POSTNATAL DEVELOPMENT OF THE CAT'S VISUAL PATHWAYS *

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INTRODUCTION

During postnatal life, there is a tremendous increase in both the weight and the volume of the brain. This increase cannot be attributed to the addition of new neurons, since mitosis of neurons is essentially completed by birth. Instead, this is due to the conjoint proliferation and elaboration of dendritic arbors and synaptic connections between neurons; this leads to enormous growth of the synaptic neuropil. The question that will be addressed here is the extent to which the development of these connections can be modified by the environment or, conversely, the extent to which these connections can develop normally in spite of experimental alterations to the normal sensory environment.

Using the visual system as a model, two fundamental questions related to this general problem in neural development are discussed. First, where in the developing visual system do the primary deficits induced by visual deprivation occur? For example, visual deprivation may cause cortical neurons to develop abnormal receptive field properties either because their inputs from the lateral geniculate nucleus develop abnormally, in which case the cortical deficits are secondary, or because these cortical neurons are the first cells in the visual pathways to be directly affected by the deprivation, in which case these deficits are primary. Second, if any of these primary sites can be defined, what are the mechanisms by which the environment affects the developmental processes?

HISTORICAL BACKGROUND

We can begin the discussion of these questions with the classical receptive field studies of neurons in the striate cortex (i.e., the primary visual cortex) by Hubel and Wiesel (1962). These authors found that most of these cortical neurons are binocular, since they could be driven by either eye, although, for any individual cell, the relative strength of the input from each of the two eyes might vary considerably. If the entire population of these cortical cells was considered, however, there was reasonable equivalence in the influence of the inputs from the contralateral and ipsilateral eyes.

Wiesel and Hubel (1963b) found that this balance could be disrupted if one eye was sutured closed soon after birth. In such monocularly deprived animals, nearly all of the neurons in the visual

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cortex could be driven only by input through the eye that had not been sutured closed (i.e., the nondeprived eye). One might then predict that binocular deprivation, or the suturing of both eyes soon after birth, would lead to twice the disruption of monocular deprivation, thereby leading to very few cortical neurons that could be influenced by visual stimuli. Surprisingly, however, rearing with binocular deprivation permitted such neurons to develop clear visual responses and a fairly balanced binocular input, although these neurons did display significant receptive field abnormalities (Wiesel and Hubel, 1965).

These findings led Hubel and Wiesel to the profound insight that deprivation *per se* was not the overriding factor in determining the extent of the abnormalities produced by these rearing conditions, but rather the balance of activity supported by the two eyes interacted in some competitive process to control the development of connections. Thus, as long as the balance of influence between the two eyes was preserved (as in binocular deprivation), many cortical cells could be influenced by both eyes. If, however, this balance was upset, with one eye receiving visual stimulation while the other was largely deprived of it, the result was much more devastating to the development of the visual system.

By examining the time course of the development of these abnormalities, Hubel and Wiesel (1970) also introduced the influential concept of a critical period for visual development. They found that normal development was disrupted only if monocular or binocular lid suture was performed during the first three months or so after birth. Deprivation during this time caused deficits that were permanent, and no amount of normal visual experience outside of the critical period could counteract the effects of visual deprivation during the critical period. Conversely, if the visual deprivation began after this critical period, no disruption of the visual pathways ensued.

In order to determine the location of the primary deficits caused by eyelid suture, Wiesel and Hubel (1963a) also studied the effects of this visual deprivation on neurons in the lateral geniculate nucleus of the thalamus and, to a limited extent, on retinal ganglion cells. They detected no abnormalities in these cells, leading them to conclude that the geniculocortical synapse represented the primary site of disruption caused by rearing with eyelid suture.

At the time Hubel and Wiesel produced the above mentioned seminal work in the early 1960s, the conventional wisdom viewed all retinal ganglion cells and geniculate neurons as divided into symmetrical on- and off- center moieties that were otherwise functionally homogeneous. Newer insights into the effects of visual deprivation were not made until new evidence appeared demonstrating that these cell populations were actually quite heterogeneous. Evidence built on these new insights indicates that, in fact, primary deficits due to early visual deprivation seem to develop at the level of the lateral geniculate nucleus. Therefore, two brief but necessary detours are taken to describe: 1) the organization of the cat's lateral geniculate nucleus; and 2) the concepts of parallel visual pathways that began with the discovery of X and Y cells in the retina by Enroth-Cugell and Robson (1966).

OVERVIEW OF THE CAT'S LATERAL GENICULATE NUCLEUS

Retinogeniculate axons are the axons of retinal ganglion cells that contribute to geniculocortical innervation. They travel through the optic nerve to terminate in the lateral geniculate nucleus, which is the principal visual nucleus of the thalamus. This nucleus is organized into a series of laminae that alternately receive input from one or the other eye. The most dorsal of these, Lamina A, is innervated by the retinogeniculate axons from the contralateral eye. Lamina A1, immediately ventral to Lamina A, receives retinogeniculate input from the ipsilateral eye. Below Lamina A1 lie the C-laminae, individually known as Laminae C, C1, C2, and C3. Lamina C is the most dorsal. Generally, the dorsal strip of lamina C contains relatively large neurons, while the rest of the C-laminae has smaller cells; this has led to the former being designated as the "magnocellular C lamina" and the latter, as the "parvocellular C laminae". Magnocellular C, like Lamina A, receives input from the contralateral eye. In addition to these laminated portions of the lateral geniculate nucleus, there are other regions, the geniculate wing and medial interlaminar nucleus, which are not well understood and need not concern us further in this account.

