

Activity-Dependent Reorganization of Afferents in the Developing Mammalian Visual System

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The early experiments of Hubel and Wiesel (1962) demonstrated that the neurons within radial columns in the primary visual cortex share many specific response properties. Each column is specific for *topography*, in that all neurons have their receptive fields in a particular portion of the visual field; for *ocular dominance*, in that all the neurons in a particular column will tend to respond more strongly to one eye than to the other; for *on- or off-center-type* in some species, in that the neurons within a column will tend to respond better to bright stimuli than to dark stimuli, or vice-versa; and for stimulus *orientation*, in that all the neurons within one column will respond selectively to bars or edges at one particular angle in the visual field. In the tangential dimension, the properties of neurons differ from one column to the next in a systematic fashion. Thus, the columns of the visual cortex are precisely organized in respect of three (or in many species, all four) of the response properties noted above. An understanding of this organization and its structural basis is essential before we can understand the mechanisms that give rise to this orderly arrangement of cortical response properties in development.

Experiments described below suggest that the major specific afferents to visual cortex are also precisely ordered in every respect in which the cortical neurons themselves are ordered. Such an orderly arrangement of afferents provides a structural basis for the tangential organization of cortical columns. The progressive reorganization of the afferent pathway in development may well be the mechanism by which the orderly arrangement of cortical columns is established. Further experiments described below indicate that relatively simple mechanisms of activity-dependent synapse rearrangement can account for the principal features of afferent organization and that the plasticity exhibited by the developing visual cortex is consistent with the existence of such mechanisms.

ORGANIZATION OF AFFERENTS IN RELATION TO CORTICAL COLUMNS

The first respect in which visual cortex is organized in the tangential domain is the map of the visual field onto the cortex, so that neighboring groups of columns represent neighboring points in the visual field (Hubel

and Wiesel 1974). The basic organization of this map was known from clinical neurology and anatomical studies and has been evident since the earliest physiological studies of Talbot and Marshall (1941). The structural basis of the topographic map is the orderly projection of neighboring retinal ganglion cells to neighboring points in the lateral geniculate nucleus and the further orderly projection from geniculate to cortex.

A second feature of the organization of the visual cortex in the tangential domain is the system of cortical ocular dominance columns. These columns disrupt the larger-scale continuity of the map of the visual field by interdigitating regions in which responses favor one eye with those that favor the other eye at a scale of about half a millimeter. The structural basis of these ocular dominance columns was revealed in experiments in which the population of geniculocortical afferent terminals serving one eye was labeled by degeneration methods or autoradiographically by transneuronal axonal transport of ^3H -sugars or amino acids injected into the vitreous humor of one eye (Hubel and Wiesel 1972; Wiesel, Hubel, and Lam 1974; Shatz, Lindstrom, and Wiesel 1977). In adult animals, the labeled afferent projection conveying information from one eye to the visual cortex takes the form of patches or stripes 350 μm to 500 μm wide, alternating with unlabeled patches of the same size that receive the other eye's projection.

Third, in several species, *on*-center and *off*-center responses are also segregated, at a scale somewhat finer than that of the ocular dominance columns (LeVay, McConnell, and Luskin 1987). This pattern of organization also appears to have its structural basis in the organization of afferents to the cortex, as revealed by experiments in which geniculocortical afferents of the two center types were recorded in alternate patches of cortical layer IV (LeVay and McConnell 1982; Zahs and Stryker 1988). The borders between *on*- and *off*-center patches were independent of those between the ocular dominance patches.

The orientation columns constitute a fourth type of columnar and tangential organization that was revealed in Hubel and Wiesel's earliest studies (1962) of visual cortex and elaborated in later reports (Hubel and Wiesel 1963, 1974a). The structural basis of orientation selectivity has, however, been difficult to establish with confidence. The original model (Hubel and Wiesel 1962) proposed that neurons with simple-type receptive fields were endowed with orientation selectivity by virtue of the alignment in the visual field of the receptive fields of the lateral geniculate nucleus neurons from which the simple cell received its input. In this case, the arrangement of afferents could constitute a structural basis for the orientation columns, just as they do for the other sorts of cortical columns. Later models (Benevento, Creutzfeldt, and Kuhnt 1972; Sillito 1980) proposed that orientation selectivity was produced largely or completely by intracortical circuitry. In this latter case, the arrangement of afferents might have nothing to do with cortical orientation columns, making them different from the other sorts of cortical columns.

