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## CHAPTER SIX

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# **Evidence for a Possible Role of Spontaneous Electrical Activity in the Development of the Mammalian Visual Cortex**

Michael P. Stryker

**A** major goal of our recent research activities on the development of the mammalian central visual system has been to determine what role, if any, is played by the electrical activity of young neurons. Although many cells exhibit electrical activity, it is the electrical activity in neurons that endows them with the capacity to transmit information over considerable distances within the mammalian brain. But even the earliest processes of growing neurons are electrically excitable, capable of function long before there is anything obviously useful for them to do. In the visual system, for example, Shatz and Kirkwood (36,54) found that effective retinogeniculate transmission is present during fetal life, when visual stimulation is completely lacking. Could it be that the electrical activity of neurons plays a special role in early development different from its role in later life? The experimental evidence reviewed below suggests that this is so; that patterns of spontaneous electrical activity that are present even in the absence of an adequate stimulus are involved in the refinement of neuronal connections leading to the formation of the adult nervous system.

### **Aspects of the Development of the Visual Cortex That Seem to Depend on Electrical Activity**

At least four types of specificity must be maintained for the proper development of the mammalian visual cortex. First, the neurons of the lateral geniculate

nucleus (LGN) must grow their axonal arbors to terminate in the right *area* of the brain: the primary visual cortex. Second, these geniculate terminations must form a single continuous *retinotopic map* within area 17. Third, the arrangement of the geniculocortical and local corticocortical connections must endow the visual cortex with a single array of *orientation columns*, used in common by inputs from the two eyes. Finally, the geniculocortical afferents serving the two eyes must segregate within layer IV of the visual cortex to form the basis of the *ocular dominance columns*, alternating largely nonoverlapping patches of terminations serving the left and right eyes.

### AREAL SPECIFICITY

In the mammalian visual cortex, there is no direct information about the possible role of electrical activity in the establishment of areal specificity in the geniculocortical projection. The early time at which this specificity is present in mammals, together with the direct evidence that electrical activity is not required for areal specificity in the fish and amphibian retinotectal systems, makes it unlikely that electrical activity is involved in this process. Rakic (49) showed that areal specificity is present during a waiting phase in which the geniculocortical afferents ramify within the cortical subplate, at a time before the neurons with which they will ultimately form their synaptic connections have migrated into the visual cortex. Harris (19) reviewed evidence from his own studies of amphibians and those of others indicating that the optic tectum is the termination site of the optic nerve, even when action potentials are blocked by tetrodotoxin (TTX).

### RETINOTOPIC MAP

At least a coarse topographic specificity can be attained in the developing retinotectal projection of the amphibian in the absence of optic nerve electrical activity (18). Retinotectal topography is formed even after electrical activity has been eliminated, in combination with disturbance of the timing or position of ingrowing retinotectal fibers (20). Such direct evidence concerning the role of electrical activity in the earliest formation of topographic order is lacking for the mammalian visual system. It seems unlikely, however, that such a basic aspect of development would differ among the vertebrates, and the fact that topographic order is evident in the initial ingrowth of retinal fibers into the synaptic layers of the LGN and superior colliculus is consistent with this notion. The formation of basic topographic order, then, is not likely to involve electrical activity.

The precision of this basic topographic order, present in the absence of electrical activity, is unknown, but it need not be great. Recent experiments by Schmidt and co-workers (7,52) on the regenerating retinotectal projection of

the goldfish strongly imply a role for patterned electrical activity in the *refinement* of topographic order. In these experiments, untreated animals were found to regenerate the projection of a damaged optic nerve in several stages. After a period of regrowth to the tectum, the visual receptive fields of clusters of regenerating retinal afferent arbors could be recorded in the tectum and were found to be in basic topographic order. However, these multiunit receptive fields were much larger than those in normal animals, which are similar in size to the fields of individual retinal ganglion cells. This finding is interpreted to indicate either that the individual regenerating arbors were initially large or that there was some degree of disorder in this projection so that each afferent arbor was not surrounded exclusively by those of the nearest neighbors of its parent retinal ganglion cell. After a further period of refinement, the multiunit receptive fields shrank to normal size. When the electrical activity of retinal ganglion cells was blocked (with TTX) or hypersynchronized (by uniform stroboscopic illumination) during this period of refinement, the multiunit receptive fields remained large, suggesting that the refinement of topographic order requires some aspect of the information present in the normal pattern of optic nerve discharge. The correlated firing of ganglion cells that are nearest neighbors (3) is proposed as the most likely source of such information.

