholine may be involved in initiating or maintaining neuronal sensitivity to experience, a role consistent with the term "neuromodulator," often applied to norepinephrine. Parallel reports of noradrenergic regulation of adult memory storage processes (e.g., Gold, 1984) suggest the possibility of a quite general role for norepinephrine systems in the governance of plastic neural processes.

On the "Chalkboard" Metaphor

An important question involves the extent to which developing sensory systems merely follow the pattern imposed upon them by sensory experience, in the manner of a "blank slate," as opposed to selectively utilizing or actively creating information in experience. At the level of the neuron, an equivalent question is whether all input promotes similar structural change. It is clear that sensory systems have strong predispositions at the time of birth; for example, the initial stages of the binocular segregation process precede eye opening in the monkey visual cortex (LeVay et al., 1980), and oriented receptive fields are present to some extent at birth (Blakemore & Van Sluyters, 1975) and

certain orientations appear to be more predisposed to arise in the absence of appropriate input in the cat (Leventhal & Hirsch, 1975). The rudimentary neural organization imposes order on its input. A phenomenon that may illustrate this is the apparent compensatory change that has been reported in intact modalities' central representations with damage to or deprivation of other modalities. For example, the auditory cortex increases in size in visually deprived or blinded animals (Gyllenstein, Malmfors, & Norrlin, 1966; Ryugo, Ryugo, Globus, & Killackey, 1975). Since auditory stimulation is equivalent in deprived and sighted animals, the size increase must depend upon some aspect of the increased reliance upon audition that becomes necessary in the absence of visual input. That is, the brain's differential use of the same auditory information determines the information's effect on brain structure. It is but a small extension of this idea to note that individual differences could be preserved even in the face of identical environmental experience.

Possible human behavioral reflections of neural predispositions to select and organize experience are also evident. For example, infants may have "hard-wired" capacities for categorical perception of phonemes (Eimas, 1975) and syntactic structure (Chomsky, 1980). The infant's behavioral and affective responses to caretaker speech can make the social interaction highly rewarding for both participants, perhaps even encouraging a phonetic adjustment to match the perceptual limitations of the infant (Fernald, 1984). An innate predisposition of the infant to smile and make noises, if it exists, could serve the infant by shaping the caretaker's speech toward an optimal form of linguistic input. Thelen (1980) has suggested that kicking and other behaviors, while serving as neural foundations of mature motor systems, can also help the infant control experience (e.g., as in communicating distress or pleasure). From this perspective, the infant may often pick and choose from an experiential smorgasbord available during development. In fact, we suspect that some types of "expected" experience may rely largely on the infant to produce them.

Early Sensory-System Development: Summary

The primary quality of experience effects in early sensory-system development that sets them apart from many later developmental processes, as well as from adult learning and memory, is the degree to which they are age dependent and subsequently irreversible. At the behavioral level, a relevant human ex-

ample may be the loss of perceived phonemic boundaries present in infants if the language to which they are exposed does not utilize them (Werker & Tees, 1984). At the neural level, the irreversibility appears to arise in at least some cases because a set of synapses has become committed to a particular pattern of organization, while synapses that could have subserved alternative patterns have been lost. A process seen in the brain that may underlie this is a rapid peaking of synapse numbers, followed by the loss of a significant proportion of them, as shown in Figure 3. The rate and extent of commitment of synapses may be regulated by both the quality of experience and intrinsic factors such as broadly acting neurochemical systems. In at least some cases, it seems clear that central system organization is not merely "painted" on the brain by experience, since both the quality of information and the way in which it is used can affect the rate of pattern formation as well as the character of the pattern.

Experience-dependent Information Storage in Later Development and Adulthood

Many of the effects of experience upon behavioral development do not appear to exhibit the relatively strict age-dependent character associated with early sensory system development. One reason for this may be that a species cannot count on certain important experiences to occur at particular points in the lifespan. Another is that much of the information that an animal or human must acquire during development or adulthood is unique to its own particular environment: informa-

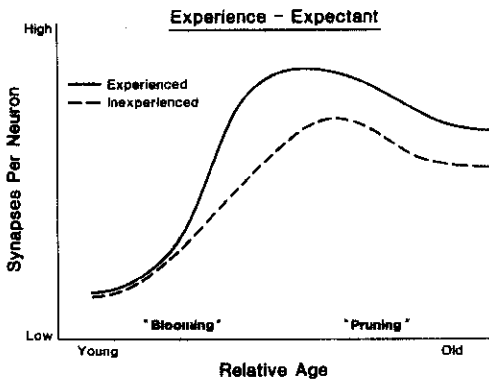


FIG. 3.—Schematic diagram of synapse over-production ("blooming") and deletion ("pruning"; Schneider, 1981) during an experience-expectant process (from Black & Greenough, 1986, Vol. 4, p. 28; copyright 1986 by Lawrence Erlbaum Associates; reprinted by permission).

tion about the physical characteristics of the surroundings, the social system and the roles of specific individuals, and, in humans, the details of one's language(s) and other formally specified cognitive capacities. It is not clear a priori whether the brain mechanisms involved in storing these kinds of information are the same as those used for experience-expectant processes, although evolution tends to produce new adaptations (such as the unique plasticity of the mammalian brain) by modifying existing systems, as opposed to creating entirely new ones. We will review some of what is known about these more mature categories of information storage and will then return to our consideration of neural mechanisms.

The Environmental Complexity Paradigm

The research that has perhaps taught us the most about mechanisms of cognitive development in animals utilizes variations in the physical and social complexity of the rearing environment. This line of research began with Hebb's (1949) rearing of rats as pets in his home for comparison with laboratory-reared animals, but most researchers have adopted less life-disrupting laboratory versions of Hebb's home. Most commonly, two or all of the following three conditions have been employed: (1) *Environmental complexity* (EC) animals are housed in groups of about a dozen in large cages filled with various objects with which the animals are free to play and explore. Often the animals are given additional daily exposure to a maze or a toy-filled field. In our work and most others', the play objects are changed and rearranged daily. (2) *Social cage* (SC) animals are housed in pairs or small groups in standard laboratory cages, without objects beyond food and water containers. (3) *Individual cage* (IC) animals are housed alone in similar or identical laboratory cages. The term "enriched condition" has been used to describe what we call environmental complexity, but we prefer the latter to emphasize that these conditions represent an incomplete attempt to mimic some aspects of the wild environment and should be considered "enriched" only in comparison to the humdrum life of the typical laboratory animal.

Behavior.—Since Hebb's (1949) initial demonstration that home-reared rats were superior to laboratory-reared rats at learning a series of complex maze patterns, a large number of experiments have confirmed that rats and mice reared in complex environments are generally superior on complex, appetitive tasks. A significant number of experiments have been directed at particular behavioral

characteristics that differentiate EC from SC and IC animals, and it seems safe to conclude that no single explanation, such as differential emotional reactivity, better use of extra-maze cues, or differential visual ability, can account for the pattern of behavioral differences that have been reported (Greenough, Madden, & Fleischmann, 1972; Krech, Rosenzweig, & Bennett, 1962; Ravizza & Herschberger, 1966; see Greenough, 1976, for review). All of these may play a role under certain circumstances, of course (Brown, 1968; Hymovitch, 1952; Myers & Fox, 1963), but the differences appear to be quite general, extending even to models of Piagetian volume-conservation tasks (Thinus-Blanc, 1981), such that the most likely explanation (if not the most satisfying in specificity) may well be that the groups differ in the amount of stored knowledge upon which they can draw in novel situations.

It appears that active interaction with the environment is necessary for the animal to extract very much appropriate information. Not only do the EC and SC conditions differ little with regard to the average intensity of energy impinging upon most sensory modalities, but merely making visual experience of a complex environment available to animals otherwise unable to interact with it has little behavioral effect. Forgyas and Forgyas (1952), for example, found little benefit to maze performance of having been housed in small cages within the EC environment. Similar results have been reported with regard to some of the brain effects of EC rearing that are described below (Ferchmin, Bennett, & Rosenzweig, 1975).

