

Figure 55. "Likely" disposition of commissural and projection fibers in the rat, taken from Figure 15 of Ramon y Cajal (1894). A = corpus callosum. B = anterior commissure. C = pyramidal tract (projection fibers). In the text, Ramón y Cajal describes, at least partially from observations with the silver chromate method on newborn rats, two interesting characteristics of the callosal system: (1) some callosal fibers appear to terminate with widely distributed axonal ramification in contralateral cortex (i.e., e and d); (2) a number of association and projection axons give off a collateral to the corpus callosum. [Innocenti, 1979]

still hypothetical possibility is suggested by a drawing (Figure 55) of Ramón y Cajal (1894). Alternatively, some neurons that send a transitory axon through the corpus callosum may send an ipsilateral one after the callosal axon has been eliminated.

ROLE OF VISUAL AFFERENT ACTIVITY IN THE DEVELOPMENT OF OCULAR DOMINANCE COLUMNS:

M.P. Stryker

Among all cortical areas the primary visual cortex has been the object of the most extensive study. One of the reasons for such interest is that the visual cortex is anatomically and physiologically well defined (see Hubel and Wiesel, 1977, for references). Furthermore, as shown 20 years ago (Wiesel and Hubel, 1963b), it is also remarkably modifiable. Thus, in normal cats and monkeys the geniculocortical terminals end in partially overlapping bands in the input layer

IV of the cortex (Hubel and Wiesel, 1972, 1977). This alternating termination of cortical afferents serving one or the other eye is thought to be the anatomical substrate for the ocular dominance "columns" or stripes. But if one eye is closed early in life, almost all of the cortical cells end up being driven exclusively by the other eye (Hubel et al., 1977). This type of functional plasticity has led to the notion that visual activity might also be important in determining the pattern of projection of the geniculate afferents in the cortex. Hubel and Wiesel and their colleagues were able to demonstrate such plasticity anatomically by the use of transsynaptic transport of tritiated markers injected into one eye. These experiments showed that, after early monocular deprivation, the normal alteration of afferents from each eye in layer IV in the form of equal territories is deranged. Thus, layer IV is occupied predominantly by terminals from the open (functional) eye (Figure 56; Wiesel and Hubel, 1963b; Shatz and Stryker, 1978). Physiological recordings from the cortex of the same animals confirm this, with the anatomical and physiological measurements of the fraction of cortex controlled by the closed eye being about 20% in the cat and 25% in the monkey (Hubel et al., 1977; Shatz and Stryker, 1978).

As is the case with monocular deprivation, very few binocularly driven cortical cells are found after early strabismus, alternating monocular occlusion, or the use of prisms to separate the visual fields in the two eyes (Hubel and Wiesel, 1965; Van Sluyters and Levitt, 1980). However, after these treatments, about one-half of the cortical population is driven by each eye. Anatomical and physiological experiments in these cases show an exaggeration of the normal separation and alternation between the afferents of the two eyes (Shatz et al., 1977).

These various plastic effects have well-defined critical periods. There are also laminar differences in the extent of this plasticity and in the timing with which these plastic changes take place. In the monkey, the critical period for the rearrangement of layer IV ends between the third and sixth postnatal weeks (LeVay et al., 1980), while in the cat it ends sometime between the sixth and twelfth weeks (Stryker, 1981). However, monocular deprivation after this time in both cat and monkey has dramatic effects on the ocular dominance of cells above and especially below layer IV.