In mammalian systems, some of the findings from Dubin's laboratory on the effects of blockade of neonatal retinal ganglion cell activity (2) suggest that electrical activity is important even in the maintenance of small receptive-field sizes in the LGN, similar to the phenomenon in the goldfish tectum that was interpreted as the maintenance of precise topographic order.

### ORIENTATION COLUMNS

Orientation columns in the mammalian visual cortex have no close parallel in amphibian and fish visual systems, and no definitive studies have been made of the role of electrical activity in their development. The role of visual experience in the development of orientation columns has been a topic of great controversy over the years. Microelectrode recording studies, beginning with the report of Hubel and Wiesel (25), have disclosed various numbers of single neurons selective for stimulus orientation in very young, visually inexperienced kittens (16,46,58). Recent metabolic labeling experiments in kittens that had been deprived of visual experience since birth (53) revealed that the cortical regions responsive to edges of a single orientation are columnar in form. Physiologic recordings have revealed an arrangement of orientation-selective neurons in neonatal monkeys very similar to that in adult animals (73); thus it is unlikely that visual experience plays an important role in the *development* of the orientation columns. Prolonged dark rearing or bilateral lid-suture, however, causes many neurons to become poorly responsive to visual stimuli or unselective for stimulus orientation, with few selective neurons remaining [for review, see

Hirsch and Leventhal (22)]. This finding, and those of selective orientation-deprivation experiments, suggests a role for visual experience in the *maintenance* of orientation columns (63).

The formation of the orientation columns in the absence of visual experience does not rule out a role for neuronal electrical activity in this process. Even in the absence of visual stimulation, there is ongoing spontaneous activity in retinal ganglion cells and central visual structures. Experiments on the possible role of spontaneous electrical activity have concentrated on the last feature of cortical organization noted above—the ocular dominance columns.

### OCULAR DOMINANCE COLUMNS

The basic features of the ocular dominance columns are shown in fig. 6.1. The projection from the two eyes to relay cells in different layers of the LGN is shown (for convenience, we illustrate only layers A and A1 in the cat, ignoring for the moment the C-laminae, the medial interlaminar nucleus, and the more elaborate structure of the primate LGN), as well as the continuation of this projection via the relay cells to alternating patches of layer IV within the primary visual cortex—area 17. These columns have numerous advantages for studying the role of spontaneous electrical activity: (a) Their normal organization has been revealed by a number of independent anatomic and physiologic

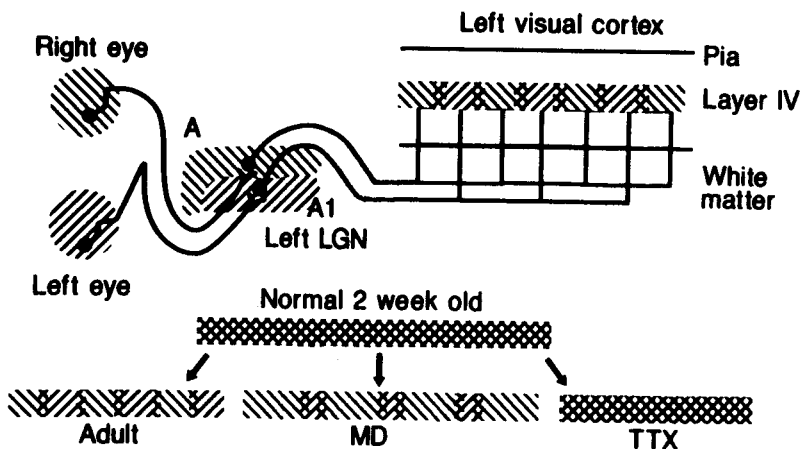
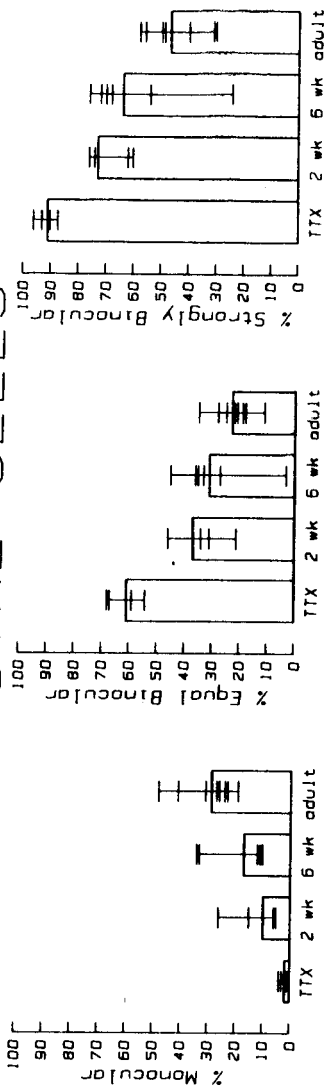
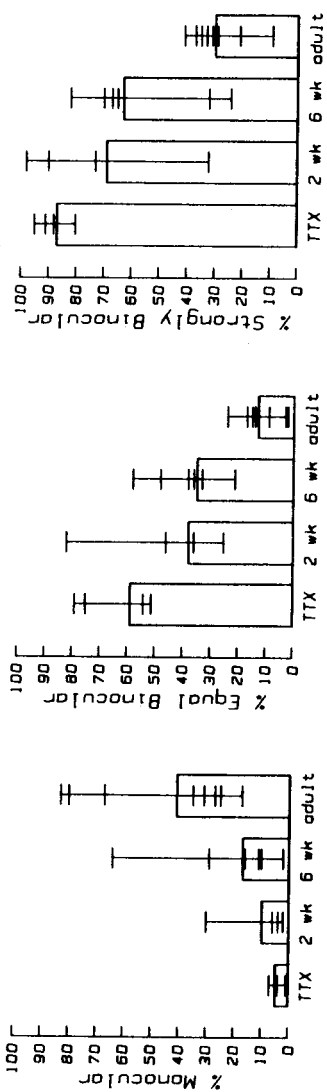