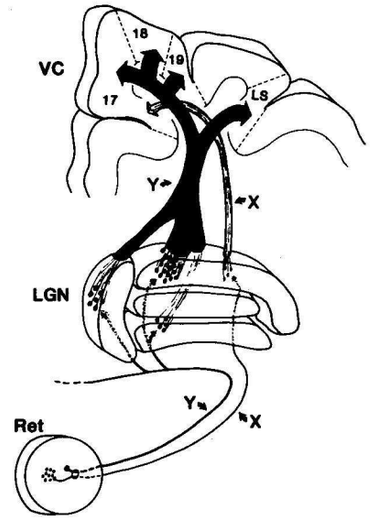

Fig. 1. Hypothetical schematic diagram of the retinogeniculocortical X and Y pathways. For clarity, only the projection pattern from one eye is illustrated. Each retinal Y cell axon diverges to innervate many cells in a number of different regions of the LGN, and each LGN Y cell innvervates a number of visual cortical cells in both the primary visual cortex (Area 17) and other visual cortical areas. Each retinal X cell provides input to relatively fewer LGN neurons in only the A laminae of the LGN. These LGN X cells then innervate cortical neurons in Area 17 only. By virtue of this difference in the divergence of the X and Y pathways, the relatively few Y cells in the retina come to dominate visual cortex. Ret, retina; LGN, lateral geniculate nucleus; VC, visual cortex. (Reprinted from Sherman, 1985a.)

PARALLEL X AND Y PATHWAYS

A number of functionally independent pathways are represented in the lateral geniculate nucleus, two of which, the X and Y pathways, are shown schematically in Figure 1 (for reviews, see Stone et al., 1979; Sherman and Spear, 1982; Sherman, 1985a). These pathways, as mentioned above, were first described as separable subpopulations of retinal ganglion cells by Enroth-Cugell and Robson (1966). More recent studies have convincingly demonstrated that retinal X and Y cells are actually the starting point of two functionally independent, parallel pathways that remain segregated through the lateral geniculate nucleus and through an as yet unspecified number of synaptic zones within the visual cortex. X cells and Y cells in both the retina and lateral geniculate nucleus can be recognized as separate populations on the basis of morphological and physiological criteria. Although it is beyond the scope of this lecture to treat these differences in detail, a brief summary of a few of the distinguishing functional characteristics follows. Most important to the premise under consideration is that X cells have smaller receptive fields than do Y cells. Thus X cells respond best to visual stimuli of high spatial frequency, which represent the fine detail in a visual scene. Y cells are much more responsive to low spatial frequencies and thus signal the basic forms in a visual scene. Also, X cells tend to have smaller somata and thinner axons than do Y cells, and as a consequence X axons conduct more slowly than do Y axons.

Each geniculate neuron is, typically, innervated by a single retinogeniculate axon. There is thus little convergence in retinogeniculate circuitry, which is one reason why the unique X and Y response properties established in retina are preserved among the postsynaptic geniculate neurons. There are, however, many more geniculate neurons than there are retinogeniculate axons, thus requiring considerable divergence in retinogeniculate circuitry.

Given the clear presence of X and Y (and other) parallel pathways involved in the processing of visual information, the key question becomes: What function is served by processing visual

information in parallel? The hypothesis proposed here, based on evidence from anatomical, physiological, and behavioral experiments, is that the fundamental and primary visual processing is done by the Y pathway and that the X cell pathway functions secondarily to maximize spatial detail or acuity. Details of this hypothesis can be found in Sherman (1985a), and other hypotheses have also been advanced (Stone et al., 1979; Lennie, 1980). Some of the logic for the hypothesis of primacy of the Y pathway is provided below in consideration of the anatomical organization of the X and Y pathways and in behavioral tests of cats that can be interpreted in the context of these pathways.

Anatomical Organization

Anatomical studies of parallel processing in the cat's visual system require prior knowledge of which neurons to be studied anatomically are X and which are Y. This has usually been accomplished by recording from these neurons intracellularly with a micropipette filled with a marker, usually horseradish peroxidase (HRP), and then iontophoresing the marker into the physiologically defined neuron. This confers the considerable advantage that, for any given neuron, both physiological and morphological data are conjointly obtained.

However, other less direct correlations between structure and function have been made. For example, Wässle and his colleagues (Wässle et al.,1981a,b) were able to establish these relationships for retinal X and Y cells: morphologically, these two cell types are quite distinct, Y cells being associated with the anatomical class of α-cells and X cells, with β-cells. These relationships were confirmed with intracellular marking as described above (Stanford and Sherman, 1985; Stanford, 1987).

More important to the present discussion, however, the ability to equate a functional class of cell to its morphological counterpart provides an anatomical basis for defining the distributions of retinal ganglion cell classes within the retina. That is, with these correlations, it is possible to use the microscope rather than the oscilloscope to determine the actual distributions of cell types. The anatomical approach permits one, in theory, to account for every neuron in realizing the distributions, whereas recording alone is always plagued by problems of unknown electrode sampling errors (see Friedlander et al., 1981; Friedlander and Stanford, 1983). Thus Wässle and his colleagues were able to demonstrate with a reasonable degree of certainty that X cells outnumber Y cells in the retina by approximately 10:1, with this ratio increasing slightly with distance from the area centralis.