This last point suggests a conceptual model (Hubel et al., 1977; Shatz and Stryker, 1978; LeVay et al., 1980; Stryker, 1981) of cortical organization that is reinforced by the work of J. Lund, Gilbert, Wiesel, Mitzdorf and Singer, and others (Mitzdorf and Singer, 1978; Gilbert and Wiesel, 1979; Lund et al., 1979). This model considers

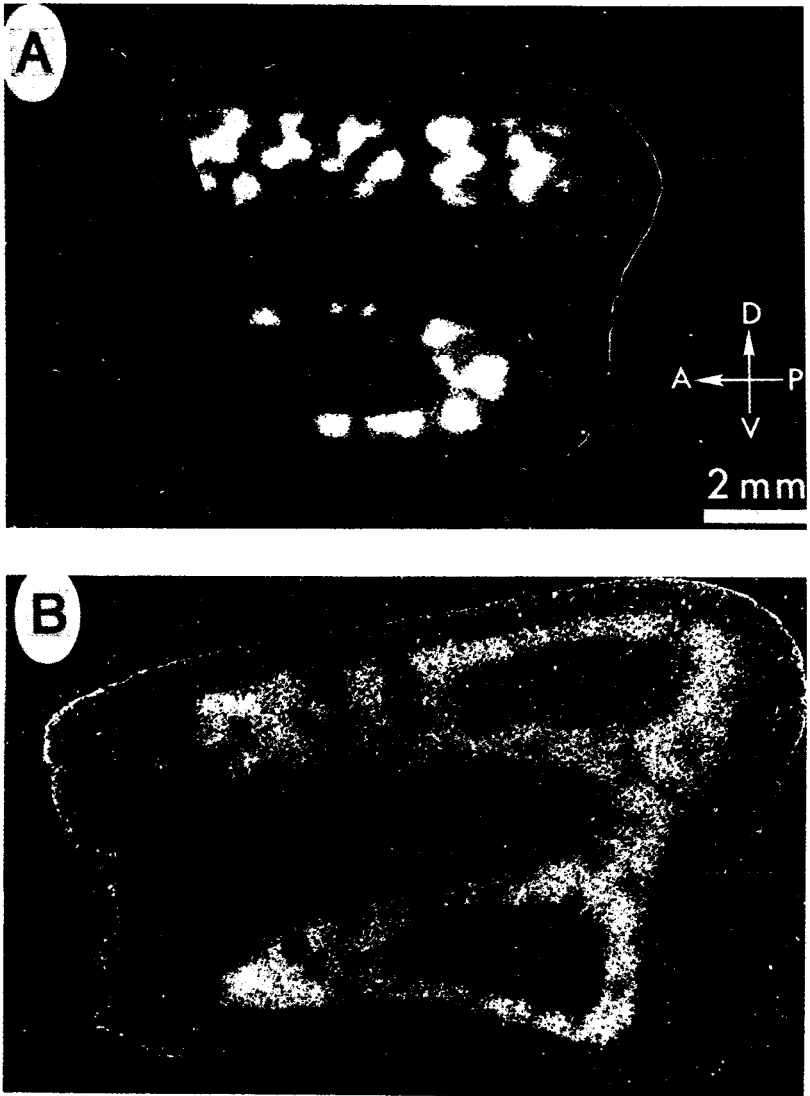


Figure 56. Dark-field autoradiographs of parasagittal sections of area 17 ipsilateral to injection of one eye with radioactive tracer in normal animal (A) and in the open eye of an animal that had been monocularly deprived from birth (B). Note that in the normal animal less than half of layer IV is occupied by label, indicating a restricted distribution of geniculocortical afferent terminals serving the injected eye; while in the deprived animal about 80% of layer IV is so labeled. D = dorsal, V = ventral, A = anterior, P = posterior. [Stryker]

the first stage of cortical information processing to be the input layer in the middle of the cortex. This layer has a major output to the upper layers, which, in turn, project heavily to the lower layers. In this model, binocular plasticity effects would be a multistage

process, with the input layer (IV) being sensitive early in life, the upper layers remaining sensitive until later, and the lower layers until even later. The degree of the monocular deprivation effects in each of the different layers is consistent with this model. In the input layer of the cat, monocular deprivation from birth leaves 20% of the cells still responding to the deprived eye; however, in the upper layers only about 5% of the cells are still driven by this eye, while in the lower layers the proportion is only about 1% (Shatz and Stryker, 1978).