Fig. 6.1. Above: The arrangement of the retinogeniculocortical projection to area 17 in the cat. Below: The arrangement of geniculocortical afferents serving the two eyes in normal 2-week-old kittens before the beginning of binocular segregation, in normal adult animals, in monocularly deprived adult animals (MD), and in animals deprived of impulse activity in both optic nerves (TTX). See text for discussion.

# TOTAL CELLS



# LAYER IV CELLS



EVIDENCE FOR AT LEAST PARTIAL SEGREGATION  
OF OCULAR DOMINANCE COLUMNS UNDER  
CONDITIONS OF BINOCULAR DEPRIVATION

The prenatal partial segregation of ocular dominance columns in the monkey, reviewed in the previous section, takes place essentially in darkness and certainly in the absence of pattern vision. Dark rearing from the age of 3 days did not prevent the completion of the segregation process in the monkey, as judged from transneuronal autoradiographic labeling (41). Indeed, abnormally little binocular interaction was found in month-old animals that had been lid-sutured near the time of birth (73).

In the cat, both electrophysiologic (58) and transneuronal autoradiographic labeling techniques have been applied to the question of whether ocular dominance segregation occurs when animals are deprived of pattern vision by either dark rearing or bilateral lid-suture. In most studies of lid-sutured animals, the proportion of binocularly driven cells is somewhat lower than normal (5,37,57,62,69,71). Studies of dark-reared animals have also reported reduced (12,42) or normal (8,15,61) proportions of binocularly driven cells. In a study attempting to map multiunit responses of geniculate afferent fibers in layer IV of area 17 in dark-reared cats, Swindale and Cynader (66) found that there were many regions in which responses could be obtained only from one eye or the other, implying that at least a functional segregation of the afferents had taken place. Such physiologic findings suggest that neither form of deprivation prevents geniculocortical afferent segregation.

The transneuronal labeling studies in visually inexperienced cats appear to be more controversial. At one extreme is Swindale's report (65) entitled "Absence of ocular dominance patches in dark-reared cats." Stryker and Harris's report (62) seems to represent the other extreme. These authors reported that some of the most distinct fluctuations in the transneuronal labeling of layer IV in both dark-reared and lid-sutured animals approached the theoretical limits set by "spillover" in the LGN (40). Even in the Swindale report (65), as well as

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Fig. 6.2. Ocular dominance findings for all cells and for layer IV cells in four animals subjected to retinal blockade (TTX) beginning at approximately 2 weeks of age and studied at about 6-8 weeks of age, compared with those in normal animals at about 2 weeks of age, at about 6-8 weeks of age, and at adulthood. Ordinates plot the percentage of cells classified as strongly binocular (25) (ocular dominance groups 3, 4, and 5), equally binocular (ocular dominance group 4), and monocular (ocular dominance groups 1 and 7). Abscissas show the different groups of animals. The histogram bars represent the pooled data from each group; data from individual animals are shown as horizontal lines. Vertical error bars span the range of data from the individual animals in each group. Note that for both the entire sample and for the layer IV cells separately, the percentage of monocular cells increases as a function of age, and the percentage of strongly and weakly binocular cells declines as a function of age. Note also that the TTX group is even less monocular and more binocular than the 2-week group. Data replotted from Stryker and Harris (62).