While the numerical superiority of retinal X cells would seem to contradict the contention that the Y cell system is the more important of the parallel pathways involved in visual processing, other experiments have shown that the relative strength of the Y pathway is greatly enhanced at successive levels as the visual cortex is reached. For instance, as mentioned above, there is considerable divergence in retinogeniculate connections, and Y axons seem to diverge much more than X axons, at both retinogeniculate and geniculocortical levels. Thus, when individual retinogeniculate axon arbors are labeled with HRP, the Y arbors occupy a much greater volume with many more synaptic boutons than is the case for X arbors. Also, each X axon innervates essentially only Lamina A or A1, while each Y axon typically innervates Lamina A or A1 and, if from the contralateral eye, the magnocellular C-laminae. Since the visual responses of thalamic neurons are dictated by their retinal input, these data suggest that the number of Y cells in the thalamus would be, proportionately, higher than the number in the retina, a conclusion supported by anatomical studies of geniculate X and Y cells.

This relationship between the structure and function of geniculate neurons is somewhat more complex than that described for retinal ganglion cells, primarily because of the morphological diversity of geniculate cells (Friedlander, et al., 1981; Stanford, et al., 1983). The Y cells are a fairly homogeneous group morphologically, and these cells correspond to the class 1 cell defined by Guillery (1966) from Golgi impregnations. The X cells are, anatomically, quite heterogeneous, involving a variety of cell types seen morphologically; they are mostly subsumed under the class 2 type described by Guillery (1966), although a minority (<5%) have the same class 1 morphology as do all Y cells. As noted below, this diversity of X cell morphology may have an interesting developmental basis.

Regardless of the explanation for the structure/function correlations, appreciation of the anatomical identity of geniculate X and Y cells permits the same sort of determination of their distributions as achieved by Wässle and colleagues (Wässle et al., 1981a,b) for retina. Unlike retina,

where the X to Y ratio is roughly 10:1, this ratio for geniculate relay cells (i.e., those projecting to cortex) is probably less than 2:1. We estimate that, on average, each retinogeniculate X axon contacts roughly 5 geniculate relay cells while each retinal Y axon innervates 25 to 50 such cells. There has thus been a major relative increase in strength of the Y pathway at the level of the lateral geniculate nucleus, and we suggest that this is largely due to the much more extensive arbors of the retinogeniculate Y axons compared to those of the X axons (see Figure 1). Analogous studies of geniculocortical axon arbors indicate that these axons exhibit a similar relative expansion as seen among retinogeniculate axons: each geniculate Y cell innervates much more cortical territory, and thus presumably many more cortical cells, than does each X axon.

As a result of different extents of axonal arborizations between X and Y axons at both the retinogeniculate and geniculocortical levels, the minority of Y retinal ganglion cells come to dominate cortical processing. This might be explained as follows. The lower spatial frequencies are especially important to the cat for spatial vision, and the Y pathway carries this information to cortex. Thus, much cortex is devoted to its analysis, but a dense retinal grain is not needed to encode these lower frequencies, which explains the low density of Y cells in retina. Once primary spatial vision is handled on the basis of lower frequencies by the Y pathway, the X pathway can be used for specialized functions, such as maximizing spatial resolution based on higher spatial frequencies. The encoding of these higher frequencies does require a relatively dense retinal grain, but since this is of less importance to the cat's spatial vision, less cortex is devoted to its analysis. It must be emphasized that, while this may be a plausible explanation of the functional organization of the X and Y pathways, it is still nothing more than a hypothesis (for further discussion, see Sherman, 1985a).

Behavioral Studies

There is also behavioral evidence in support of this hypothesis. An interesting difference between the X and Y pathways in cats that serves as a background for the behavioral studies is the nature of geniculocortical projections: geniculate X cells innervate only striate cortex, while Y cells, as a population, directly innervate striate cortex plus many areas of extrastriate cortex (see Fig. 1). Thus complete bilateral destruction of striate cortex produces a cat with no cortical representation of the X pathway and some unspecified but significant proportion of the Y pathway still intact. Several investigators have reported that such destriate cats suffer remarkably minor losses of visual function, mostly limited to a mild acuity loss and sensitivity deficits limited to higher spatial frequencies (Berkeley and Sprague, 1979; Lehmkuhle et al., 1982). Thus, part of the Y pathway seems sufficient for fairly normal spatial vision, especially if visual stimuli do not involve fine details.

Although it is getting ahead of the story, early eyelid suture disrupts the development of geniculate Y cells, and it is interesting that such visually deprived cats respond very poorly on tests of visual function, behaving almost as if blind, and their sensitivity losses, as predicted, are considerable for lower spatial frequencies. This, too, is consistent with the relative importance suggested for the Y pathway. Of particular interest is the clear demonstration that normally reared cats with removal of striate cortex see much better than do cats reared with eyelid suture and no such cortical removal. This implies that, no matter how abnormally developed the striate cortex is as a result of early eyelid suture, there must be other primary sites of abnormal development to explain the poor vision suffered by these cats. A global failure of geniculate Y cells to develop is consistent with this logic, since, as shown by Figure 1, such a failure would indirectly affect all areas of visual cortex.

EFFECTS OF REARING WITH EYELID SUTURE

There is now considerable evidence that rearing with eyelid suture prevents the normal development of most, but not all, Y cells in the lateral geniculate nucleus (Sherman et al., 1972; reviewed in Sherman and Spear, 1982). Geniculate X cells develop relatively normally during eyelid suture, as do retinal X and Y cells. This raises two key questions. First, to what extent can abnormal development described in other visual structures be explained as secondary to this failure of Y cell development at the level of the lateral geniculate nucleus? Second, what are the developmental mechanisms that cause Y cells to be differentially affected by these deprivations?

Superior Colliculus

Data that address the first question have been obtained from a number of experiments. However, for the purposes of the present discussion, studies of the superior colliculus can serve to illustrate the effects of abnormally low geniculate Y cell numbers on other visual structures. The superior colliculus is an important subcortical visual structure located dorsally and anteriorly in the midbrain. It has 7 layers, but its dorsal three layers, which are purely visual and homologous to the optic tectum of nonmammalian vertebrates, are all that concern us here. Both retina and visual cortex provide innervation to the superior colliculus.