AFFERENTS TO SINGLE-ORIENTATION COLUMNS

We have now investigated the arrangement of the geniculocortical afferents that provide the thalamic input to orientation columns by recording from afferent terminal arbors in the major input layer, layer IV, of the cortex (Chapman, Zahs, and Stryker 1990, and in preparation). As originally suggested by Helen Sherk, the factor that prevents one from discriminating the electrical activity produced by the many afferent terminal arbors through which a microelectrode must pass on its way through the cortex is not the small size of their extracellularly recorded action potentials in comparison to the electrical noise of the microelectrode, since the microelectrode noise can be as little as $5 \mu\text{V}$ while afferent spikes are $10 \mu\text{V}$ to $100 \mu\text{V}$. Instead, it is the ongoing discharge of cortical cells, which produce spikes of some hundreds of microvolts, that occludes recognition of most of the signals from afferents. By silencing the cortical discharge, it becomes routine to record and plot 10 to 40 afferent receptive fields on a single vertical penetration through the visual cortex.

The design of our experiment was to align a microelectrode so that it passed down a single orientation column in the primary visual cortex of the ferret. Recordings made at a series of cortical depths guaranteed this alignment and allowed us to determine the preferred orientation of the cortical cells before withdrawing the electrode to a position in layer III just above the major input layer. In the earlier experiments, cortical cells were then silenced by killing them, using superfusion of the excitotoxin kainic acid (Zahs and Stryker 1988). In later experiments, the cortical cells were silenced more quickly and with less damage by superfusing them with muscimol, a potent analogue of the inhibitory neurotransmitter GABA that acts on the postsynaptic GABA_A receptors. Once the cortical cells were silent, the microelectrode was advanced again slowly into and through layer IV, where the action potentials of many afferent single units were individually discriminable. These units had visual response properties identical to those of their parent cell bodies recorded in the lateral geniculate nucleus (LGN), and their responses to electrical stimulation of the LGN confirmed that they were the terminals of geniculate cells. In most experiments, the use of a blind procedure ensured that the plotting of the afferent receptive fields was not influenced by knowledge of the prior results from the cortical cells.

Figure 16-1 shows the results of this experiment for three cases. In the cases illustrated, the afferent receptive fields, shown as ellipses, were disposed about an elongated region of the visual field, and the axes of elongation matched the preferred orientations of the cortical cells. Both of these findings were generally true. In 16 out of a total of 18 such experiments, the afferent receptive fields were found to be elongated with better than 90% confidence (and with at least 99.99% confidence in 13 of the 16 cases). The agreement between cortical orientation selectivity and the principal axis of elongation of the collection of afferent receptive fields is