in that of Mower et al. (47), autoradiographs from dark-reared animals clearly showed periodic fluctuations in the transneuronal labeling of layer IV, although these fluctuations were less pronounced than those in the normal animals illustrated. Kalil (34) reported that average peak-to-trough fluctuations in the labeling of layer IV were 2.0 in dark-reared and lid-sutured cats, 2.9 in normal cats, and as high as 4.8 in strabismic cats. Mower et al. (47) measured peak-to-trough ratios and reported values of 1.9 and 2.1 for dark-reared and lid-sutured cats, respectively. Thus all reports agree that considerable anatomic segregation of afferents takes place—perhaps as much as takes place in the monkey in utero—even under conditions of complete visual deprivation (dark rearing). None of the findings from visually deprived cats were similar to those of TTX-treated cats (62).

A remaining area of uncertainty is to what to attribute the generally less pronounced fluctuations in transneuronal labeling seen in visually deprived animals compared with normals. Some part of the smaller degree of fluctuation in the cortical labeling is likely to be due to greater geniculate “spillover” in the dark-reared animals. However, this seems unlikely to account for the entire difference between visually deprived and normal animals. It is important that other transneuronal labeling methods that may differ in the extent of the “spillover” artifact be applied to dark-reared and lid-sutured animals (1).

One hypothesis to account for the difference between the labeling patterns in normal and deprived animals, along lines suggested by Swindale and Cynader (66), is that under conditions of visual deprivation, geniculocortical afferents may segregate the most profuse and functionally most effective portions of their arbors but may not completely lose fine, relatively ineffective and relatively poorly labeled, branches. Verification of this hypothesis will require the examination of substantial numbers of single geniculocortical afferent arbors, using techniques like those in Refs. 14, 17, and 32.

#### EVIDENCE FOR FAILURE OF OCULAR DOMINANCE SEGREGATION UNDER CONDITIONS OF BILATERAL RETINAL BLOCKADE

Stryker and Harris (60,62) used physiologic recording and transneuronal autoradiographic labeling to demonstrate the failure of ocular dominance segregation under conditions of bilateral retinal blockade. Figure 6.2 illustrates the low proportion of monocularly driven neurons in animals subjected to binocular impulse blockade (TTX). Figure 6.3 shows the abnormally low values of another physiologic index of ocular dominance segregation, the monocularity index, in similarly TTX-treated animals, in normal animals of various ages, and in control groups for the systemic effects of TTX, the eye-injection procedure (using vehicle solution), and visual pattern and light deprivation. It is evident that the data from TTX-treated animals are out of the range of variation

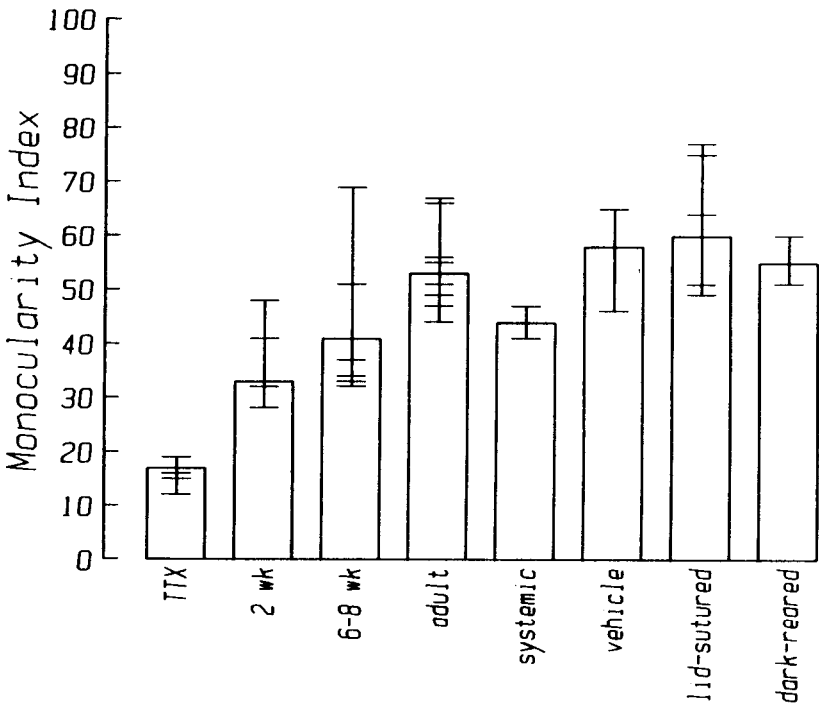


Fig. 6.3. Monocularity index—the physiologic index of binocular segregation [calculated as described in Stryker and Harris (62)]—from physiologic data for eight groups of animals. Histogram bars represent the values of this index for the pooled data from each group. Data from each individual animal are indicated by short horizontal lines. Vertical lines are error bars that display the range of individual animal data in each group. Groups are as identified in fig. 6.2, plus “systemic” for the animals receiving systemic infusions of TTX and “vehicle” for the animals receiving intravitreal injections of the citrate buffer solution. Note that the data from the experimental group (TTX) are out of the range of variation found in normal animals, whereas data from all control groups overlap with normal data. Data replotted from Stryker and Harris (62).