Hoffmann (1973) investigated the visual inputs to the superior colliculus in cats. He described two pathways from retinal Y cells. One is a direct retinocollicular pathway that mostly crosses in the optic chiasm to innervate the superior colliculus from the contralateral eye. The other is an indirect pathway involving a neuronal chain: a retinal Y cell innervates a geniculate Y cell that, in turn, innervates a corticocollicular cell; this indirect pathway provides fairly balanced, binocular input to the superior colliculus. There is no evidence of any involvement of the X pathway in collicular innervation. In an elegant series of experiments, Wickelgren and Sterling (1969a,b) worked out the effects on the response properties of collicular neurons after lesioning visual cortex and/or rearing cats with eyelid sutures. These authors found that, in normal cats, cells in the SC, much like the corticocollicular cells in the visual cortex, had binocular receptive fields, were most responsive to moving stimuli, and preferred stimuli moving in a particular direction. Removal of visual cortex and early binocular deprivation produced nearly the same changes in collicular neurons. The receptive fields of these cells were now dominated by input from the contralateral eye with no directional selectivity and generally poor responses that showed no preference for moving stimuli. Whatever the explanation for these changes in responses, it is interesting that removal of cortex mimics the effects on the superior colliculus of early binocular deprivation, as if the direct retinocollicular pathway, which would not be directly affected by cortical removal in normally reared cats, develops fairly normally during binocular deprivation.

A similar conclusion is reached from Wickelgren and Sterling's studies of monocular deprivation, although the analysis is more complicated. Such deprivation produces collicular cells that respond essentially only to activation of the nondeprived eye, and they do so fairly normally, regardless of whether the nondeprived eye is ipsilateral or contralateral to the colliculus in question. This mimics the responses of the corticocollicular cells of these cats. However, if the visual cortex is removed in these cats, then the collicular responses are indistinguishable from those seen in normally reared cats with cortex removed (and, as noted, are also the same as that found in binocularly deprived cats). This effect of decortication is most dramatic for the colliculus contralateral to the deprived eye. Here, before the cortical removal, responses are normal, but only to the nondeprived eye, as if the deprived eye had no influence whatsoever over these neurons; after decortication, the deprived eye dominates cellular responses of collicular cells, although direction selectivity and the preference for moving targets is now lost. Whatever the explanation for this dramatic change, one conclusion is clear: removal of cortex eliminates any differences in collicular responses caused by early monocular deprivation. Thus the direct retinocollicular pathway must develop fairly normally in these visually deprived cats, and the abnormalities seen in colliculus are imposed by an abnormal corticocollicular input.

Later experiments by Hoffmann and Sherman (1974, 1975) extended these conclusions. These authors used electrical stimulation to determine the inputs to the superior colliculus in visually deprived cats. They found that the direct retinocollicular pathways developed normally after visual deprivation, but that the indirect pathway involving corticocollicular innervation was interrupted somewhere between the deprived eye and colliculus. Because electrical activation of the corticocollicular pathway produced fairly normal responses in visually deprived cats, Hoffmann and Sherman concluded that the indirect pathway to colliculus was disrupted subcortically. These authors went further to suggest (Hoffmann and Sherman, 1974,1975) that all of the data from these experiments are consistent with the notion that a single primary deficit, occurring among geniculate Y cells, can account for the entire spectrum of deficits shown by Wickelgren and Sterling in the superior colliculus. The abnormalities seen among SC cells are thus secondary to a disruption of the normal Y cell pathway ascending through the lateral geniculate nucleus to the visual cortex.

Retinogeniculate Connections

The mechanisms that cause development of the Y cell pathway to be selectively affected by lid suture have yet to be securely defined. However, anatomical studies of geniculate cells and their retinal afferents in visually deprived cats, using the aforementioned techniques of marking physiologically defined neurons, have provided a number of important insights.

Lateral geniculate nucleus. Some factors that contribute to the Y cell dysfunction following early visual deprivation were suggested by anatomical studies of geniculate neurons (Friedlander et al., 1982). As expected from earlier microelectrode sampling studies, these authors recorded a significant number of cells in the lateral geniculate nucleus of monocularly deprived cats that were quite abnormal, responding poorly, or not at all, to visual stimuli. However, the conduction velocity of the retinal inputs to many of these neurons suggested that they were innervated by Y cell axons. Morphologically, these neurons were unlike any geniculate cells previously described in normal cats, having very small somata and extensive but tortuous and beaded dendritic arbors. More surprisingly, a significant number of geniculate neurons were found that had the morphological features typical of normal Y cells (i.e., class 1) but were driven by input from retinal X cells. As noted above, such class 1 X cells were relatively rare in normal cats (<5%), but 1/3 of geniculate X cells innervated by the deprived eye had such class 1 morphology. Recent evidence indicates that binocular deprivation causes similar abnormalities in structure/function relationships among geniculate neurons (Raczkowski et al., 1982).

Retinogeniculate Axons

These effects of visual deprivation on geniculate neuronal morphology support the notion that the developmental deficits resulting from such deprivation reflect a disruption in the normal retinogeniculate connections. More direct evidence for this notion is provided by intracellular labeling of retinogeniculate arbors in visually deprived cats (Sur et al., 1982). As described above, normal retinogeniculate X axons support terminal arbors that are restricted to the geniculate A-laminae; those of Y axons ramify extensively in the geniculate A-laminae and, if from the contralateral eye, the magnocellular C lamina.