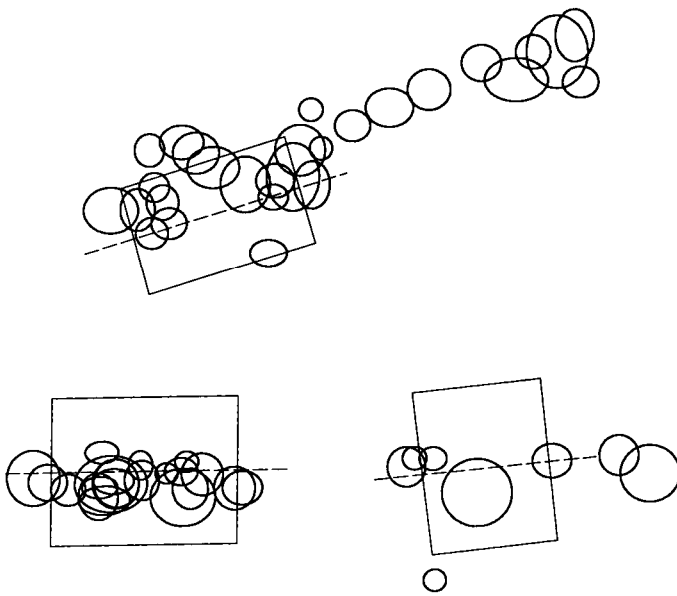


Figure 16-1. Receptive fields of a layer III cortical cell and the collection of geniculocortical afferents recorded in layer IV immediately below the cortical cell in three separate experiments. The cortical receptive fields are drawn as rectangles, and the dashed lines indicate the preferred orientations for the cortical cells as determined from orientation tuning histograms. Each ellipse is the receptive-field center of a single geniculocortical afferent terminal. Note that the principal axis of elongation of the collection of afferent receptive fields matches the preferred orientation of the cortical neuron in each case. Data from Chapman et al. (1989) and (1991).

illustrated for these 16 cases in Figure 16-2. While there are three cases of mismatch by as much as 25 degrees, overall the match is good, as indicated by the proximity of the data points to the line drawn to the prediction of perfect agreement between the orientation of the collection afferent receptive fields and that of the cortical cells.

The findings of this experiment are exactly as would be predicted by the Hubel and Wiesel (1962) model. These findings would appear to be surprising, at least at first sight, if orientation selectivity were produced by purely intracortical mechanisms. This experiment thus provides strong evidence that, at least in adult animals, orientation columns are similar to the other cortical columns in that their arrangements correspond to, and may be determined by, the arrangement of their geniculocortical afferent inputs. As discussed below, however, such an arrangement of input might also be expected if orientation selectivity were produced initially by some intracortical mechanism, following which afferent terminals were allowed to refine or stabilize in a manner that depends on the correlation between cortical and afferent activity. Thus, such findings in adult animals do not answer the chicken-and-egg question of who organizes whom—do the afferents come first and organize the cortical columns, or vice versa? For that we need to turn to studies of development.

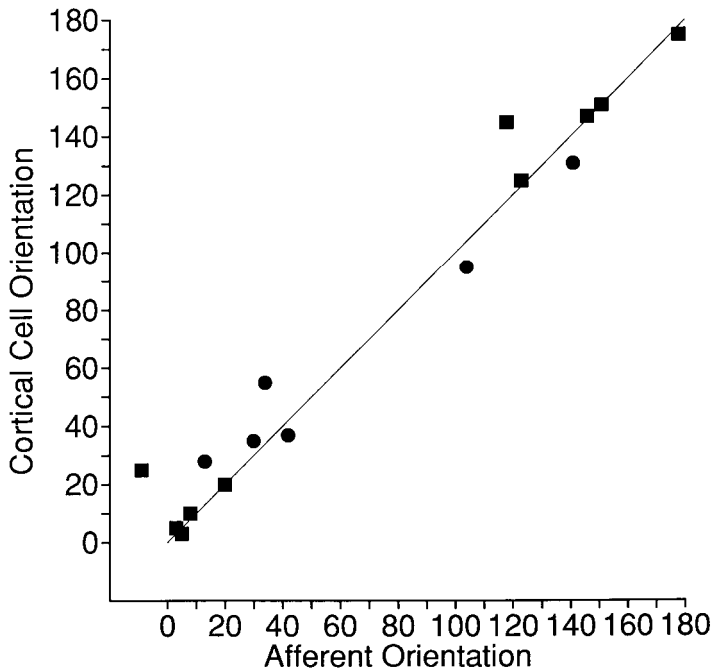


Figure 16-2. Scatter plot of the relationship between the preferred orientation of the cortical neuron (ordinate) and the principal axis of elongation of the collection of afferent receptive fields (abscissa) in the 16 of 18 experiments at which the collection of afferent receptive fields was significantly elongated. Line is drawn to indicate the predicted results of a perfect match between afferent and cortical orientations. Squares plot experiments done using a blind procedure in which the experimenter plotting the afferent receptive fields was unaware of the results from the cortical neuron recordings. Note that the match between cortical and afferent orientations is generally good and that there is no case of large mismatch. Data from Chapman et al. (1989) and (1991).