of the other groups, whereas none of the data from the control groups differ significantly from those of normal adult animals. Figure 6.4 shows grain-count measurements, corrected for geniculate “spillover,” of the transneuronal autoradiographic labeling of layer IV produced by injection into one eye of a normal and a TTX-treated cat. The data from the TTX-treated animals show no sign of periodic fluctuation, unlike the data from any of the other groups.

Unfortunately, neither of these methods is free from possible artifact. For example, the binocular responses obtained from the microelectrode studies could result from a profusion of intrageniculate or corticocortical binocular

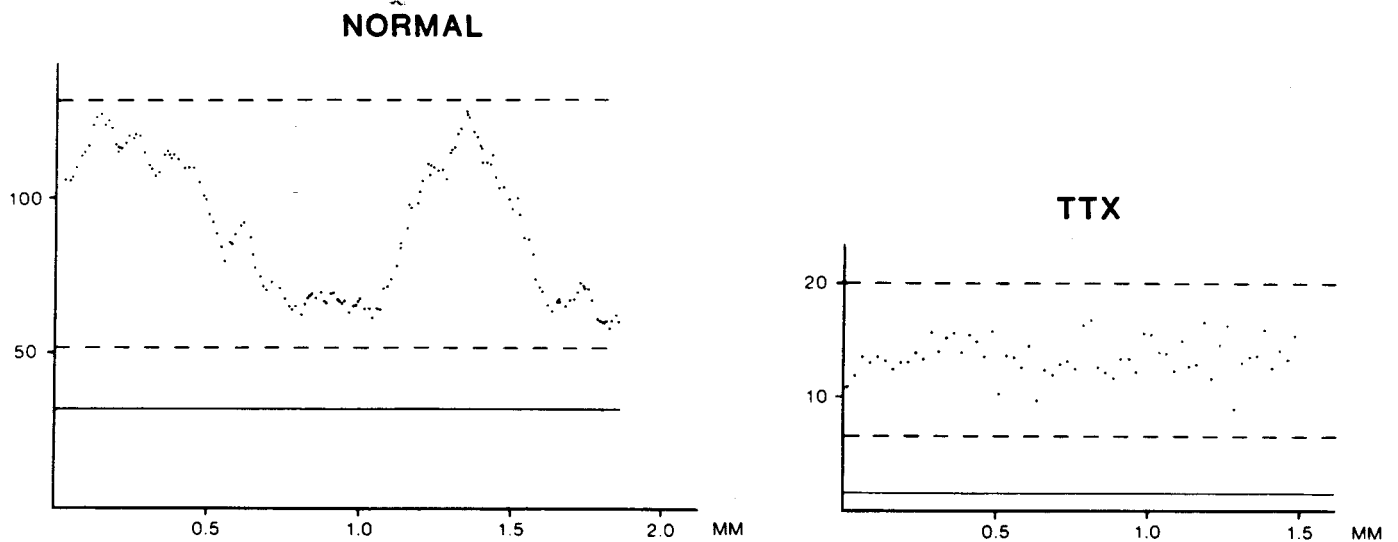


Fig. 6.4. Grain counts from layer IVc of the visual cortex ipsilateral to the injected eye in a normal cat perfused at 35 days of age and in a cat subjected to bilateral retinal impulse blockade from 2 to 8 weeks of age (TTX). Ordinates plot distance (in mm) along the base of layer IV. Abscissas plot grain density per 1000  $\mu\text{m}^2$ . Background grain density indicated by solid horizontal line. Theoretical maximal and minimal grain densities calculated from geniculate spillover measurements are indicated by dashed lines. Note that fluctuations in cortical grain densities approach theoretical maxima and minima in the normal animal but there are no significant fluctuations in the TTX animal. Data replotted from Stryker and Harris (62).

connections rather than from a failure of geniculocortical afferent segregation. The geniculate physiology showed that geniculate cells remained at least predominantly monocularly driven, but a subtle alteration at that level or even a gross alteration in corticocortical connections, however unlikely, might not have been detected. Similarly, the lack of fluctuation in cortical transneuronal labeling could result from a spillover artifact at the geniculate or cortical level that was not properly accounted for by the geniculate measurements. It would be of value to confirm the conclusions of the study of Stryker and Harris (62), using other transneuronal labeling methods (1), single axon reconstructions (14,17,32), and metabolic labeling techniques for demonstrating overall patterns of binocular responsiveness (13).