Until a few years ago, there was little data to suggest the nature of the maturational processes underlying this plasticity. Then the anatomical studies of Rakic (1976b) in the fetal monkey and Hubel and Wiesel (Hubel et al., 1977) in the neonatal monkey revealed that geniculocortical terminals for the two eyes initially overlap in the cortex. Similarly, in the 2-week-old cat, injection of radioactive tracers into one eye does not label alternating bands in layer IV, as it does in the adult; rather, the entire extent of the kitten's layer IV is labeled uniformly (Figure 57; LeVay et al., 1978; LeVay and Stryker, 1979). In the cat, segregation of afferents into ocular dominance bands begins by the third postnatal week, which is also about the time for the beginning of the critical period for monocular deprivation. The segregation of the ocular dominance bands is practically complete by 6 weeks of age.

Further evidence for the early intermingling between the two eyes' afferents in the cortex was provided by physiological recordings in layer IV of neonatal monkeys, which revealed the presence of binocular cells at the borders of ocular dominance columns, even though all neurons are monocular in layer IV of the adult (Hubel et al., 1977; LeVay et al., 1980). Similarly, recordings in 2-week-old kittens (before any evidence of segregation can be detected anatomically) do not reveal any appropriate alternation of ocular dominance that might have indicated segregation, even though most cells in the adult are monocular, with some binocularity only at column borders (LeVay et al., 1978; Shatz and Stryker, 1978). These physiological results suggest that geniculocortical terminals initially make functional synaptic contacts in an unsegregated pattern.

A final piece of evidence indicating an initial lack of segregation between the geniculocortical afferents of the two eyes comes from reconstructions of large HRP-filled geniculocortical axons terminating in upper layer IV of the cat. Ferster and LeVay (1978) reconstructed such axons in the adult and found (as did Gilbert and Wiesel, 1979) that these individual adult Y-axons arborize in two or three ocular dominance columns; the arbors are dense within these columns but then make no or very few contacts in the areas in between,