HOW DO GENICULOCORTICAL AFFERENTS COME TO BE ORGANIZED IN DEVELOPMENT? THE OCULAR DOMINANCE COLUMNS

We know little with certainty about the mechanisms of thalamocortical afferent organization in development. A large body of evidence in many systems indicates that the generation of appropriate numbers of target neurons, their migration to appropriate positions, the outgrowth of axons, their navigation along appropriate pathways, their recognition of the target structure, and their formation of at least coarsely topographic maps are all governed by molecular mechanisms of specificity and all take place normally in the absence of neuronal activity (reviewed in Harris and Holt 1990).

At least a coarse topographic specificity appears to be present in the growth of afferent arbors into the cortical plate from the subplate zone, within which they may have become organized during a waiting period of as long as several weeks (Shatz and Luskin 1986). In several respects,

however, the geniculocortical afferents appear to exhibit little specificity in their initial growth into the cortical plate, and a number of results suggest that afferents organize under the influence of patterns of neural activity. In particular, the initial growth of eye-specific inputs into the visual cortex does not take place in the form of ocular dominance patches. Instead, geniculocortical afferents serving the two eyes initially make connections to the cortex in a completely overlapping pattern (Rakic 1977; Hubel, Wiesel, and LeVay 1977; LeVay, Stryker, and Shatz 1978; LeVay, Hubel, and Wiesel 1980). Ocular dominance patches then develop by the progressive segregation of these initially overlapping inputs. This development was most clearly revealed by the progressive changes in the transneuronal labeling pattern of visual cortex following an injection into one eye of animals at different ages, as shown in Figure 16-3.

Nearly all of our work on the development of geniculocortical afferent specificity has focused on the ocular dominance columns. The profound influence of neural activity on their development and plasticity makes them an excellent model system for studies of the organization of neural connections. This influence was noted long ago in the clinic, where surgical removal of cataracts that had been acquired in adulthood "miraculously" restored sight. In contrast, when patients with cataracts that had occluded vision in one eye from the time of birth were treated by similar surgery, useful vision was not restored in spite of the fact that no serious histological damage was evident in the retina or in visual structures in the brain (Senden 1960).

Changes in the developing visual system in experimental animals can explain such clinical findings. Most neurons in the cat's visual cortex ordinarily respond to stimulation through either eye (Hubel and Wiesel 1962). Such binocular responses in the visual cortex are unaffected by even years of monocular visual deprivation in adult animals, but as little as a few days or weeks of monocular visual experience during a sensitive period in early life leaves most cortical neurons unresponsive to the eye whose vision had been occluded (Wiesel and Hubel 1963a; Hubel and Wiesel 1970). In young monocularly deprived animals, the two eyes were entirely normal, and neurons driven by the deprived eye in the lateral geniculate nucleus, which is the major source of input to visual cortex, appeared to be nearly normal (Wiesel and Hubel 1963b). Thus, neonatal monocular visual deprivation produces a change in the visual cortex, where inputs from the two eyes first have the opportunity to interact on single neurons, rather than at some more peripheral stage of the visual system.

Binocular visual deprivation for a similar period in early life produces no ill effects, suggesting that the changes produced by unilateral visual deprivation are due to a competitive interaction between the geniculocortical afferents serving the two eyes rather than merely to disuse of the occluded eye's afferents (Wiesel and Hubel 1965). This conclusion is reinforced by failure of monocular deprivation to produce changes either in the most peripheral portion of the visual field, which is viewed through