### **The Nature of the Role of Electrical Activity in the Development of Ocular Dominance Columns**

The different effects of dark rearing and retinal impulse blockade, reviewed in the previous section, strongly suggest that the spontaneous electrical activity of retinal ganglion cells plays an important role in the development of ocular dominance columns in the visual cortex; the major difference between these two treatments is the presence or absence of spontaneous activity. One hypothesis is that the requirement for electrical activity in the development of this system is merely permissive. It is possible that the LGN and visual cortex are made generally dysfunctional by retinal activity blockade, and that the failure of ocular dominance segregation under these conditions is a nonspecific effect due to a reduction in the amount of impulse activity. The great vigor of cortical visual responses immediately upon removal of the retinal blockade is not what would be expected under this hypothesis, but no finding of the previous experiments directly contradicts it. Under this hypothesis, the experiments on the consequences of impulse blockade tell us nothing about the mechanisms of normal development. In this sense, then, the permissive hypothesis is completely *ad hoc*.

An alternative hypothesis is that electrical activity plays an instructional role. Under an instructional hypothesis, it is the *pattern* rather than the amount of activity that is important for development. Experiments by Mastronarde (44,45) and others (3,4,50) have revealed that the spontaneous discharge of retinal ganglion cells does have a pattern; it is not completely random. In uniform illumination, or even in total darkness, the discharges of neighboring ganglion cells of the same type are closely correlated over a few to some tens of milliseconds. There are also longer-term (one to a few minutes) fluctuations in the discharge rates of retinal ganglion and lateral geniculate neurons in darkness, in which the activity is correlated within one eye but not between the two eyes (43,51). Such patterns of spontaneous discharge could be the source of the information that distinguishes the geniculocortical afferent terminals

erving the left eye from those serving the right, allowing them to segregate into eye-specific patches. Thus, the pattern of spontaneous activity present in normal development could play an instructional role in the formation of ocular dominance columns if geniculocortical connections were to develop by aggregating the terminals that were simultaneously active and segregating those with different activity.

This hypothesis is consistent with inferences from studies of experimental strabismus and alternating monocular occlusion in which binocular segregation seemed to be enhanced by projecting different images onto corresponding points in the two eyes (26,68). Such manipulations were presumed to disrupt the similarity of the discharge patterns of retinal ganglion cells in the two eyes that would ordinarily be produced by binocular visual stimulation. It was hypothesized that the maintenance of binocular connections required such a similarity of the discharge patterns in the two eyes (6). The notion of the "Hebb synapse," one in which the synaptic connection becomes stronger as a result of the correlation between presynaptic and postsynaptic activity, was proposed to account for such a loss of cortical binocularity upon disruption of binocular visual stimulation, and various physiologic mechanisms were proposed for constructing such a correlation-sensitive synaptic connection (9,59).

The instructional hypothesis is particularly attractive because it can be used to explain not only the TTX findings but also, at least in a general way, both the normal development of ocular dominance columns and all of the various forms taken by ocular dominance columns under different conditions of visual deprivation. Figure 6.5 shows the axon-terminal rearrangements that are thought to underlie the normal development of ocular dominance columns and their abnormal development resulting from early monocular visual deprivation (MD), experimental strabismus, and binocular impulse blockade (TTX). Under the instructional hypothesis, the various developmental outcomes can be explained as follows: At 2 weeks of age, terminals serving the left and right eyes are approximately uniformly distributed among the postsynaptic cortical cells. In normal development, small local fluctuations in the relative density of terminals serving the two eyes become magnified over the following weeks; in situations where one eye is slightly more effective than the other eye, the discharges of the terminals serving the more effective eye become more closely correlated with those of the postsynaptic cell, leading to a strengthening of their connection. Because the spontaneous discharges of the terminals serving one eye are correlated with one another, but not with those of the terminals serving the other eye, the terminals of the more effective eye on a particular postsynaptic cell reinforce one another, thus competing with those of the other eye (e.g., for available synaptic space or a trophic factor). Eventually, in normal development, as the animal spends an increasing amount of time awake and alert, with proper eye alignment and simultaneous binocular vision, visual stimulation causes the discharges to become correlated between the two eyes, ending the