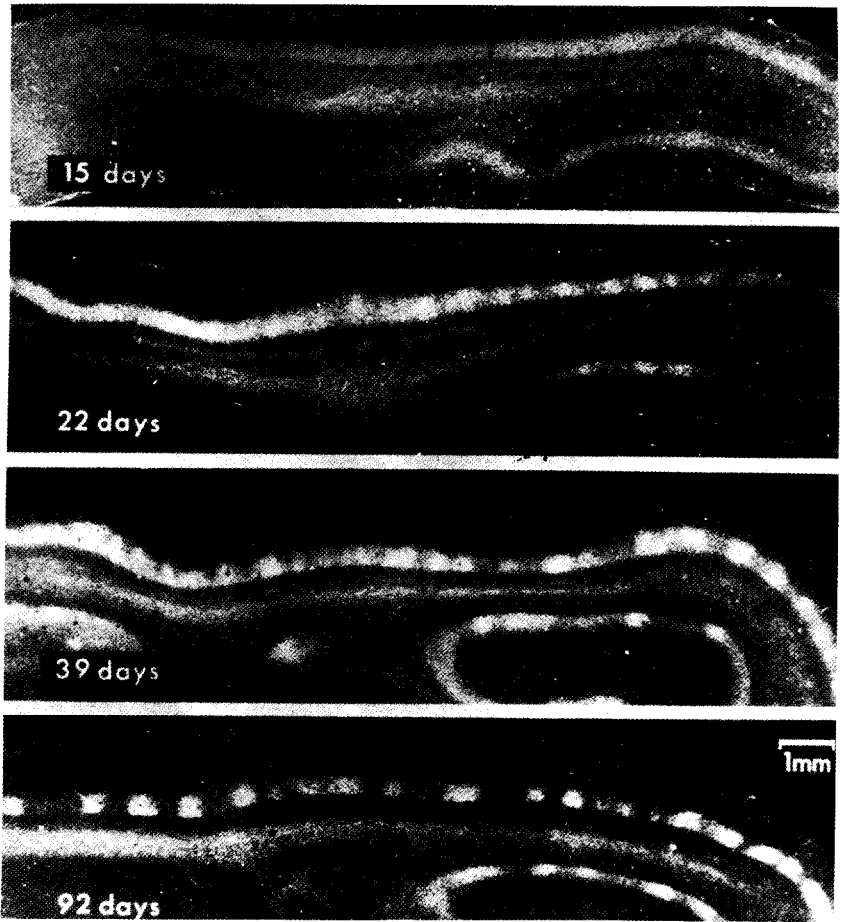


Figure 57. Postnatal development of ocular dominance columns in the cat as shown by transneuronal transport of [^3H]proline injected into one eye. These are dark-field autoradiographs of the visual cortex at four different ages, ipsilateral to the injected eye. Horizontal sections, midline at the top of each figure, anterior to the left. At 15 days of age the afferents are spread uniformly along layer IV, completely intermingled with the (unlabeled) afferents serving the contralateral eye. At later ages the afferents progressively aggregate into clumps—the anatomical basis for the physiologically defined ocular dominance columns. The gaps are occupied by unlabeled afferents serving the other eye. [LeVay et al., 1978]

where the fibers from the other eye presumably end (Figure 58, A). However, LeVay and Stryker (1979) found a different pattern of termination in the kitten, where single Y-axons arborize over large areas, with no gaps in their terminal fields (Figure 58, B). Electron microscopic examination reveals that these axons make numerous small, immature *en passant* synapses throughout their terminal fields. Taken together, all of the above pieces of evidence make it clear that the phenomenon of progressive postnatal segregation of LGN affer-