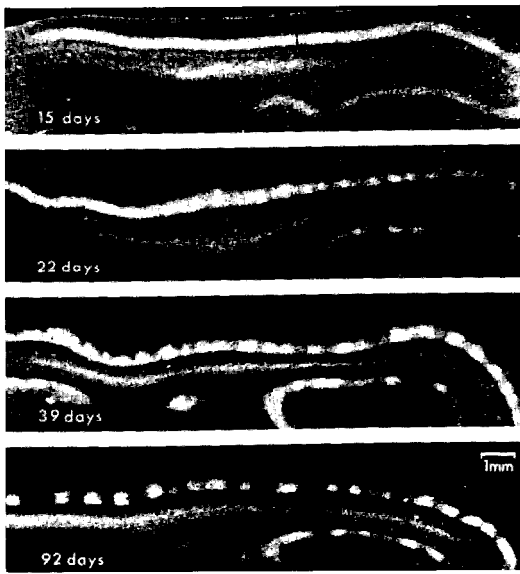


Figure 16-3. Development of ocular dominance in the cat. Progressive changes in the pattern of transneuronal labeling of the projection from one eye to the visual cortex of the cat. The ipsilateral eye of each kitten was injected with [^3H]-proline approximately one week before perfusion at the ages indicated. Sections of the visual cortex were exposed autoradiographically and were photographed in a dark field, making the labeled regions bright. Note that labeling is uniform along the major input layer of cortex at 15 days, indicating that afferents serving the labeled eye spread over the entire tangential extent of the layer and were completely intermingled with those serving the other eye. Following this time, labeling becomes increasingly patchy, as the afferent terminals serving the two eyes segregate. Data from experiments of LeVay, Stryker, and Shatz (1978).

only one eye, or in a region of LGN and visual cortex in which input from the seeing eye was experimentally removed (Guillery 1972; Sherman et al. 1974). The changes of binocular connections in the developing visual cortex also do not depend on light deprivation, since effects similar to those of monocular occlusion were produced when the image of one eye was merely blurred (Wiesel and Hubel 1963a). Instead they appear to be due entirely to alterations of the spatial and temporal patterns of neural discharge in geniculocortical afferents. Perhaps the most striking finding is that equal amounts of neural activity presented asynchronously to the two eyes, by occlusion of each eye on alternate days or by surgically or optically misaligning images in the two eyes, cause the partial segregation of visual responses into ocular dominance columns to become nearly absolute (Hubel and Wiesel 1965; Van Sluyters and Levitt 1985). In such a cortex each cortical column contains cells driven exclusively by one eye or the other. This phenomenon strongly suggested that the relative timing of neural activity in the two eyes played an important role in preserving some binocular connections in development.

The most sensitive period for these deprivation effects is at the time at

which the geniculocortical afferent terminals are rearranging from their initial projection pattern of complete overlap during normal development. Thus, the plasticity produced by monocular deprivation may represent merely the outcome of the normal developmental process in the presence of abnormal patterns of activity.

These experiments demonstrate that alterations in visual experience can alter the course of geniculocortical afferent segregation and cause ocular dominance columns to form abnormally. Ocular dominance columns do not form at all, however, when neural activity is blocked. Stryker and Harris (1986) stopped all neural activity in the two eyes by repeatedly injecting tetrodotoxin (TTX), the voltage-sensitive sodium channel blocker, during the period in which ocular dominance columns normally develop. This treatment also dramatically reduced neural activity in LGN and visual cortex. The effect of the treatment was to cause geniculocortical afferents to remain in their infantile state of complete overlap. Figure 16-4 shows the uniform transneuronal labeling pattern following injection of [³H]-proline into one eye of a 45-day-old kitten in which neural activity in both eyes had been blocked continuously beginning at 14 days of age, prior to the time that ocular dominance columns begin to segregate in normal development. Compare this labeling pattern to the clearly patchy, segregated pattern observed in the normal 39-day-old kitten shown in the next to last panel of Figure 16-3. This failure of eye-specific segregation was apparent physiologically as well, in that nearly all neurons in the cortex were driven well through both eyes, in contrast to the situation in normal animals in which many neurons are strongly dominated or driven exclusively by one eye or the other. These experiments suggest that the normal developmental rearrangement of geniculocortical synaptic connections to form ocular dominance columns requires neural activity. Since ocular dominance columns form, to a considerable extent, *in utero* in the monkey (Rakic 1977; DesRosiers et al. 1978; LeVay, Wiesel, and Hubel 1980) and in cats reared with bilateral lid suture or in total darkness, it appears that the maintained activity of retinal ganglion cells in darkness is sufficient for segregation and that visually driven activity is not required.