Morphology.—Following initial reports that several regions of the cerebral cortex were heavier and thicker in EC than in IC rats (Bennett, Diamond, Krech, & Rosenzweig, 1964) and had larger neuronal cell bodies and more glial (i.e., supportive) cells (Diamond, 1967; Diamond, Rosenzweig, Bennett, Lindner, & Lyon, 1972), detailed studies began to indicate probable differences in the number of synaptic connections. Differences in the amount of dendrite per neuron, that is, the amount of surface available for synaptic connections, of up to 20% were reported in the upper visual cortex of rats reared in EC versus IC environments from weaning to late adolescence (Greenough & Volkmar, 1973; Holloway, 1966). Values for SC rats were intermediate, although generally closer to those of IC rats, in the Greenough and Volkmar study, and this has tended to be the case in other experiments in which such a group has been included. Small differences

in the frequency of postsynaptic spines (see Fig. 1) favoring EC rats were also reported (Globus, Rosenzweig, Bennett, & Diamond, 1973), suggesting that synapses were not merely spaced farther apart on the longer dendrites of the EC rats. A direct demonstration that EC rats exceeded IC rats in synapses per neuron in upper visual cortex by 20%–25% (Turner & Greenough, 1985) led us to consider what similar extremes might result if all neurons in the human brain were equally plastic. The difference of about 2,000 synapses per neuron in the rat would translate into many trillions of synapses on the 100–200 billion neurons of the human brain!

While EC-IC differences (in male rats) are greatest in the occipital, or visual, region of the cerebral cortex, they occur in other neocortical regions as well, including those associated with audition and somesthesia and also regions somewhat functionally comparable to the human frontal cortex (Greenough, Volkmar, & Juraska, 1973; Rosenzweig, Bennett, & Diamond, 1972; Uylings, Kuypers, Diamond, & Veltman, 1978). Differences in dendritic field size following similar differential rearing have also been reported in subcortical regions such as the rat hippocampal formation and monkey and rat cerebellum (Floeter & Greenough, 1979; Juraska, Fitch, Henderson, & Rivers, 1985; Pysh & Weiss, 1979), suggesting that this later plasticity is not a phenomenon unique to regions like cerebral cortex that are most prominent in mammals. A surprising finding is that different patterns of EC-IC differences in visual cortex and hippocampus are found in males and females (Juraska, 1984; Juraska et al., 1985). Males show greater differences across environmental extremes in the visual cortex, whereas females show greater differences in some regions of the hippocampus. Although the behavioral significance of this is still under investigation, it suggests that very similar experiences may have different effects on individually different brains.

Adult Brain Morphology

Until relatively recently, it was widely assumed that, except for certain cases of response to brain damage, the brain acquired all of the synapses it was going to have during development, and that further plastic change was probably accomplished through modification of the strength of preexisting connections. While some morphological and electrophysiological data suggest that changes in the strength of existing connections may occur in response to experience manipulations (see Greenough & Chang, 1985, for review), it has

now become quite clear that new connections may arise as a result of differential housing conditions and other manipulations throughout much, if not all, of the life of the rat, and presumably of other higher mammals as well. Bennett et al. (1964) had actually reported quite early that cortical weight differences induced by EC versus IC housing occurred in adult rats, but over a decade passed before reports appeared that dendritic field size was affected by these conditions in both young adult (Juraska, Greenough, Elliott, Mack, & Berkowitz, 1980; Uylings, Kuypers, & Veltman, 1978) and middle-aged (Green, Greenough, & Schlumpf, 1983) rats. While direct measurements of synapses per neuron have yet to be reported in adults under these conditions, the correspondence between dendritic field and synapse-per-neuron measures in younger animals (Greenough & Volkmar, 1973; Juraska, 1984; Turner & Greenough, 1985) gives us considerable confidence that the increase in adult postsynaptic surface is paralleled by an increase in synapse numbers. While not all neuron types affected by postweaning exposure to differential environmental complexity may be affected by these environments in adult animals, there is little question at this point that the cerebral cortex, and also the cerebellar cortex (Greenough, McDonald, Parnisari, & Camel, 1986), retain the capacity to form new synaptic connections in response to new experiences.

Effects of Training on Adult Brain Morphology

There has not yet been a specific demonstration of what might be represented by the changes in synaptic connections brought about by differential environmental complexity, nor are the details of the relationships between brain structure and behavioral performance very clear. If we follow the rather hazy terminology of "accumulated knowledge" used above, then one might suggest that these changes have something to do with storing (and/or accessing) that knowledge. A simple view of nearly a century ago (Ramon y Cajal, 1893; Tanzi, 1893), which has been embellished by the more detailed theorizing of Hebb (1949) and many others, is that memory, in both the very broad and the psychologically more specific sense, might be encoded in the functional pattern of connections between neurons. While demonstrating unequivocally the involvement of brain phenomena in learning or memory has been a difficult process for a variety of reasons, it is possible to perform experiments the outcomes of which would be either compatible

or incompatible with such an interpretation. For example, if the changes in synaptic organization that occur in complex environments are involved in storage of information from the experience, then we might be able to detect similar morphological changes in animals trained on specific learning tasks.

Since the experience of training probably provides a more limited range of information than that available in the complex environment, we might expect the morphological effects of training to be more limited (and harder to detect). In the first experiment of this sort, young adult rats were trained on a changing series of patterns in the Hebb-Williams maze (the maze Hebb used in the initial test of home-reared rats) over a period of about 25 days (Greenough, Juraska, & Volkmar, 1979). In the visual cortex of the trained animals, two types of neurons had more dendrite than in nontrained animals, while a third type was unaffected. The unaffected type was one that had been altered in previous EC studies. Thus training affected a measure related to synaptic connectivity, and the effects were more localized and specific than were those of the complex environment experience.

In a similar experiment, Bennett, Rosenzweig, Morimoto, and Hebert (1979) exposed weanling rats to a changing series of mazes in their rearing cages for 30 days. The visual cortices of these animals were heavier than those of rats kept in IC cages for the same period. Rats housed with an unchanging simple maze pattern were intermediate between these groups, suggesting that the information available in the changing-maze patterns was an important aspect of their results.

A problem in the interpretation of these results and, in fact, in the interpretation of the environmental complexity findings as well, is the possibility that brain effects might arise from stress, sensory stimulation, motor activity, or other nonspecific consequences of the training procedure, rather than from the information acquired through training. This problem is, of course, not trivial, and it has been one of the major difficulties in a long history of previous experiments designed to elucidate the molecular biological underpinnings of the memory process (see Dunn, 1980; Greenough & Maier, 1972; and Rose, 1981, for perspectives on this work). No single experiment (and maybe no set of experiments) can rule out all alternatives, but the involvement of generally acting factors such as hormonal or metabolic consequences of a training procedure can be examined using a

within-animal control. One advantage of the rat for such work is that the bulk of fibers from each eye cross to the opposite side of the brain, such that the use of a split-brain procedure, combined with occlusion of one eye, can restrict visual input from training largely to one hemisphere. Chang and Greenough (1982) performed such an experiment, again using the changing maze patterns. A control group indicated that there were no interhemispheric differences as a result of insertion of the eye occluder (an opaque rat-sized contact lens) for a few hours each day. The group trained with the same eye covered each day, in contrast, had more apical dendritic branches on visual cortex neurons in the hemisphere opposite the trained eye, a result incompatible with effects of generally acting hormonal or metabolic effects. Thus the changes brought about by maze training were specifically a consequence of visual input from the training experience.