Monocular or binocular deprivation had relatively little effect on the morphology of retinogeniculate X axons, although there was some slight increase in the volume of their terminal arbors. Retinogeniculate Y arbors, on the other hand, were drastically affected by these forms of visual deprivation. The terminal arbors of most Y axons were quite abnormally small in the A-laminae, both in volume and in the number of synaptic terminals. Some of these Y axons, in fact, had no terminal arbor at all in the A-laminae. Curiously, the contralaterally projecting arbors of the deprived Y axons in the magnocellular C-lamina seemed entirely normal, even when no other arbor was present in Lamina A. The observation that deprived Y arbors fail to develop normally where X arbors exist (the A-laminae) but do so where X arbors do not extend (the C-laminae) suggests a developmental mechanism of competitive interactions between these two classes of retinogeniculate arbor, and this is considered more fully below.

Thus the failure of geniculate Y cells to develop normally during eyelid suture can readily be explained on the basis of these morphological abnormalities among retinogeniculate axon arbors. The inability of many Y axons to innervate the A-laminae explains why few Y cells develop, and many poorly responsive cells with abnormal morphology may receive insufficient retinal input to develop normally. Also, the large number of geniculate X cells with class 1 morphology, given the normal association of this morphology with Y inputs, suggests that many geniculate cells that normally would have accepted Y inputs instead receive X inputs, and this is consistent with the abnormally large retinogeniculate X arbors after visual deprivation.

While experiments that compare the structure/function relationships of neurons in the X and Y cell pathways in normal and deprived animals can describe the outcome of disrupting normal visual input, they provide no evidence concerning the reasons why the Y cell pathway is more susceptible to alterations in the normal visual environment. Since it is well documented that these disruptions only occur if lid suture is performed during the critical period, it seems reasonable that some insight into this question might be gained by examining the development of the parallel X and Y pathways.

NORMAL DEVELOPMENT OF RETINOGENICULATE ARBORS

Prenatal Development

The most thorough study of prenatal development of retinogeniculate axons has recently been described by Shatz (1983). By injecting different anatomical tracers in the two eyes of embryonic kittens, Shatz found that the first retinal axons reach the lateral geniculate nucleus at about embryonic day 32 (E32). These first axons to reach the lateral geniculate nucleus emanate exclusively from the contralateral eye. About three days later, axons from the ipsilateral eye invade the lateral geniculate nucleus and, initially, there is considerable overlap in the territory occupied by the axons from the two eyes. Then begins a gradual segregation of the inputs from the two eyes until, at birth, the afferent input to the nucleus is essentially adult-like in terms of its laminar segregation pattern.

By making very small injections of tracer into the optic tract, Sretavan and Shatz (1984) labeled single retinogeniculate axons in prenatal kittens. At first (E43), the ingrowing retinal axons exhibit short, fine side branches along their entire length within the lateral geniculate nucleus. During the next few prenatal weeks, these side branches eventually disappear as a mature arbor forms that is strictly limited to its appropriate laminar pattern. Unfortunately, it has not yet proved technically feasible to determine whether the axons studied by Shatz and her co-workers prenatally arose from retinogeniculate X axons, Y axons, or both. Therefore, studies of prenatal development cannot directly address the question of whether differences in the embryonic development of retinogeniculate X and Y axons contribute to the more damaging effects of early visual deprivation on the Y pathway. However, studies of postnatal development can and do.

Postnatal Development

The morphological features of retinogeniculate arbors in kittens at various postnatal ages have been recently described, and at the postnatal ages tested, it has been possible to identify X and Y axons (Sur et al., 1984; Friedlander et al., 1985). Retinogeniculate X axons develop much earlier than Y axons. The X axons already form large arbors in the A-laminae by three weeks postnatal (the earliest age tested), and there is a slight, but significant, decrease in their terminal arbor sizes until twelve weeks after birth, by which time the adult pattern is attained. In contrast at three weeks of age few Y axons have yet even reached the A-laminae, although many from the contralateral eye already have begun to form their arbors in the C- laminae. During the succeeding weeks, there is a monotonic increase in the size of these Y arbors in the A-laminae until, like the X axons, they attain their adult form at approximately 12 weeks of age. This suggests that retinogeniculate X axons develop and mature much earlier than do Y axons, and this conclusion is consistent with other studies of development of retinal ganglion cells and optic tract axons (Walsh et al., 1983; Ramoa et al., 1988).

The following hypothesis is suggested to account both for this pattern of postnatal retinogeniculate development as well as the effects of visual deprivation on this development (reviewed in Sherman, 1985b). Retinogeniculate X axons innervate the lateral geniculate nucleus first, and, as the only retinal innervation in the A-laminae, they are able to innervate geniculate cells fairly indiscriminately. They thus have large arbors by 3 weeks postnatal. As the later developing Y axons enter the A-laminae, they must compete with the already present X arbors for control of geniculate cells, and they compete successfully only for synaptic space on morphological class 1 neurons. Thus, under normal conditions, the vast majority of class 1 cells are Y, and X axons innervate all the remaining geniculate cells. Visual deprivation somehow disrupts this process by placing the later developing retinogeniculate Y axons at a competitive disadvantage; it is interesting in this regard that the elaboration of these retinogeniculate Y arbors in the A-laminae occurs nearly entirely during the critical period as defined by Hubel and Wiesel (1970; see above). Although the rules that govern this presumed competition are far from clear, the fact that retinogeniculate Y axons are able, during visual deprivation, to establish normal terminal arbors in the C-laminae, which is the only major site in the lateral geniculate nucleus that retinal X cells normally do not innervate, strongly suggests that competitive interactions do, in fact, underlie this developmental process.