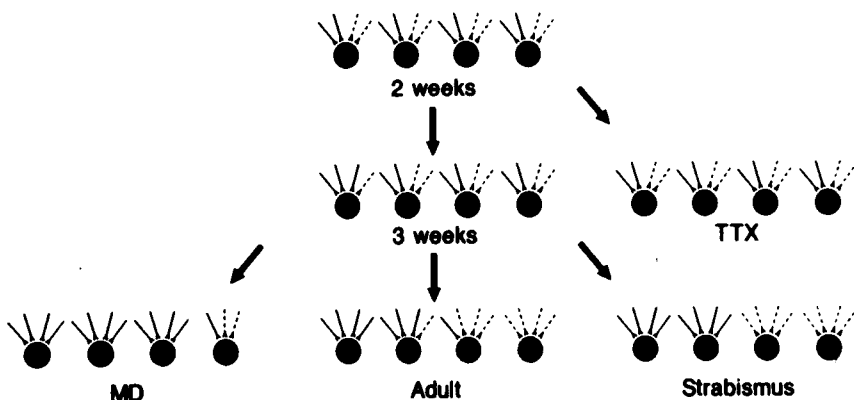


Fig. 6.5. The process of binocular segregation in terms of presynaptic geniculocortical terminals (solid and dashed clubs) contacting cortical cells (filled circles). See text for discussion.

process of binocular segregation short of completion. In the case of experimental strabismus, visual stimulation does not cause the discharge activities of the two eyes to become correlated, and the segregation process is enhanced over that in normal development. In the case of monocular deprivation, the enhanced correlation of discharge produced by visual stimulation of one eye competes successfully against the lower level of correlated discharge in the occluded eye. In animals treated binocularly with TTX, rearrangement of terminals would not take place without discharge activity.

### Experimental Tests of an Instructional Role for Electrical Activity in the Development of Ocular Dominance Columns

To test whether retinal ganglion cell discharge activity is permissive or instructional for the development of ocular dominance columns, we used animals in whom we could control all electrical activity coming from the eye to the brain. Most earlier studies used visual deprivation to allow inferences to be made about the patterns of activity created in the developing visual system. Consideration of the effects of spontaneous discharge activity, which has now been shown to be important in normal development (62), puts these inferences about presumed activity patterns on a much less secure footing. Our strategy was therefore to eliminate all naturally occurring discharge activity and to create patterns of discharge that could be controlled by the experimenter.

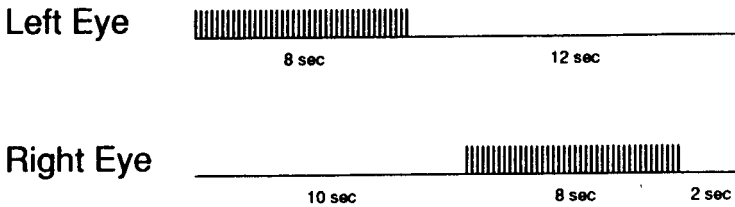
Regardless of the specific mechanisms of synaptic rearrangement during development, the first test of a permissive versus instructional role for electrical

activity is whether the amount or the pattern of activity is important. Our first experiment was to rear animals with binocular impulse blockade during the period of ocular dominance column formation and with chronic electrical stimulation of the optic radiations. Although optic-radiation stimulation is poorly controlled because of the heterogeneous population of afferent and efferent axons stimulated, if such random electrical activity was sufficient to allow geniculocortical afferent rearrangement, strong support would be provided for the permissive role for electrical activity. The outcome of this experiment was no different from that of binocular impulse blockade alone (60). This experiment failed to support a permissive role, but it supported an instructional role only indirectly.

Our next experiment was a more enlightening test of the role of correlated discharge activity (64, and in preparation). We raised two groups of kittens with binocular impulse blockade during the period of cortical binocular segregation in normal animals: from 2 weeks until 6–8 weeks of age. We had previously shown that this treatment alone completely blocks binocular segregation. In one group of three kittens, we placed chronic stimulating electrodes into both optic nerves. Through these electrodes we delivered electrical activity alternately to the two nerves, in the pattern shown in the top part of fig. 6.6. Any mechanism for binocular segregation that depends on the correlation of activity within each eye or the lack of such correlation between the two eyes should proceed easily in these animals. In a second group of five kittens, we placed a chronic stimulating electrode in the optic tract through which we delivered electrical activity simultaneously to the retinal ganglion cell axons in the two optic nerves in the pattern shown in the lower part of fig. 6.6. Any correlation-sensitive mechanism for binocular segregation should fail under these conditions, since there is the same correlation between terminals serving the two eyes as there is within the population of terminals serving one eye. Because both nerve and tract electrodes delivered maximal X and Y volleys (10, 11), the amount and pattern of activity within each optic nerve was exactly the same under the two conditions. Thus, if the role of activity is permissive, the two experimental conditions should have identical outcomes. If, on the other hand, the role of activity is instructional, opposite outcomes would be expected.