One further experiment increases our confidence in both the generality of the morphological effects of training in adult rats and in the unlikelihood that these effects result from general hormonal or metabolic causes (Greenough, Larson, & Withers, 1985). In it, rats were trained to reach, bilaterally or unilaterally, either with the forepaw they preferred to use or the nonpreferred forepaw, into a tube for food. A strong preference for reaching with one paw was accomplished by placing a partition next to the tube that made reaching with the opposite forepaw difficult. Extensive training on the nonpreferred paw permanently reversed reaching preference, as had been demonstrated previously (Peterson, 1951). It is not clear that something like "handedness" in humans is being reversed in these rats, as opposed to the animals' merely using the paw with which they had developed more skill or even thinking that the contingency required them to continue reaching with the trained paw. We examined the neurons in the forelimb region of the cortex whose axons project to the spinal region that governs reaching. Animals trained with both paws had dendrites that were more highly branched than those of nontrained animals, and hemispheres opposite trained forelimbs in unilaterally trained animals had more branches than the other hemisphere. Analysis of the hindlimb region of motor cortex in unilaterally trained rats indicated no similar pattern of asymmetry, so the structural change was specific to both the hemisphere and the cortical area most directly involved in the learned task. We must realize, however, that this reaching task involves many other areas

of the brain, as became evident when we examined metabolism of various brain areas in rats performing the task (see Greenough, 1984). The complex tasks used in developmental psychology research are similarly likely to involve multiple brain areas, and explanations of the role of the brain in such tasks that focus on a single region (e.g., Diamond, 1985), while interesting, are likely to be incomplete.

Experience-dependent Information Storage: Possible Mechanisms

Given that complex environment experience and experience in learning tasks alter these estimates of synapse number, the process whereby the new synapses arise is of significant interest. There appear to be two obvious possibilities: (1) The process of synapse overproduction that we described with regard to early sensory-system development might continue. That is, excess synapses, the existence of which would be transient unless they were confirmed by some aspect of neural activity, might be continually produced on a nonsystematic basis. Since the nature and timing of these sorts of experiences could not be anticipated, synapse formation would have to occur chronically throughout the brain (or in regions that remain plastic). The effects of environmental complexity or training would arise because a proportion of these synapses became permanent as a result of experience-associated neural activity (Changeux & Danchin, 1977; Cotman & Nieto-Sampedro, 1984; Greenough, 1978). (2) The production of new synapses in later development and adulthood might be dependent upon experience-associated neural activity. That is, synapses would be formed as a result of the activity of neurons in information-processing and/or neuromodulatory systems. The synapses might be generated nonsystematically at the outset, with some aspect of patterned neuronal activity determining the survival of a subset of them (Greenough, 1984). The synapses formed in this case would be localized to regions involved in the information-processing activity that caused their formation.

The first hypothesis is attractive, given the tendency of evolution to conserve mechanisms. It also provides a very simple way for a proper set of connections to come to encode a memory. The second hypothesis has its own attractions, such as the relatively lower amount of metabolic resources required for local, experience-dependent synapse formation and the reduction in potential "noise" in the nervous system that might be associated with chronic generation and degeneration of

synapses. Most of the same genes would probably be involved in the construction or stabilization of synapses, regardless of the initiating event. Moreover, the initiating event for intrinsic and extrinsic triggering of synapse formation could involve a final common pathway or common mechanism, such as the activation of neuromodulatory systems. Finally, the second hypothesis has been made far more attractive by the recent appearance of data that are more consonant with it than with the first.

Rapid, Active Synapse Formation in the Adult Brain

Two lines of evidence have emerged that can be interpreted as suggesting a dynamic synapse-formation process in response to experience-associated neural activity in the adult brain. The first arises from a phenomenon induced by electrical stimulation of neurons that has been proposed as a model for adult long-term memory, long-term potentiation (LTP). In the hippocampus and a number of other brain regions, stimulation of axons at high frequencies can give rise to an increased postsynaptic response to test stimuli (Bliss & Lømo, 1973; see Teyler & Fountain, 1987, in this issue). With proper stimulus sequences, this elevated responsiveness can persist for up to several weeks. There are several hypotheses as to its neural basis. One, that additional synapses are formed, is based on the work of Lee, Schottler, Oliver, and Lynch (1980) and Lee, Oliver, Schottler, and Lynch (1981), who reported that synapses form in the hippocampus *in vivo* and in an *in vitro* tissue slice preparation following LTP-inducing stimulation. The synapses form surprisingly rapidly. Chang and Greenough (1984) noted that synapses formed within 10–15 min *in vitro*. This rate of formation is simply too rapid to arise from the chronic synapse turnover proposed in the first hypothesis. Regardless of whether LTP is related to memory, or synapse formation to LTP, the fact remains that the adult brain, or at least the hippocampus, is capable of generating new synapses rapidly in response to neural activity.

The second finding involves what we believe to be a marker of newly forming synapses, polyribosomal aggregates (PRA), the protein-synthesizing "factories" of cells. Steward (1983) reported that PRA were found frequently within postsynaptic spines (otherwise rare) during the process of re-formation of synapses that occurs following damage to a part of the hippocampus. Hwang and Greenough (1984) similarly found, in a develop-

mental study, a large increase in the number of PRA in spines in rat visual cortex during periods of peak synapse formation, compared to adult values. Thus, in both situations, PRA in spines appear to indicate the formation of new synapses. We do not know, of course, that synapse formation in late development or adulthood resembles early development or the response to damage. However, if it does, a recent finding suggests that behavioral experience can promote synapse formation, as the second hypothesis above suggests. If animals in environments of different complexity formed equivalent numbers of synapses, but more synapses were confirmed or stabilized in ECs, we might expect the frequency of PRA in spines to be equivalent across the groups. Greenough, Hwang, and Gorman (1985) studied synapses in upper visual cortex of rats reared for 30 days after weaning in EC, SC, or IC environments. PRA were considerably more frequent in spines in the EC animals, suggesting that more new synapses were forming.

Given our knowledge that there are more synapses per neuron in EC rats, and other data indicating that PRA in spines marks newly formed synapses, this result suggests that experience-dependent synapse formation occurs in the developmental environmental complexity paradigm. Of course we must keep in mind that PRA may aggregate in spines to perform functions associated with increased activity of synapses or modification of their strength. We now need to find other ways to identify newly forming synapses and must determine whether similar increases in spine-located PRA occur in adult animals during learning. The data to this point, however, suggest that synapses form *in response to experience from which information is to be stored* in the postweaning environmental complexity paradigm.

Summary of Later Development and Adult Learning

The data reviewed here suggest that there is a fundamental difference between the processes governing the formation of synapses in early, age-locked sensory system development and those governing synapse formation during later development and adulthood. Experience-expectant processes found in early development appear to produce a surplus of synapses, which are then pruned back by experience to a functional subset. In later development and adulthood, synapses appear to be generated in response to events that provide information to be encoded in the nervous system. This later expe-

rience-dependent synapse formation may differ from that of early development in that it is localized to regions involved in processing information arising from the event, but may be similar in that synapses are initially formed on a relatively unpatterned basis, with aspects of neural activity resulting from the event determining the selective preservation of a subset of them. The cumulative effect of many such individual experiences may appear to be a smoothly increasing supply of synapses, as shown in Figure 4.

Some Cautionary Notes

Presumably we need not point out to most readers that neuroscience involves significant amounts of disagreement and controversy, as do other disciplines, and some of what is said here would be considered controversial by certain of our colleagues. For simplicity, we have painted a much more straightforward picture here than probably exists. For example, there is significant evidence for an active synapse-formation component in early sensory development. Winfield (1981), for example, noted that the peak number of synapses per neuron was lower in visually deprived than in normal kittens, suggesting that visual stimulation promotes extra synapse formation (although it remains possible that this reflects reduced preservation of synapses in a population that is intrinsically generated over time). There is also evidence

for a burst of synapse formation and axonal and/or dendritic growth at eye opening or first exposure to light in rodents. Several studies have indicated a burst of synapse formation at about the time of eye opening (Blue & Parnavelas, 1983; Hwang & Greenough, 1984; Miller, 1981; Miller & Peters, 1981), although there is some evidence that the burst may begin prior to eye opening (e.g., Valverde, 1971), leaving open the possibility of an intrinsic trigger. Exposure of rats to light for the first time at later than the normal age of eye opening may also trigger some synapse formation (Cragg, 1967), as well as the synthesis of protein (Rose, 1967), including tubulin, a major molecular component of axons and dendrites (Cronly-Dillon & Perry, 1979). In an artificial imprinting situation, in which chicks were exposed to light for the first time in the form of a flashing amber stimulus, RNA and protein synthesis in the forebrain increased dramatically (Bateson, Rose, & Horn, 1973; Horn, Rose, & Bateson, 1973). And, during the recovery that can be made to occur in monocularly deprived monkeys by reversing which eye is sutured shut, there is evidence for active extension of the axons associated with the previously deprived eye (LeVay et al., 1980). Thus, while synapse overproduction appears to be a dominant aspect of the early organization of the visual system, it is likely to be accompanied by some experience-dependent growth. Nonetheless, on the basis of the evidence to date, the relative emphasis on intrinsic generation and experiential selection on a sensory system-wide basis seems quite clear in early development, and the generation of synapses in later development and adulthood appears to be much more dependent upon extrinsically originating events. It thus seems reasonable to view sensitive period versus continuing developmental information-storage phenomena from this perspective.