EFFECTS OF REARING WITH MONOCULAR ENUCLEATION

Data from an analogous series of experiments in which one eye was removed in kittens at various ages also lend support to this notion that the developmental time course of retinogeniculate X and Y axons is important in the regulation of their competitive interactions.

Postnatal Enucleation

In one set of studies, the projections of retinogeniculate axons were examined in cats that had one eye removed soon after birth (Guillery, 1972; Hickey, 1975). Retinogeniculate axons from the remaining eye "sprouted"to innervate geniculate laminae that normally received retinal input from the enucleated eye (i.e., lamina A if the remaining eye was ipsilateral, and lamina A1, if contralateral). Such sprouting only occurred if the enucleation was performed within the first 10 postnatal days. Garraghty et al. (1986b) later demonstrated that all of this sprouting was due to retinogeniculate Y axons: every X axon from the remaining eye innervated only the proper lamina, and every Y axon extended part of its arbor across the interlaminar zone into the inappropriate lamina.

Several explanations were proposed for this clear difference between retinogeniculate X and Y axons. One was the possibility that, due to the rapid later growth of these Y axons, they enjoyed a competitive advantage in the ability to occupy the denervated geniculate zones. To test this, Garraghty et al. (1986a) tried to place the developing Y axons at a disadvantage by suturing closed the remaining eye when the other was,removed. In such cats, the retinogeniculate X arbors were still strictly limited to their appropriate laminae. That the retinogeniculate Y axons were indeed at a disadvantage during this rearing condition seems evident, because very little of their arbors formed in the appropriate laminae where X axons already had a foothold; instead, most of these Y arbors were devoted to the inappropriate laminae, while only a small part of these arbors invaded inappropriate laminae when the remaining eye was left open. Thus even when given an advantage, X axons do not sprout.

Prenatal Enucleation

If competitive advantage does not explain why Y but not X axons can sprout, then perhaps it has to do with the age of enucleation. It might be that the later maturing Y axons still possess the capacity to sprout for a week or so after birth, at which time their advanced maturity precludes such plasticity, and the earlier maturing X axons have already passed this maturation stage by birth. Garraghty et al. (1988) tested this possibility by investigating retinogeniculate development in cats that had been monocularly enucleated at E44. At this early age, even X axons should still be sufficiently immature to sprout unless such ability is never conferred to them. Although the prenatal enucleations so obscured geniculate lamination patterns that clear interpretation of the data is difficult, the innervation patterns of these cats are nonetheless strikingly similar to those obtained in postnatally enucleated cats: retinogeniculate X arbors are confined to a zone in the A-laminae that seems appropriate for their eye of origin, while many of the Y arbors span the entire A-laminae.

This inability of retinal X cell axons to sprout, therefore, seems not to be due to their earlier development. While the mechanisms governing sprouting are unknown, these data suggest that fundamentally different rules might apply to the X and Y pathways in terms of retinogeniculate development. Perhaps the X pathway, being the first to innervate the lateral geniculate nucleus, is somehow constrained to terminate only in laminae appropriate to the eye of origin. This might be necessary, for instance, to insure that the normal lamination pattern is formed during the early stages of geniculate development. Later arriving pathways, such as the Y pathway, might then be shaped more by competitive interactions, following rules that are less rigid than those defining the development of the X axons that establish lamination in the geniculate.

CONCLUSIONS

Some of the most important conclusions from the experiments described above are as follows. First, if the processes underlying the development of the visual pathways are to be understood, an

appreciation of the heterogeneity in the pathway from the retina through the lateral geniculate nucleus to the visual cortex is essential. There is now ample evidence that the development of the X and Y pathways are governed by very different mechanisms. Second, the hypothesis that all primary sites of abnormalities due to early visual deprivation are cortical seems untenable in light of the data that have become available since the early studies of Hubel and Wiesel (1962, 1963, 1965, see above). A major primary abnormality is induced by visual deprivation in the retinogeniculate connections of the Y pathway. Finally, although the reasons for the relative susceptibility of the Y pathway to perturbations of the developing visual environment have not yet been defined, the experiments described here do suggest that the late development of the retinogeniculate Y axons' and the fact that they must compete during the critical period with the already established X axons' contributes to the severity of the deficits seen in the Y pathway of visually deprived cats.

What criteria were used to define X and Y cell responses?

A number of different response properties were used to distinguish between X cells and Y cells. First, it should be mentioned that X and Y cells, in both the retina and the lateral geniculate nucleus, have an antagonistic center/surround receptive field organization. For both of these classes of cells, also, the elements that contribute to the center and surround sum stimuli fairly linearly. That is, for an "on" center cell, the output of the cell will be the sum of the illumination of the "on" center and the antagonistic "off" surround. Y cells, however, have an additional, non-linear component within their receptive fields. One commonly used test to distinguish Y cells involves using a stimulus that can evoke this nonlinear response; this is usually done by flashing a relatively high spatial frequency sine-wave grating on the receptive field and observing the nonlinear response. This typically appears as a "doubling" response, a response at twice the temporal rate of the stimulus. Unlike the linear component in a Y cell's receptive field, the doubling response is independent of the spatial phase, or position, of the grating within the receptive field. The presence of a nonlinear component, which produces this doubling, is thus one criterion used to distinguish X from Y cells in our experiments. Another characteristic that can separate these two groups of cells is receptive field center size; at any given retinal eccentricity, Y cells have receptive field centers that are approximately three times larger than those of X cells. Finally, axonal conduction velocity can also be used to distinguish X and Y cells. Y cells have axons that conduct action potentials at 30 to 40 meters per second while X cell axons conduct only at approximately one half that velocity.