Is there information in the pattern of maintained activity of retinal ganglion and geniculate cells in darkness? In adult cats, neighboring ganglion cells of the same center type tend to fire together over time periods of a millisecond to a few tens of milliseconds, and this correlation of activity decreases with increasing distance across the retina (Mastrorarde 1983). Activity correlated over longer time scales is also present (Rodieck and Smith 1966; Levick and Williams 1964). Even before the retinal circuitry has developed *in utero*, ganglion cells have rhythmic activity, and the activities of neighboring neurons may be correlated (Maffei and Galli 1990). Such correlated activity within one eye, and its absence between the two eyes, could be the source of the information used by the developing visual system to distinguish the afferents serving one eye from those serving the other.

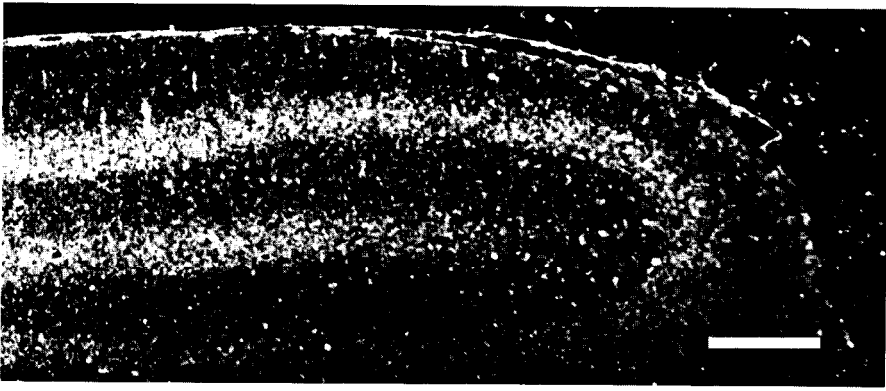


Figure 16-4. Transneuronal labeling pattern produced as described for Figure 16-3 in the visual cortex of a cat subjected to bilateral retinal activity blockade beginning at 14 days of age and continuing until the time of perfusion at 45 days of age. Note that unlike normal cats illustrated in Figure 16-3, the labeling pattern is uniform, indicating complete overlap between afferents serving the two eyes. Scale: 1 mm. Unpublished data from experiments of Stryker and Harris (1986).

Stent (1973) and Changeux and Danchin (1976) proposed mechanisms to account for the effects of visual deprivation during early life. These mechanisms were formally similar to the rule described by Hebb (1949), which postulates that synapses are strengthened to the extent that the activities of pre- and postsynaptic neurons are correlated and that synapses are weakened otherwise. A Hebb rule for the adjustment of geniculocortical synaptic strengths would be expected to allow the geniculocortical afferents serving each eye to remain together in normal development, since their correlated activities would allow them to cooperate in activating the cortical cells to which they provided input. The absence of correlation between activity in the two eyes would not allow cooperative activation of cortical cells and would therefore cause the two eyes' afferents to segregate from one another. It was suggested that such a rule could also explain the effects of early monocular and binocular visual deprivation, alternating monocular occlusion and experimental strabismus, and the effects of binocular activity blockade.