Finally, our dichotomy of information-storage mechanisms is based upon studies of a limited number of brain regions. Although many developing systems within the brain other than the visual system go through phases of synapse overproduction, and experience effects on various aspects of the development of these systems have been reported, it remains quite possible that other systems may operate in different ways. Similarly, experience-dependent synapse formation is quite probably not characteristic of all regions of the later-developing and adult nervous system, and there may be other mechanisms with quite different properties whereby nervous systems store information. Recently, for

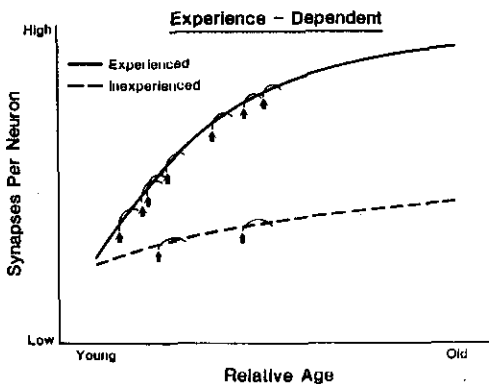


FIG. 4.—Schematic diagram of synapse formation and selective retention during an experience-dependent process. The arrowheads mark salient experiences that generate local synaptic overproduction and deletion (small curves). The cumulative effect of such synaptic blooms and prunes is a smooth increase in synapses per neuron, which is greater for the animals with more experience (from Black & Greenough, 1986, Vol. 4, p. 38; copyright 1986 by Lawrence Erlbaum Associates; reprinted by permission).

example, we found that an electrophysiologically detectable phenomenon in the hippocampal dentate gyrus (perhaps similar to LTP), which was apparent immediately after postweaning rearing in a complex environment, had entirely disappeared within 30 days (Green & Greenough, 1986). In contrast, dendritic branching differences induced in visual cortex in this paradigm are relatively stable for at least that long (Camel, Withers, & Greenough, 1986).

Thus, while the separation of experience effects upon brain development into categories based upon the existence of neural anticipation of the experience is compatible with current data, these categories may well not be comprehensive. Nonetheless, recognition (1) that a common aspect of early development of sensory systems may be overproduction of synapses in expectation of experiences that will determine their selective survival, and (2) that later developmental and adult information storage may involve synapse formation triggered by experience, may offer a new level of understanding of phenomena previously described as merely related or unrelated to sensitive periods in development.

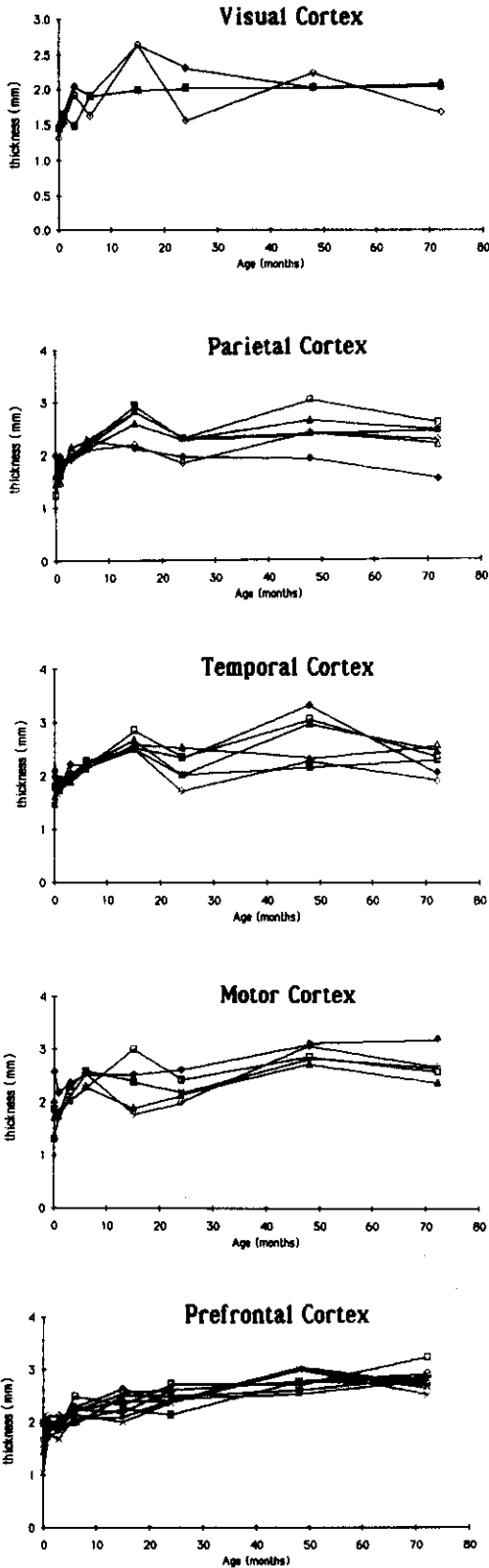
Some Guidelines for Studying Effects of Experience on Development

Monolithic approaches, in which the development of the brain (or the organism) is treated as a unitary phenomenon, are unlikely to be very useful and, in fact, may be misleading. For example, Epstein (1974a, 1974b) has proposed that "phrenoblysis," or spurts of growth of the whole brain during selected periods of development (purportedly corresponding to stages of cognitive development), characterizes species as diverse as humans and mice. While findings of others have failed to replicate Epstein's observations in either species (e.g., Hahn, Walters, Lavooy, & DeLuca, 1983; McCall, Meyers, Hartman, & Roche, 1983) and Epstein's analytical procedures have been discredited (Marsh, 1985), the general concept, that the brain as a whole develops in bursts or stages, continues to attract attention to phenomena that probably do not exist (e.g., Spreen, Tupper, Risser, Tuokko, & Edgell, 1984). Certainly any recommendations that educational practices be modified to accommodate such bursts (e.g., Epstein & Toepfer, 1978) are not appropriate at this stage. Several lines of evidence indicate that, while discrete brain regions definitely progress through something like "spurts," in terms of such processes as the generation of nerve cells and of connections between them, different brain regions do so

out of synchrony and in a reliable developmental sequence. First, some older but generally ignored data on human cerebral cortex development (Conel, 1939-1967), which we have plotted in Figure 5, show rather striking differences in the pattern of growth across brain regions. While many regions of the cortex show some synchrony in the pattern of thickness fluctuations with age, other regions are not in synchrony with them. Rather than showing clear peaks, for example, the prefrontal cortex appears to continue to grow thicker throughout the first 6 years of life. A similar relative delay in the development of frontal brain regions is evident in the protracted (10-14 years) process of achieving stable synaptic density values in human frontal cortex (Huttenlocher, 1979), compared with the rapid stabilization (1-2 years) seen in human visual cortex (Huttenlocher et al., 1982). A metabolic parallel, perhaps, to these reports is the Chugani and Phelps (1986) report that glucose utilization in human infants was initially highest in sensorimotor cortex and only later rose in the frontal cortex.