Figure 6.7 shows that these two experimental conditions do indeed have opposite outcomes for our physiologic index of binocular segregation. The data from animals treated with simultaneous activation of afferents from the two eyes (O.T. Stim) are indistinguishable from those of animals treated with binocular impulse blockade alone (TTX) and are more binocular than data from normal animals of the same age (6–8 wk). In contrast, the data from animals treated with alternate activation of the two optic nerves (O.N. Stim) are dramatically less binocular than those seen in any of the other experimental or control groups and are similar to those found in animals subjected to experimental

## Alternate (Optic Nerve) Stimulation



## Simultaneous (Optic Tract) Stimulation

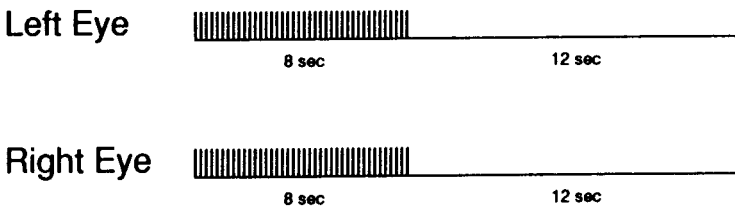


Fig. 6.6. Patterns of impulse activity produced by electrical stimulation in the left and right optic nerves of two groups of animals. Stimuli were delivered to each nerve at 5/sec for 8 sec, followed by 12 sec without stimulation. See text for discussion. Redrawn from Stryker and Strickland (64).

strabismus or alternating monocular occlusion. In the alternate stimulation group, ocular dominance columns were also evident in the clustering of neurons encountered successively along electrode tracks according to eye preference, whereas nearly all neurons were equally driven by the two eyes in the simultaneous stimulation group. Transneuronal labeling of the geniculocortical projection revealed periodic fluctuation in the labeling of one eye's projection in the alternate stimulation group, whereas the labeling was uniform in the simultaneous stimulation group.

It is difficult to reconcile these findings with anything other than an instructional role for electrical activity in the formation of cortical ocular dominance columns. These findings reveal that the formation of ocular dominance columns can be controlled by the *pattern* of afferent electrical activity. Although effects of stimulus frequency on the development of the peripheral nervous system have been demonstrated (67), the present effects are different in that

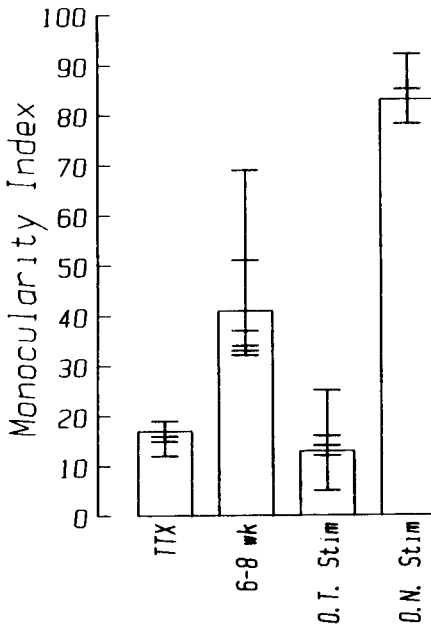


Fig. 6.7. Monocular index like that in fig. 6.3—the physiologic index of binocular segregation—for four groups of animals studied at 6–8 weeks of age: animals subjected to binocular impulse blockade with no electrical stimulation (TTX); normal animals (6–8 wk); animals subjected to binocular impulse blockade plus simultaneous activation of the two optic nerves, using an optic-tract stimulating electrode (O.T. Stim); and animals subjected to binocular impulse blockade plus alternate activation of the two optic nerves, using two stimulating electrodes (O.N. Stim). Data from Stryker and Strickland (64).

they depend on the *relative* timing of activity in the afferent pathways from the two eyes to the cortex.

It is tempting to speculate that the mechanisms that underlie the phenomenon of activity-dependent synaptic rearrangement may be quite general in the developing nervous system and may underlie much of the specificity that is attained during fetal and neonatal life. The fact that spontaneous electrical activity appears to be sufficient, at least in some circumstances, to drive these mechanisms suggests that they could operate *in utero*. Thus, abnormalities in the pattern of electrical activity in the fetus could, themselves, be a cause of birth defects.

However, little is known about the mechanisms that underlie this process other than that they depend on correlated activity. Discovering the cellular bases of the mechanisms is a principal goal of current research.

## Acknowledgments

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