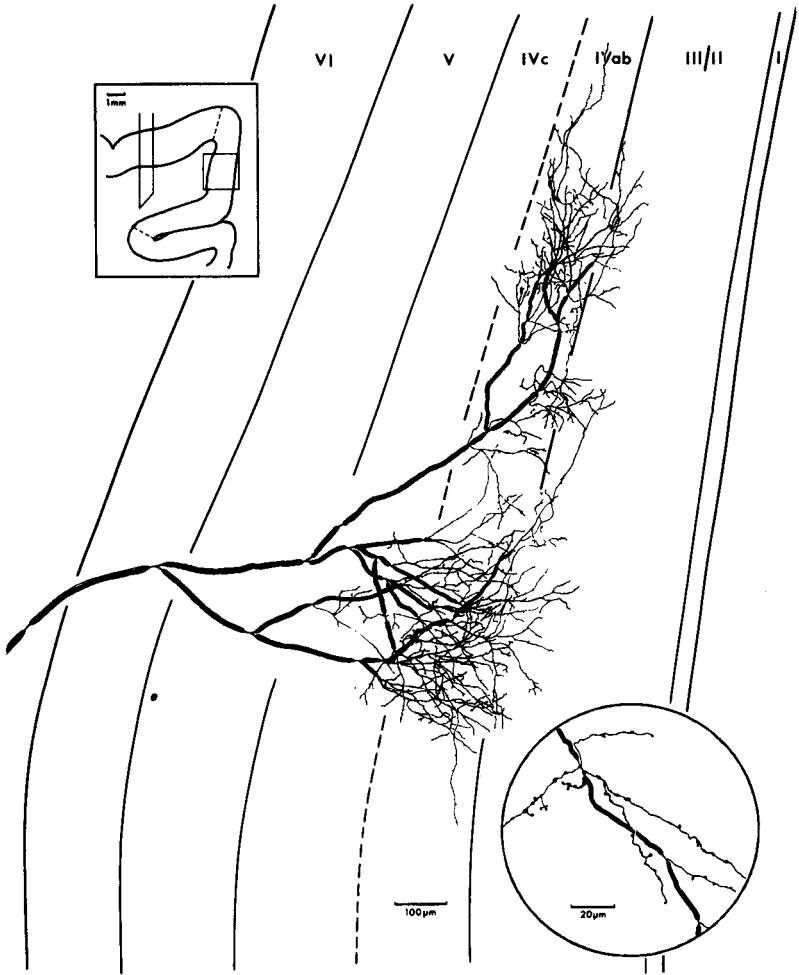


Figure 58 A. Arborization of a large geniculocortical afferent in an adult cat. This axon was filled with horseradish peroxidase from an extracellular injection into the optic radiation (see inset, *top left*). Camera lucida reconstruction from 16 successive coronal sections, each 100 μm thick. In its overall form and laminar distribution, this axon resembles the one reconstructed from a young kitten (Figure 58,B). It differs from it in four respects: (1) the arborization is not uniform but is divided into four clumps (two are superimposed in the lower part of the reconstruction); (2) the arborization is myelinated; (3) the mode of branching is no longer mainly dichotomous: as seen in the inset, *lower right*, several daughter branches can arise from each node of Ranvier; and (4) the boutons—either of the terminal or *en passage* variety—are easily recognizable specializations on the terminal axon branches. [Ferster and LeVay, 1978]

ents is real and is effected (or accomplished) by individual axons in their normal development.

A mechanism based on Hebb's (1949) proposals could possibly account for the normal development of this segregation as could the