In the light of these findings, the report by Rakic, Bourgeois, Eckenhoff, Zecevic, and Goldman-Rakic (1986; see also Goldman-Rakic, 1987, in this issue) that there is a striking temporal synchrony across cortical areas in developmental changes in density of synapses is rather surprising. Interpreting synaptic density measures can be difficult, since they do not clearly reflect either the number of synapses within a functional area or the number of synapses per nerve cell. Turner and Greenough (1985) found that while the number of synapses per neuron was about 20% higher in rats reared in complex environments, the density of synapses (in neuropil, as in Rakic et al., 1986) did not differ in these groups, apparently because the tissue volume of the dendrites, axons, glial cells, blood vessels, etc. necessary for additional synapses pushed the new synapses as far apart as they were in IC rats. As Bennett et al. (1964) had shown years earlier, the volume of the cortex as a whole simply increases to accommodate these needs.

Thus, while counterexamples exist, it seems clear that asynchrony in brain development merits theoretical attention. Theorists have argued that by staggering the developmental schedule for maturation of different brain regions, the human species (and other mammals, for which such patterns are also evident) may have gained substantial advantages, most importantly by allowing one developmental system to provide a suitable



framework for a subsequent, experience-sensitive system (Black & Greenough, 1986; Turkewitz & Kenny, 1982). This "stage setting" possibility is most interesting for human development, for example, where early social and communicative skills can establish the foundations for adult language, and where early visual and motor skills can help the infant master spatial and causal relations. The active participation of the infant in acquiring and organizing experience becomes paramount if one process is setting the stage for a subsequent experience-dependent process. In summary, sensitive periods must be characterized in terms of their time course, the brain regions and mechanisms employed, and the organism's involvement in shaping experience.

This perspective may be helpful to both developmental psychologists and neuroscientists in explaining the meaning of infancy. For example, a conjecture that a particular developmental process has a sensitive period(s) (e.g., language acquisition) can now generate testable hypotheses about neural changes that must accompany it. For example, a fixed time course for language acquisition would suggest a peak in cortical thickness or synaptic numbers shortly before the start of a hypothetical experience-expectant period. Such predictions could be quite specific about what brain regions are involved and when the changes occur. After examination of appropriate brain tissue, findings of different time courses or the involvement of other brain regions can reflect back on the original theory, suggesting different influences and constraints. Given the complex and long period of language acquisition, a theory invoking a single, protracted "sensitive period" may eventually be expanded to reflect the multiple involvement of many brain regions, each with its own time course and experiential sensitivities, as has

FIG. 5.—Cortical thickness in humans is plotted as a function of age and region of the cerebral cortex. Symbols within regions identify particular sites that were measured (data from Conel, 1939–1967). Postnatal changes in cortical thickness indirectly reflect the addition or deletion of brain components, for example, synapses, neurons and supporting cells, blood vessels. A tendency for a peak in cortical thickness between 10 and 20 months of age is evident at many sites in visual, parietal, temporal, and motor cortex, and a second peak may also occur near 50 months of age at some sites. A clear pattern of peaks and troughs is much less evident in prefrontal cortex, which seems to increase gradually in thickness over the first 4 years of life.

recently been proposed for visual development (Harwerth, Smith, Duncan, Crawford, & von Noorden, 1986).

References

- Bateson, P. P. G. (1979). How do sensitive periods arise and what are they for? *Animal Behavior*, *27*, 470-486.
- Bateson, P. P. G., Rose, S. P. R., & Horn, G. (1973). Imprinting: Lasting effects on uracil incorporation into chick brain. *Science*, *181*, 576-578.
- Bear, M. F., & Singer, W. (1986). Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature*, *320*, 172-176.
- Bennett, E. L., Diamond, M. C., Krech, D., & Rosenzweig, M. R. (1964). Chemical and anatomical plasticity of brain. *Science*, *146*, 610-619.
- Bennett, E. L., Rosenzweig, M. R., Morimoto, H., & Hebert, M. (1979). Maze training alters brain weights and cortical RNA/DNA ratios. *Behavioral and Neural Biology*, *26*, 1-22.
- Black, J. E., & Greenough, W. T. (1986). Induction of pattern in neural structure by experience: Implications for cognitive development. In M. E. Lamb, A. L. Brown, & B. Rogoff (Eds.), *Advances in developmental psychology* (Vol. 4, pp. 1-50). Hillsdale, NJ: Erlbaum.
- Blakemore, C., & Van Sluysers, R. C. (1975). Innate and environmental factors in the development of the kitten's visual cortex. *Journal of Physiology*, *248*, 663-716.
- Blasdel, G. G., Mitchell, D. E., Muir, D. W., & Pettigrew, J. D. (1977). A physiological and behavioural study in cats of the effect of early visual experience with contours of a single orientation. *Journal of Physiology*, *265*, 615-636.
- Bliss, T. V. P., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *Journal of Physiology*, *232*, 331-356.
- Blue, M. E., & Parnavelas, J. G. (1983). The formation and maturation of synapses in the visual cortex of the rat: I. Quantitative analysis. *Journal of Neurocytology*, *12*, 697-712.
- Boothe, R. G., Greenough, W. T., Lund, J. S., & Wrege, K. (1979). A quantitative investigation of spine and dendritic development of neurons in visual cortex (area 17) of *Macaca nemestrina* monkeys. *Journal of Comparative Neurology*, *186*, 473-490.
- Brown, M. C., Jansen, J. K. S., & Van Essen, D. (1976). Polyneuronal innervation of skeletal muscle in new-born rats and its elimination during maturation. *Journal of Physiology*, *261*, 387-422.
- Brown, R. T. (1968). Early experience and problem solving ability. *Journal of Comparative and Physiological Psychology*, *65*, 433-440.
- Brunjes, P. C., Schwark, H. D., & Greenough, W. T. (1982). Olfactory granule cell development in normal and hyperthyroid rats. *Developmental Brain Research*, *5*, 149-159.
- Buisseret, P., & Imbert, M. (1976). Visual cortical cells: Their developmental properties in normal and dark-reared kittens. *Journal of Physiology*, *255*, 511-525.
- Camel, J. E., Withers, G. S., & Greenough, W. T. (1986). Persistence of visual cortex dendritic alterations induced by postweaning exposure to a "superenriched" environment in rats. *Behavioral Neuroscience*, *100*, 810-813.
- Chang, F.-L. F., & Greenough, W. T. (1982). Later-alized effects of monocular training on dendritic branching in adult split-brain rats. *Brain Research*, *232*, 283-292.
- Chang, F.-L. F., & Greenough, W. T. (1984). Transient and enduring morphological correlates of synaptic activity and efficacy change in the rat hippocampal slice. *Brain Research*, *309*, 35-46.
- Changeux, J.-P., & Danchin, A. (1977). Biochemical models for the selective stabilization of developing synapses. In G. A. Cottrell & P. M. Usherwood (Eds.), *Synapses* (pp. 705-712). New York: Academic Press.
- Chomsky, N. (1980). On cognitive structures and their development: A reply to Piaget. In M. Piatelli-Palmarini (Ed.), *Language and learning* (pp. 35-52). Cambridge, MA: Harvard University Press.
- Chugani, H. T., & Phelps, M. E. (1986). Maturation changes in cerebral function in infants determined by [18]FDG positron emission tomography. *Science*, *231*, 840-843.
- Clopton, B. M., & Winfield, J. A. (1976). Effect of early exposure to patterned sound on unit activity in rat inferior colliculus. *Journal of Neurophysiology*, *39*, 1081-1089.
- Coleman, P. D., Flood, D. G., Whitehead, M. C., & Emerson, R. C. (1981). Spatial sampling by dendritic trees in visual cortex. *Brain Research*, *214*, 1-21.
- Coleman, P. D., & Riesen, A. H. (1968). Environmental effects on cortical dendritic fields: I. Rearing in the dark. *Journal of Anatomy*, *102*, 363-374.
- Conel, J. L. (1939-1967). *The postnatal development of the human cerebral cortex* (Vols. 1-8). Cambridge, MA: Harvard University Press.
- Corrigan, J. G., & Carpenter, D. L. (1979). Early selective visual experience and pattern discrimination in hooded rats. *Developmental Psychobiology*, *12*, 67-72.
- Cotman, C. W., & Nieto-Sampedro, M. (1984). Cell biology of synaptic plasticity. *Science*, *225*, 1287-1294.