A MATHEMATICAL MODEL OF OCULAR DOMINANCE COLUMN DEVELOPMENT

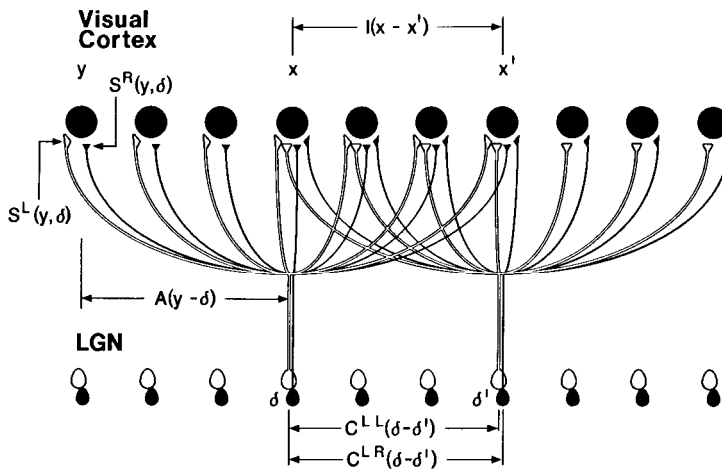
By explaining, at a qualitative level, how a simple neural mechanism could produce precise patterns of connections in development, the Hebb rule was tremendously appealing. Quantitatively, however, it was not clear whether such an explanation would work with realistic elements. It was also not clear what degree or extent of correlated activity in the retina or LGN was necessary for such an explanation to work, what pattern of initial connections was compatible with such an explanation, and what the

role of intracortical interconnections in the process was. Finally, a genuine model of development should allow one to predict the widths of the ocular dominance columns from the input parameters.

Miller, Keller, and Stryker (1989) constructed and analyzed a mathematical model of the development of ocular dominance columns capable of addressing quantitative questions. The model, illustrated in Figure 16-5, incorporates a minimal set of features consistent with the experiments above. First, there are two sets of afferents in the model, corresponding to the two eyes or to the layers of the LGN that serve the two eyes, and these afferents initially make widespread overlapping connections, some of which become ineffective or are removed in development. The extent of synapses between these afferent arbors and the cortical cells is described by the arbor function A in the model. Second, correlated activity among afferents serving one eye, and the absence of correlation between the eyes, plays an important role. The correlation functions between the afferents serving the left eye is described by the C^{LL} function in the model and that between the two eyes by the C^{LR} function. Third, postsynaptic activity in the cortex is communicated via intracortical synaptic connections. These pathways by which cortical cells influence one another's activity are described by the I (corticocortical interaction) function in the model. Finally the change in strength S of each synaptic connection between the afferents and the cortical cells was hypothesized to change by a Hebb rule, as described in the differential equation at the bottom of Figure 16-5, and the model was carried forward in time from its initial state.

This model was studied mathematically by linear stability analysis, and the evolution of its neural connections was simulated in the computer. The model robustly reproduces many of the biological phenomena described above. Figure 16-6 shows the similarity between real ocular dominance columns on the left and those produced by the model. Ocular dominance columns formed with a characteristic spacing in the presence of activity, and the model reproduced the known effects of monocular deprivation on column size and spacing. Receptive fields refined during development, and afferent arbors broke up into patches resembling those observed anatomically. All of these similarities between the model and biological development indicate that a simple rule for synaptic plasticity in a system with initial connectivity like that of the developing visual cortex can at least in principle account for the rich structure observed biologically.

A new insight obtained from the mathematical analysis was that the spacing of the ocular dominance columns was determined by the corticocortical interaction I function if that function selected a spacing small enough to contain the initial afferent arbor A . If the corticocortical interaction function I selected a spacing that was too large, then the spacing would be constrained by the maximum that could be sustained by the arbor function A . A sufficient spread of the correlation function C^{LL} was



$$\partial_t S^L(x, \delta, t) = \lambda A(x-\delta) \sum_{y, \beta} I(x-y) [C^{LL}(\delta-\beta) S^L(y, \beta, t) + C^{LR}(\delta-\beta) S^R(y, \beta, t)] - \text{DECAY}$$

$$\partial_t S^R(x, \delta, t) = \lambda A(x-\delta) \sum_{y, \beta} I(x-y) [C^{RR}(\delta-\beta) S^R(y, \beta, t) + C^{RL}(\delta-\beta) S^L(y, \beta, t)] - \text{DECAY}$$