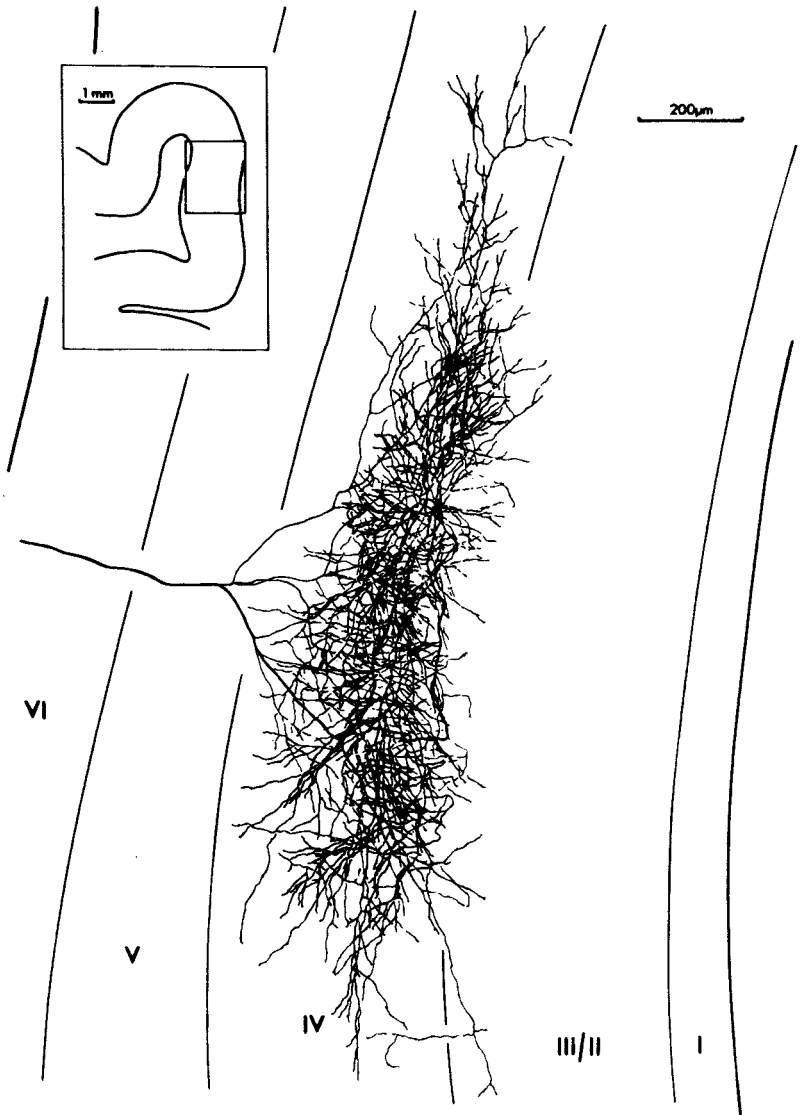


Figure 58 B. Arborization of a single geniculocortical afferent in the visual cortex of a 17-day-old kitten, i.e., just prior to the beginning of columnar segregation. This is a camera lucida reconstruction made from 25 successive coronal sections, each 100 μm thick, of an axon impregnated with the rapid Golgi method and embedded in Epon according to the method of Nevin and coworkers (1978). The axon arborizes profusely and uniformly over a disc-shaped area that is more than 2 mm in diameter. The entire arborization is unmyelinated; the myelin sheath of the afferent trunk probably leaves off in layer VI at the point where the impregnation begins. [LeVay and Stryker, 1979]

results of rearing with monocular deprivation or strabismus. One might propose that, if the presynaptic inputs to a cortical cell fire and shortly thereafter the target cell itself fires, then the synapses between them will be strengthened; while if the postsynaptic cell does not fire, these synapses will be weakened. It might be further proposed that, early in development (e.g., at 2 weeks in the cat), some layer IV cells are driven slightly more strongly by one eye and others by the other eye, so that there are fluctuations in the strength of driving by each eye within a basically random arrangement of fibers from the lateral geniculate nucleus.

When the case of monocular deprivation is considered in light of these proposals, it is likely that there would be only random, spontaneous activity in the synapses of the deprived eye. On the other hand, the nondeprived eye would receive patterned visual input; since the topography of visual projections is already well established by 2 weeks of age, neighboring LGN afferents in the cortex would have receptive fields close together in space and would therefore be likely to fire simultaneously, driving the postsynaptic cell by spatial summation. Thus, axons of the nondeprived eye would succeed in driving their target cells, while the deprived eye axons, firing only in a nonsynchronous fashion, would not. The result of this process would be that cortical cells would be taken over by the open eye, except for those cells that initially had no input from this eye, or such a small input that it could not drive the cells. In the cases of strabismus or alternating monocular occlusion, where each eye receives patterned visual input, the eye that drove a given cell more strongly in the beginning would tend to take over that cell, thus reinforcing the initial random biases. The addition of constraints in the form of a conservation of synapse number or the area over which axons are correlated would then yield the periodic alternating pattern of ocular dominance columns. Following such reasoning, normal development might be conceived to lie somewhere in between the case for strabismus and no firing at all; that is, axons serving a given eye would be more correlated with each other than with those of the other eye, but would still often tend to fire simultaneously with the other eye's fibers because of similar visual input. The outcome of this would be a range of ocular dominance values that might result in the ocular dominance columns.

Although such a discussion is quite speculative, the visual cortex seems to be a region of the brain amenable to producing evidence for such an activity-dependent mechanism, if it does indeed exist. One possible test of this hypothesis might be to destroy the proposed

correlation in firing between fibers of the same eye to see whether this would prevent the formation of ocular dominance columns. To this end, Stryker (1981)* raised kittens in the dark, hoping thereby to prevent correlated activity from removing all patterned visual signals. However, subsequent anatomical study of these animals showed that ocular dominance columns still formed (though perhaps incompletely) in the cortex. In this regard, it will be recalled that in the monkey the columns develop to some extent in utero, before any patterned visual experience (Rakic, 1976b, 1977). Therefore, if activity does play a role in columnar segregation, *spontaneous* activity must be sufficient. In fact, there is evidence for a correlation of maintained activity between neighboring ganglion cells within one eye in the dark (Arnett and Spraker, 1981). Since much of a kitten's life is spent in sleep, such evidence might suggest a mechanism underlying development in both the normal and dark-reared cases.