- Crabtree, J. W., & Riesen, A. H. (1979). Effects of the duration of dark rearing on visually guided behavior in the kitten. *Developmental Psychobiology*, *12*, 291-303.
- Cragg, B. G. (1967). Changes in visual cortex on first exposure of rats to light: Effect on synaptic dimensions. *Nature*, *215*, 251-253.
- Cragg, B. G. (1975a). The development of synapses in kitten visual cortex during visual deprivation. *Experimental Neurology*, *46*, 445-451.
- Cragg, B. G. (1975b). The development of synapses in the visual system of the cat. *Journal of Comparative Neurology*, *160*, 147-166.
- Cronly-Dillon, J., & Perry, G. W. (1979). The effect of visual experience on tubulin synthesis during a critical period of visual cortex development in the hooded rat. *Journal of Physiology*, *293*, 469-484.
- Cynader, M., Berman, N., & Hein, A. (1976). Recovery of function in cat visual cortex following prolonged deprivation. *Experimental Brain Research*, *25*, 139-156.
- Cynader, M., & Chernenko, G. (1976). Abolition of direction selectivity in the visual cortex of the cat. *Science*, *193*, 504-505.
- Cynader, M., & Mitchell, D. E. (1980). Prolonged sensitivity to monocular deprivation in dark-reared cats. *Journal of Neurophysiology*, *43*, 1026-1040.
- Diamond, A. (1985). Development of the ability to use recall to guide action, as indicated by infants' performance on A-B. *Child Development*, *56*, 868-883.
- Diamond, M. C. (1967). Extensive cortical depth measurements and neuron size increases in the cortex of environmentally enriched rats. *Journal of Comparative Neurology*, *131*, 357-364.
- Diamond, M. C., Rosenzweig, M. R., Bennett, E. L., Lindner, B., & Lyon, L. (1972). Effects of environmental enrichment and impoverishment on rat cerebral cortex. *Journal of Neurobiology*, *3*, 47-64.
- Dunn, A. J. (1980). Neurochemistry of learning and memory: An evaluation of recent data. *Annual Review of Psychology*, *31*, 343-390.
- Eayrs, J. T., & Ireland, K. F. (1950). The effect of total darkness on the growth of the newborn albino rat. *Journal of Endocrinology*, *6*, 386-397.
- Eimas, P. D. (1975). Speech perception in early infancy. In L. B. Cohen & P. Salapatek (Eds.), *Infant perception* (pp. 193-231). New York: Academic Press.
- Epstein, H. T. (1974a). Phrenoblysis: Special brain and mind growth periods: I. Human brain and skull development. *Developmental Psychobiology*, *7*, 207-216.
- Epstein, H. T. (1974b). Phrenoblysis: Special brain and mind growth periods: II. Human mental development. *Developmental Psychobiology*, *7*, 217-224.
- Epstein, H. T., & Toepfer, C. F., Jr. (1978). A neuroscience basis for reorganizing middle grades education. *Educational Leadership*, *35*, 656-660.
- Feng, A. S., & Rogowski, B. A. (1980). Effects of monaural and binaural occlusion on the morphology of neurons in the medial superior olivary nucleus of the rat. *Brain Research*, *189*, 530-534.
- Ferchmin, P. A., Bennett, E. L., & Rosenzweig, M. R. (1975). Direct contact with enriched environments is required to alter cerebral weights in rats. *Journal of Comparative and Physiological Psychology*, *88*, 360-367.
- Fernald, A. (1984). The perceptual and affective salience of mother's speech to infants. In L. Feagans, C. Garvey, & R. Golinkoff (Eds.), *The origins and growth of communication* (pp. 5-29). Norwood, NJ: Ablex.
- Fifkova, E. (1968). Changes in the visual cortex of rats after unilateral deprivation. *Nature*, *220*, 379-381.
- Fifkova, E. (1970). The effect of unilateral deprivation on visual centers in rats. *Journal of Comparative Neurology*, *140*, 431-438.
- Fiske, J. (1909). *The meaning of infancy*. Boston: Houghton Mifflin. (Original work published 1883)
- Floeter, M. K., & Greenough, W. T. (1979). Cerebellar plasticity: Modification of purkinje cell structure by differential rearing in monkeys. *Science*, *206*, 227-229.
- Forgays, D. G., & Forgays, J. W. (1952). The nature of the effect of free-environmental experience in the rat. *Journal of Comparative and Physiological Psychology*, *45*, 322-328.
- Fox, M. W. (1966). Neuro-behavioral ontogeny: A synthesis of ethological and neurophysiological concepts. *Brain Research*, *2*, 3-20.
- Globus, A. (1975). Brain morphology as a function of presynaptic morphology and activity. In A. H. Riesen (Ed.), *The developmental neuropsychology of sensory deprivation* (pp. 9-91). New York: Academic Press.
- Globus, A., Rosenzweig, M. R., Bennett, E. L., & Diamond, M. C. (1973). Effects of differential experience on dendritic spine counts in rat cerebral cortex. *Journal of Comparative and Physiological Psychology*, *82*, 175-181.
- Gold, P. E. (1984). Memory modulation: Neurobiological contexts. In G. Lynch, J. L. McGaugh, & N. M. Weinberger (Eds.), *Neurobiology of learning and memory* (pp. 374-382). New York: Guilford.
- Goldman-Rakic, P. S. (1987). Development of cortical circuitry and cognitive function. *Child Development*, *58*, 601-622.
- Gordon, B., Presson, J., Packwood, J., & Scheer, R. (1979). Alteration of cortical orientation selectivity: Importance of asymmetric input. *Science*, *204*, 1109-1111.