You discussed data from studies that recorded from X cells and Y cells in kittens and in visually deprived cats. Which response properties can also be used to distinguish X and Y cells in these animals?

That actually presents somewhat of a problem. While we have well documented criteria for making this distinction in normal adult animals, some question always remains about how reliably the criteria used in the adult animal can distinguish cell groups in an immature system, or one that has been experimentally modified. We can only address this issue indirectly by citing some of the results of the experiments discussed here. In three to four week old kittens, for instance, which represent the earliest developmental age of the animals used in these experiments, there was a very good correlation among the responses normally associated with the two cell classes. Perhaps the strongest evidence, however, comes from those experiments in which retinal ganglion cell axons were identified in the optic tract and subsequently filled with horseradish peroxidase. When these experiments were performed in kittens, the retrogradely filled cell bodies demonstrated in the retina showed the same correlation between physiological and morphological cell class that had previously been demonstrated in adult cats. That is, the Y cells displayed alpha morphology, and the X cells, beta morphology.

Are there any abnormalities in visually deprived cats in the X cell pathway in either the lateral geniculate nucleus or the visual cortex?

There seems to be very little effect of these rearing paradigms on the X pathway. The only effect that has been documented at this time is a slight increase in receptive field center size among retinal and geniculate X cells. It should be emphasized, however, that there is some controversy concerning this increase in receptive field size among X cells; some laboratories have reported this effect while others have been unable to detect any change in the receptive fields of these neurons.

REFERENCES

Berkeley, M.A. and J.M. Sprague, 1979, Striate cortex and visual acuity functions in the cat, *J. Comp. Neurol.*, 187:679.

Enroth-Cugell, C. and J.G. Robson, 1966, The contrast sensitivity of retinal ganglion cells of the cat, J. *Physiol. (London)*, 187:517.

Friedlander, M.J., C. S. Lin, L.R. Stanford, and S. Murray Sherman, 1981, Morphology of functionally identified neurons in the lateral geniculate nucleus of the cat, *J. Neurophysiol.*, 46:80.

Friedlander, M.J., K.A.C. Martin, and C. Vahle-Hinz, 1985, The structure of the terminal arborizations of physiologically identified retinal ganglion cell Y axons in the kitten, *J. Physiol. (London)*, 359:293.

Friedlander, M.J. and L.R. Stanford, 1984, The effects of monocular deprivation on the distribution of cell types in the LGNd: A sampling study with fine-tipped micropipettes, *Exp. Brain Res.*, 53:451.

Friedlander, M.J., L.R. Stanford, and S. Murray Sherman, 1982, Effects of monocular deprivation on the structure/function relationship of individual neurons in the cat's lateral geniculate nucleus, *J. Neurosci.*, 2:321.

Garraghty, P.E., C.J. Shatz, D.W. Sretavan, and M. Sur, 1988, Axon arbors of X and Y retinal ganglion cells are differentially affected by prenatal disruption of binocular inputs, *Proc. Natl.. Acad. Sci. USA*, 85:7361.

Garraghty, P.E., M. Sur, and S.M. Sherman, 1986a, The role of competitive interactions in the postnatal development of X and Y retinogeniculate axons, *J. Comp. Neurol.*, 251:198.

Garraghty, P.E., M. Sur, R.E. Weller, and S.M. Sherman, 1986b, The morphology of retinogeniculate X and Y axon arbors in monocularly enucleated cats, *J. Comp. Neurol.*, 251:216.

Guillery, R.W., 1966, A study of Golgi preparations from the dorsal lateral geniculate nucleus of the adult cat, *J. Comp. Neurol.*, 128:21.

Guillery, R.W., 1972, Experiments to determine whether retinogeniculate axons can form translaminar collateral sprouts in the dorsal lateral geniculate nucleus of the cat, *J. Comp. Neurol.*, 146:407.

Hickey, T.L., 1975, Translaminar growth of axons in the kitten dorsal lateral geniculate nucleus following removal of one eye, *J. Comp.Neurol.*, 161:259.

Hoffman, K.-P., 1973, Conduction velocity in pathways from retina to superior colliculus in the cat: a correlation with receptive field properties, *J. Neurophysiol.*, 36:409.

Hoffman, K.-P., and S.M. Sherman, 1974, Effects of early monocular deprivation on visual input to cat superior colliculus, *J. Neurophysiol.*, 37:1267.

Hoffman, K.-P., and S.M. Sherman, 1975, Effect of early binocular deprivation on visual input to cat superior colliculus, *J. Neurophysiol.*, 38:1049.

Hubel, D.H., and T.N. Wiesel, 1962, Receptive fields, binocular interaction, and functional architecture in the cat's visual cortex, *J. Physiol. (London)*, 160:106.

Hubel, D.H. and T.N.Wiesel, 1970, The period of susceptibility to the physiological effects of unilateral eye closure in kittens, *J. Physiol. (London)*, 206:419.