On the hypothesis that patterns of spontaneous activity might be crucial to the segregation of the ocular dominance bands, Harris and Stryker (see Stryker, 1981) have conducted experiments aimed at eliminating all activity in the pathway from the eyes, again trying thereby to prevent the segregation of geniculocortical afferents. In these experiments, kittens were raised from the second to sixth post-natal week with tetrodotoxin (TTX) in the vitreous humor; this treatment was shown in control studies to silence completely transmitted ganglion cell activity. Anatomical examination of 6-week-old animals reared in this way revealed no evidence of segregation of geniculate afferents in layer IV, indicating that this segregation can at least be postponed by the toxin. This was confirmed physiologically. As would be expected from the progressive segregation of ocular dominance columns, recordings from normal 2-week, 6-week, and adult cats show that there are fewer strongly binocular cells and more monocular neurons as maturation proceeds. The TTX-treated animals at 6 weeks have even more binocular cells than do normal animals at 2 weeks of age; further, practically all of the cortical cells were driven well by both eyes at the sixth week, when only about half would be so driven in the normal kitten. This preservation of binocularity in the total population of cortical cells was more striking for the cells of the input layer (IV). Future experiments will use both alternate and simultaneous stimulation of the two optic nerves (which still conduct spikes in this case) during TTX blockade of retinal activity. If the activity-dependent model of segregation is valid, then alternate stimulation should allow segregation of afferents from the lateral genic-

*Also M. Cynader and M. Stryker, unpublished.

ulate nucleus; while simultaneous stimulation, in which afferents from both eyes activate postsynaptic cells together, should not permit segregation.

The various experiments described above are consistent with a role for patterned spontaneous activity independent of sensory input in the normal development of ocular dominance columns. This hypothesis is strengthened by a recent study in primates showing that enucleation of one eye before birth abolishes formation of ocular dominance columns (Rakic, 1981a).

MODIFIABILITY OF VISUAL CORTEX UNDER SENSORY DEPRIVATION: M.S. Cynader

The alteration of neuronal properties by unusual visual exposure is by now a well-documented phenomenon in cat and primate visual cortex. Selective visual exposure conditions during postnatal development have been shown to alter the distribution and incidence of orientation selectivity, direction selectivity, and binocular convergence among cortical neurons (Wiesel and Hubel, 1963b; Hirsch and Spinelli, 1970; Cynader et al., 1975; Cynader and Cmetneko, 1976). The most extensive study has been devoted to the modification of binocular convergence onto single cortical cells following deprivation of vision in one eye. Wiesel and Hubel (1963b) initially demonstrated that monocular lid suture early in life causes the deprived eye to lose functional connections with the visual cortex. The retina is normal in this case; however, in the dorsal lateral geniculate nucleus (LGd), there is shrinkage of cells in the lamina corresponding to the deprived eye, while in the visual cortex ocular dominance columns in layer IV corresponding to the open eye expand at the expense of the columns subserving the closed eye (Wiesel and Hubel, 1963a); LeVay et al., 1981). Furthermore, recordings in the visual cortex of cats and monkeys after monocular deprivation show that most neurons are driven exclusively by the nondeprived eye. In other words, after monocular deprivation there is a series of changes that includes alterations in the LGd, in the distribution of geniculocortical terminals within the cortex, and in the ocular dominance of cortical neurons themselves.

From the work of Guillery and coworkers (Guillery, 1972; Sherman et al., 1974) and Wiesel and Hubel (1965), it is evident that the monocular deprivation effects at the level of LGd are not simply a consequence of disuse, since a partial lesion in the retina of the open eye prevents shrinkage of cells at the corresponding locus in the deprived