- Gouze, J.-L., Lasry, J.-M., & Changeux, J.-P. (1983). Selective stabilization of muscle innervation during development: A mathematical model. *Biological Cybernetics*, *46*, 207-215.
- Green, E. J., & Greenough, W. T. (1986). Altered synaptic transmission in dentate gyrus of rats reared in complex environments: Evidence from hippocampal slices maintained in vivo. *Journal of Neurophysiology*, *55*, 739-750.
- Green, E. J., Greenough, W. T., & Schlumpf, B. E. (1983). Effects of complex or isolated environments on cortical dendrites of middle-aged rats. *Brain Research*, *264*, 233-240.
- Greenough, W. T. (1976). Enduring brain effects of differential experience and training. In M. R. Rosenzweig & E. L. Bennett (Eds.), *Neural mechanisms of learning and memory* (pp. 255-278). Cambridge, MA: MIT Press.
- Greenough, W. T. (1978). Development and memory: The synaptic connection. In T. Teyler (Ed.), *Brain and learning* (pp. 127-145). Stamford, CT: Greylock.
- Greenough, W. T. (1984). Structural correlates of information storage in the mammalian brain: A review and hypothesis. *Trends in Neurosciences*, *7*, 229-233.
- Greenough, W. T., & Chang, F.-L. C. (1985). Synaptic structural correlates of information storage in mammalian nervous systems. In C. W. Cotman (Ed.), *Synaptic plasticity and remodeling* (pp. 335-372). New York: Guilford.
- Greenough, W. T., Hwang, H. M., & Gorman, C. (1985). Evidence for active synapse formation, or altered postsynaptic metabolism, in visual cortex of rats reared in complex environments. *Proceedings of the National Academy of Sciences (USA)*, *82*, 4549-4552.
- Greenough, W. T., Juraska, J. M., & Volkmar, F. R. (1979). Maze training effects on dendritic branching in occipital cortex of adult rats. *Behavioral and Neural Biology*, *26*, 287-297.
- Greenough, W. T., Larson, J. R., & Withers, G. S. (1985). Effects of unilateral and bilateral training in a reaching task on dendritic branching of neurons in the rat motor-sensory forelimb cortex. *Behavioral and Neural Biology*, *44*, 301-314.
- Greenough, W. T., Madden, T. C., & Fleischmann, T. B. (1972). Effects of isolation, daily handling, and enriched rearing on maze learning. *Psychonomic Science*, *27*, 279-280.
- Greenough, W. T., & Maier, S. F. (1972). Molecular changes during learning: Behavioral strategy: A comment on Gaito and Bonnet. *Psychological Bulletin*, *78*, 480-482.
- Greenough, W. T., McDonald, J., Parnisari, R., & Camel, J. E. (1986). Environmental conditions modulate degeneration and new dendrite growth in cerebellum of senescent rats. *Brain Research*, *380*, 136-143.
- Greenough, W. T., & Schwark, H. D. (1984). Age-related aspects of experience effects upon brain structure. In R. N. Emde & R. J. Harmon (Eds.), *Continuities and discontinuities in development* (pp. 69-91). Hillsdale, NJ: Plenum.
- Greenough, W. T., & Volkmar, F. R. (1973). Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Experimental Neurology*, *40*, 491-504.
- Greenough, W. T., Volkmar, F. R., & Juraska, J. M. (1973). Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. *Experimental Neurology*, *41*, 371-378.
- Guillery, R. W. (1972). Binocular competition in the control of geniculate cell growth. *Journal of Comparative Neurology*, *144*, 117-130.
- Gyllenstein, L., Malmfors, T., & Norrlin, M. L. (1966). Growth alteration in the auditory cortex of visually deprived mice. *Journal of Comparative Neurology*, *126*, 463-470.
- Hahn, M. E., Walters, J. K., Lavooy, J., & DeLuca, J. (1983). Brain growth in young mice: Evidence on the theory of phrenoblysis. *Developmental Psychobiology*, *16*, 377-383.
- Harwerth, R. S., Smith III, E. L., Duncan, G. C., Crawford, M. L. J., & von Noorden, G. K. (1986). Multiple sensitive periods in the development of the primate visual system. *Science*, *232*, 235-238.
- Hebb, D. O. (1949). *The organization of behavior*. New York: Wiley.
- Hirsch, H. V. B., & Spinelli, D. N. (1970). Visual experience modifies distribution of horizontally and vertically oriented receptive fields in cats. *Science*, *168*, 869-871.
- Holloway, R. L. (1966). Dendritic branching: Some preliminary results of training and complexity in rat visual cortex. *Brain Research*, *2*, 393-396.
- Horn, G., Rose, S. P. R., & Bateson, P. P. G. (1973). Monocular imprinting and regional incorporation of tritiated uracil into the brains of intact and "split-brain" chicks. *Brain Research*, *56*, 227-237.
- Hubel, D. H., & Wiesel, T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *Journal of Physiology*, *206*, 419-436.
- Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Research*, *163*, 195-205.
- Huttenlocher, P. R., de Courten, C., Garey, L. J., & Van Der Loos, H. (1982). Synaptogenesis in human visual cortex—evidence for synapse elimination during normal development. *Neuroscience Letters*, *33*, 247-252.
- Hwang, H. M., & Greenough, W. T. (1984). Spine formation and synaptogenesis in rat visual cor-

- tex: A serial section developmental study. *Society for Neuroscience Abstracts*, 14, 579.
- Hymovitch, B. (1952). The effects of experimental variations on problem solving in the rat. *Journal of Comparative and Physiological Psychology*, 45, 313-321.
- Juraska, J. M. (1984). Sex differences in dendritic response to differential experience in the rat visual cortex. *Brain Research*, 295, 27-34.
- Juraska, J. M., Fitch, J., Henderson, C., & Rivers, N. (1985). Sex differences in the dendritic branching of dentate granule cells following differential experience. *Brain Research*, 333, 73-80.
- Juraska, J. M., Greenough, W. T., Elliott, C., Mack, K. J., & Berkowitz, R. (1980). Plasticity in adult rat visual cortex: An examination of several cell populations after differential rearing. *Behavioral and Neural Biology*, 29, 157-167.
- Kasamatsu, T., & Pettigrew, J. D. (1976). Depletion of brain catecholamines: Failure of ocular dominance shift after monocular occlusion in kittens. *Science*, 194, 206-209.
- Krech, D., Rosenzweig, M. R., & Bennett, E. L. (1962). Relations between brain chemistry and problem-solving among rats raised in enriched and impoverished environments. *Journal of Comparative and Physiological Psychology*, 55, 801-807.
- Lee, K. S., Oliver, M., Schottler, F., & Lynch, G. (1981). Electron microscopic studies of brain slices: The effects of high-frequency stimulation on dendritic ultrastructure. In G. A. Kerkut and H. V. Wheal (Eds.), *Electrophysiology of isolated mammalian CNS preparations* (pp. 189-212). New York: Academic Press.
- Lee, K. S., Schottler, F., Oliver, M., & Lynch, G. (1980). Brief bursts of high-frequency stimulation produce two types of structural change in rat hippocampus. *Journal of Neurophysiology*, 44, 247-258.
- LeVay, S., Wiesel, T. N., & Hubel, D. H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *Journal of Comparative Neurology*, 191, 1-51.
- Leventhal, A. G., & Hirsch, H. V. B. (1975). Cortical effect of early selective exposure to diagonal lines. *Science*, 190, 902-904.
- Marsh, R. W. (1985). Phrenoblysis: Real or chimera? *Child Development*, 56, 1059-1061.
- McCall, R. B., Meyers, E. C., Jr., Hartman, J., & Roche, A. F. (1983). Developmental changes in head-circumference and mental-performance growth rates: A test of Epstein's phrenoblysis hypothesis. *Developmental Psychobiology*, 16, 457-468.
- Meisami, E. (1975). Early sensory influences on regional activity of brain ATPases in developing rats. In M. A. B. Brazier (Ed.), *Growth and development of the brain* (pp. 51-74). New York: Raven.
- Miller, M. (1981). Maturation of rat visual cortex: I. A quantitative study of Golgi-impregnated pyramidal neurons. *Journal of Neurocytology*, 10, 859-878.
- Miller, M., & Peters, A. (1981). Maturation of rat visual cortex: II. A combined Golgi-electron microscope study of pyramidal neurons. *Journal of Comparative Neurology*, 203, 555-573.
- Mirmiran, M., & Uylings, H. (1983). The environmental enrichment effect upon cortical growth is neutralized by concomitant pharmacological suppression of active sleep in female rats. *Brain Research*, 261, 331-334.
- Mitchell, D. E., Freeman, R. D., Millodot, M., & Haegerstrom, G. (1973). Meridional amblyopia: Evidence for modification of the human visual system by early visual experience. *Vision Research*, 13, 535-558.
- Mitchell, D. E., & Timney, B. (1984). Postnatal development of function in the mammalian nervous system. In J. M. Brookhart & V. R. Mountcastle (Eds.), *Handbook of physiology, Section 1: The nervous system* (Vol. 3, pp. 507-555). Bethesda, MD: American Physiological Society.
- Mos, L. P. (1976). Light rearing effects on factors of mouse emotionality and endocrine organ weight. *Physiological Psychology*, 4, 503-510.
- Movshon, J. A., & Van Sluyters, R. C. (1981). Visual neuronal development. *Annual Review of Psychology*, 32, 477-522.
- Mower, G. D., Christen, W. G., & Caplan, C. J. (1983). Very brief visual experience eliminates plasticity in the cat visual cortex. *Science*, 221, 178-180.
- Myers, R. D., & Fox, J. (1963). Differences in maze performance of group- vs. isolation-reared rats. *Psychological Reports*, 12, 199-202.
- O'Brien, R. A. D., Ostberg, A. J., & Vrbova, G. (1978). Observations on the elimination of polyneuronal innervation in developing mammalian skeletal muscle. *Journal of Physiology*, 282, 571-582.
- Olson, C. R., & Freeman, R. D. (1978). Monocular deprivation and recovery during sensitive period in kittens. *Journal of Neurophysiology*, 41, 65-74.
- O'Shea, L., Saari, M., Pappas, B., Ings, R., & Stange, K. (1983). Neonatal 6-hydroxydopamine attenuates the neural and behavioral effects of enriched rearing in the rat. *European Journal of Pharmacology*, 92, 43-47.
- Parnavelas, J. G., & Globus, A. (1976). The effect of continuous illumination on the development of cortical neurons in the rat: A Golgi study. *Experimental Neurology*, 51, 637-647.
- Parnavelas, J. G., Globus, A., & Kaups, P. (1973). Continuous illumination from birth affects