Lehmkuhle, S., K.E. Kratz, and S.M. Sherman, 1982, Spatial and temporal sensitivity of normal and amblyopic cats, *J. Neurophysiol.*, 48:372.
Lennie, P., 1980, Parallel visual pathways, *Vision Res*, 20:561.
Raczkowski, D., L.R. Stanford, and S.M. Sherman, 1982, Binocular lid suture causes the development of abnormal structure/function relationships among lateral geniculate neurons of the cat, *Soc. Neurosci. Abst.*, 8:816.
Ramoa, A.S., G. Campbell, and C.J. Shatz, 1988, Dendritic growth and remodelling of cat retinal ganglion cells during fetal and postnatal development, *J. Neurosci.*, 8:4239.
Shatz, C. J., 1983, The prenatal development of the cat's retinogeniculate pathway, *J. Neurosci.*, 3:482.
Sherman, S.M., 1985a, Functional organization of the W-, X-, and Y-cell pathways: a review and hypothesis, in: "Progress in Psychobiology and Physiological Psychology," Vol. 11, Sprague, J.M., and Epstein, A.N., eds., Academic Press, New York, p. 233.
Sherman, S.M., 1985b, Development of retinal projections to the cat's lateral geniculate nucleus, *Trends Neurosci.*, 8:350.
Sherman, S.M., K.-P. Hoffmann, and J. Stone, 1972, Loss of a specific cell type from dorsal lateral geniculate nucleus in visually deprived cats, *J. Neurophysiol.*,35:532.
Sherman, S.M., and P.D. Spear, 1982, Organization of the visual pathways in normal and visually deprived cats, *Physiol. Rev.*, 62: 738.
Sretavan, D.W., and C.J. Shatz, 1984, Prenatal development of retinogeniculate axons during the period of segregation, *Nature*, 308:845.
Stanford, L.R., 1987, X-cells in the cat retina: Relationships between the morphology and physiology of a class of cat retinal ganglion cells, *J. Neurophysiol.*, 58:940.
Stanford, L. R., M.J. Friedlander, and S.M. Sherman, 1983, Morphological and physiological properties of geniculate W-cells of the cat: A comparison with X- and Y-cells, *J. Neurophysiol.*, 50:582.
Stanford, L.R. and S..M. Sherman, 1984, Structure/function relationships of retinal ganglion cells in the cat, *Brain Res.*, 297:381.
Stone, J., B. Dreher, and A. Leventhal, 1979, Hierarchical and parallel mechanisms in the organization of visual cortex, *Brain Res. Rev.*, 1: 345.
Sur, M., A.L. Humphrey, and S.M. Sherman, 1982, Monocular deprivation affects X- and Y-cell retinogeniculate terminations in cats, *Nature*, 300:183.
Sur, M., R.E. Weller, and S.M. Sherman, 1984, Development of X- and Y-cell retinogeniculate terminations in kittens, *Nature*, 310:246.
Walsh, C., E.H. Polley, T.L. Hickey, and R.W. Guillery, 1983, Generation of cat retinal ganglion cells in relation to central pathways, *Nature*, 302:611.
Wässle, H., B.B. Boycott, and R.B. Illing, 1981a, Morphology and mosaic of on- and off-beta cells in the cat retina and some functional considerations, *Proc. R. Soc. Lond. [Biol.]*, 212:177.
Wässle, H., L. Peichl, and B.B. Boycott, 1981b, Morphology and topography of on- and off-alpha cells in the cat retina, *Proc. R. Soc. Lond. [Biol.]*, 212: 157.
Wickelgren, B.G., and P. Sterling, 1969a, Influence of visual cortex on receptive fields in the superior colliculus of the cat, *J. Neurophysiol.*, 32:16.
Wickelgren, B.G., and P. Sterling, 1969b, Effects on the superior colliculus of cortical removal in visually deprived cats, *Nature*, 224:1032.
Wiesel, T.N. and D.H. Hubel, 1963a, Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body, *J. Neurophysiol.*, 26, 978.
Wiesel, T.N., and D.H. Hubel, 1963a, Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body, *J. Neurophysiol.*, 26:978.
Wiesel, T.N., and D.H. Hubel, 1963b, Single-cell responses in striate cortex of kittens deprived of vision in one eye, *J. Neurophysiol.*, 26: 1003.
Wiesel, T.N., and D.H. Hubel, 1965, Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens, *J. Neurophysiol.*, 28:1029.

THEORETICAL APPROACHES AND CELLULAR ANALOGS OF FUNCTIONAL PLASTICITY IN THE DEVELOPING AND ADULT VERTEBRATE VISUAL CORTEX *

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INTRODUCTION

Visual cortical neurons acquire their functional identity through a number of developmental events, particularly those occurring postnatally, when the animal starts to explore its outside environment. Once the integrative properties of neurons are expressed, do they process incoming signals in the same way throughout life, or can they be considered as adaptive devices capable of modifying their functional properties? This chapter will discuss the importance of activity dependent processes involved in functional plasticity, and the determination of the learning capacities of cells in the primary visual cortex of developing and adult mammals.

Three types of approaches will be presented in the study of visual cortical epigenesis. The first step is theoretical, and consists in defining rules of synaptic plasticity which could account for the rapid functional changes observed during a critical postnatal period in kitten visual cortex (area 17). The hypothesis is that co-activity, i.e., temporal correlation between pre- and post-synaptic activity or between activities in different afferent fibers, controls synaptic efficiency changes. A specific algorithm of synaptic plasticity ("covariance hypothesis"), which has been applied previously in cerebellum (Sejnowski, 1977) and in visual cortex (Bienenstock et al., 1982), has been used to simulate the functional reorganization due to manipulation of visual input during postnatal development, and the predictions that result will be discussed.

A second approach, based on electrophysiological recordings in vivo, is a biological implementation of the covariance algorithm, and demonstrates cellular analogs of visual cortical plasticity. Four protocols have been devised, where locally imposed patterns of activity in the cortex of anesthetized and paralyzed animals induce long-term functional changes during the time of recording of individual neurons. The common aspect of these protocols is the external control (by the experimenter) of the temporal contingency between given characteristics of the visual message and imposed levels of post-synaptic activity of the recorded cell.

Finally, the third approach addresses the synaptic nature of the functional modifications. Possible biophysical mechanisms, which could explain how changes in the co-activity level increase or decrease the efficiency of transmission of neocortical synapses, will be outlined.

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