- spine density of neurons in the visual cortex of the rat. *Experimental Neurology*, **40**, 742-747.
- Pearlman, C. (1983). Impairment of environmental effects on brain weight by adrenergic drugs in rats. *Physiology and Behavior*, **30**, 161-163.
- Peterson, G. M. (1951). Transfers of handedness in the rat from forced practice. *Journal of Comparative and Physiological Psychology*, **44**, 184-190.
- Pettigrew, J. D., & Kasamatsu, T. (1978). Local perfusion of noradrenaline maintains visual cortical plasticity. *Nature*, **271**, 761-763.
- Purves, D., & Lichtman, J. W. (1980). Elimination of synapses in the developing nervous system. *Science*, **210**, 153-157.
- Pysh, J. J., & Weiss, M. (1979). Exercise during development induces an increase in Purkinje cell dendritic tree size. *Science*, **206**, 230-232.
- Rakic, P., Bourgeois, J.-P., Eckenhoff, M. F., Zecevic, N., & Goldman-Rakic, P. S. (1986). Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. *Science*, **232**, 232-235.
- Ramon y Cajal, S. (1893). New findings about the histological structure of the central nervous system. *Archiv fur Anatomie und Physiologie (Anatomie)*, pp. 319-428.
- Rasch, E., Swift, H., Riesen, A. H., & Chow, K. L. (1961). Altered structure and composition of retinal cells in dark-reared mammals. *Experimental Cell Research*, **25**, 348-363.
- Ravizza, R. J., & Herschberger, A. C. (1966). The effect of prolonged motor restriction upon later behavior of the rat. *Psychological Record*, **16**, 73-80.
- Rose, S. P. R. (1967). Changes in visual cortex on first exposure to light. *Nature*, **215**, 253-255.
- Rose, S. P. R. (1981). What should a biochemistry of learning and memory be about? *Neuroscience*, **6**, 811-821.
- Rosenzweig, M. R., Bennett, E. L., & Diamond, M. C. (1972). Chemical and anatomical plasticity of brain: Replications and extensions. In J. Gaito (Ed.), *Macromolecules and behavior* (2d ed., pp. 205-277). New York: Appleton-Century-Crofts.
- Rothblat, L. A., & Schwartz, M. (1979). The effect of monocular deprivation on dendritic spines in visual cortex of young and adult albino rats: Evidence for a sensitive period. *Brain Research*, **161**, 156-161.
- Ruiz-Marcos, A., & Valverde, F. (1969). The temporal evolution of the distribution of dendritic spines in the visual cortex of normal and dark raised mice. *Experimental Brain Research*, **8**, 284-294.
- Ryugo, D. K., Ryugo, R., Globus, A., & Killackey, H. P. (1975). Increased spine density in auditory cortex following visual or somatic deafferentation. *Brain Research*, **90**, 143-146.
- Schneider, G. E. (1981). Early lesions and abnormal neural connections. *Trends in Neurosciences*, **4**, 187-192.
- Schüz, A. (1978). Some facts and hypotheses concerning dendritic spines and learning. In M. A. B. Brazier & H. Petsche (Eds.), *Architectonics of the cerebral cortex* (pp. 129-135). New York: Raven.
- Senden, M. von (1960). *Space and sight: The perception of space and shape in the congenitally blind before and after operation*. Glencoe, IL: Free Press.
- Sherman, S. M. (1973). Visual field defects in monocularly and binocularly deprived cats. *Brain Research*, **49**, 25-45.
- Sherman, S. M. (1977). The effect of cortical and tectal lesions on the visual fields of binocularly deprived cats. *Journal of Comparative Neurology*, **172**, 231-246.
- Singer, W. (1986). Neuronal activity as a shaping factor in postnatal development of visual cortex. In W. T. Greenough & J. M. Juraska (Eds.), *Developmental neuropsychobiology*. New York: Academic Press.
- Spreen, O., Tupper, D., Risser, A., Tuokko, H., & Edgell, D. (1984). *Human developmental neuropsychobiology*. New York: Oxford University Press.
- Steward, O. (1983). Polyribosomes at the base of dendritic spines of CNS neurons: Their possible role in synapse construction and modification. *Cold Spring Harbor Symposia on Quantitative Biology*, **48**, 745-759.
- Tanzi, E. (1893). Facts and inductions in current histology of the nervous system. *Rivista sperimentale di freniatria e medicina legale delle mentali alienazioni*, **19**, 419-472.
- Tees, R. C. (1979). The effect of visual deprivation on pattern recognition in the rat. *Developmental Psychobiology*, **12**, 485-497.
- Tees, R. C., & Cartwright, J. (1972). Sensory preconditioning in rats following early visual deprivation. *Journal of Comparative and Physiological Psychology*, **81**, 12-20.
- Teyler, T. J., & Fountain, S. B. (1987). Neuronal plasticity in the mammalian brain: Relevance to behavioral learning and memory. *Child Development*, **58**, 668-712.
- Thelen, E. (1980). Rhythmical behavior in infancy: An ethological perspective. *Developmental Psychology*, **17**, 237-257.
- Thinus-Blanc, C. (1981). Volume discrimination learning in golden hamsters: Effects of the structure of complex rearing cages. *Developmental Psychobiology*, **14**, 397-403.
- Thompson, W., Kuffler, D. P., & Jansen, J. K. S. (1979). The effect of prolonged reversible block of nerve impulses on the elimination of polyneuronal innervation of newborn rat skeletal muscle fibres. *Neuroscience*, **4**, 271-281.
- Tieman, S. B., & Hirsch, H. (1982). Exposure to lines of only one orientation modifies dendritic

- morphology of cells in the visual cortex of the cat. *Journal of Comparative Neurology*, **211**, 353-362.
- Timney, B., Mitchell, D. E., & Cynader, M. (1980). Behavioral evidence for prolonged sensitivity to effects of monocular deprivation in dark-reared cats. *Journal of Neurophysiology*, **43**, 1041-1054.
- Turkewitz, G., & Kenny, P. A. (1982). Limitations on input as a basis for neural organization and perceptual development: A preliminary theoretical statement. *Developmental Psychobiology*, **15**, 357-368.
- Turner, A. M., & Greenough, W. T. (1985). Differential rearing effects on rat visual cortex synapses. I. Synaptic and neuronal density and synapses per neuron. *Brain Research*, **329**, 195-203.
- Uylings, H. B. M., Kuypers, K., Diamond, M. C., & Veltman, W. A. M. (1978). Effects of differential environments on plasticity of dendrites of cortical pyramidal neurons in adult rats. *Experimental Neurology*, **62**, 658-677.
- Uylings, H. B. M., Kuypers, K., & Veltman, W. A. M. (1978). Environmental influences on neocortex in later life. *Progress in Brain Research*, **48**, 261-274.
- Valverde, F. (1970). The Golgi method: A tool for comparative structural analyses. In W. J. H. Nauta & S. O. E. Ebbesson (Eds.), *Contemporary research methods in neuroanatomy* (pp. 12-31). New York: Springer-Verlag.
- Valverde, F. (1971). Rate and extent of recovery from dark-rearing in the mouse. *Brain Research*, **33**, 1-11.
- Werker, J. F., & Tees, R. C. (1984). Cross-language speech perception: Evidence for perceptual reorganization during the first year of life. *Infant Behavior and Development*, **7**, 49-63.
- Wiesel, T. N., & Hubel, D. H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. *Journal of Neurophysiology*, **26**, 1003-1017.
- Wiesel, T. N., & Hubel, D. H. (1965). Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *Journal of Neurophysiology*, **28**, 1029-1040.
- Wiesel, T., & Raviola, E. (1977). Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature*, **266**, 66-68.
- Winfield, D. A. (1981). The postnatal development of synapses in the visual cortex of the cat and the effects of eyelid closure. *Brain Research*, **206**, 166-171.

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