Figure 16-5. Cartoon illustrating elements of the model of Miller et al. (1989). (1) Afferents from the lateral geniculate nucleus (LGN in figure) project to the visual cortex. Afferents (open and filled ellipses) serving each of the two eyes make equivalent initial projections to the cortex. Synaptic interconnections among cortical cells (filled circles) may be either excitatory (illustrated as more local, direct connections) or inhibitory (illustrated as more distant connections via inhibitory interneurons). (2) The afferents project to all cortical cells in a compact region, making a terminal arborization; the strength of the connection between a cortical point y and a geniculate point δ is given by the arbor function $A(y-\delta)$, which is zero outside the arbor radius. (3) The degree of correlation in firing among incoming afferents from retinotopic positions δ and δ' is represented by the correlation functions $C^{LL}(\delta-\delta')$, $C^{RR}(\delta-\delta')$ (not illustrated), and $C^{LR}(\delta-\delta')$ gives the correlation between a left eye afferent from δ and a right eye afferent from δ' , etc. (4) Each synapse has a physiological strength, which varies with time during development. This is illustrated by the functions $S^L(y, \delta)$ and $S^R(y, \delta)$. (5) Finally, there is some influence of activity at a cortical point x' on the strength of synapses at a cortical point x . This spread of influence, as a function of distance, is summarized in the corticocortical interaction function $I(x-x')$, which may be both excitatory and inhibitory at different distances. See text for discussion.

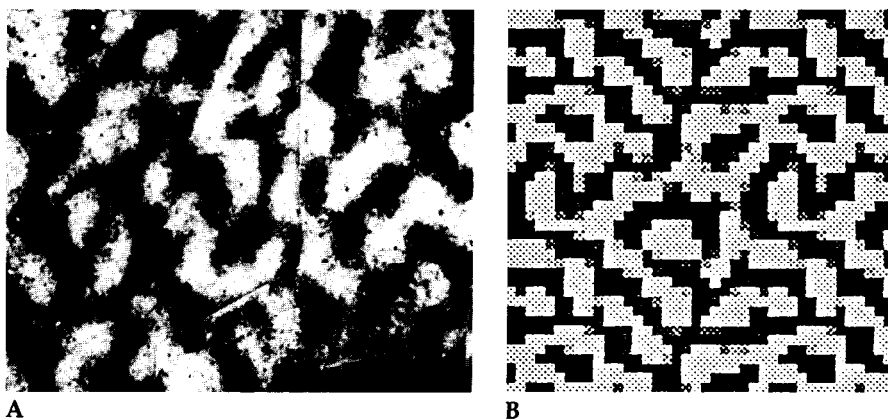


Figure 16-6. Left: Tangential view of ocular dominance columns labeled in flat-mounted section through layer IV of cat visual cortex by transneuronal transport of wheat-germ agglutinin conjugated to horseradish peroxidase injected into one eye. Data from Anderson et al. (1988). Right: Simulated ocular dominance columns from model of Miller et al. (1989) shown in a similar view. Note similarity between the tangential arrangements of ocular dominance columns in the experimental observations and model.

important for allowing monocular cortical neurons to develop at all, but beyond that its role was purely permissive, and it played no role in setting the spacing of ocular dominance patches.

An important feature of the model is that each of the parameters can be, and has been to a limited extent, measured experimentally. The correlation functions C^{LL} and C^{LR} may be measured by straightforward cross-correlation studies in the LGN. To date, such data is available in quantity only for the retina in adult animals, but there is no technical barrier to obtaining it from the LGN in kittens at the ages at which ocular dominance columns begin to form. The arbor function A may be measured from anatomical reconstructions of geniculocortical afferent arbors like the one illustrated in LeVay and Stryker (1979) or others labeled using more modern techniques. An exact measurement of A would also take the spread of the dendrites of postsynaptic cortical cells into account; while this would be straightforward to do, it may well be that those dendrites are quite short at the relevant time in development. The corticocortical interaction function I may be measured by experiments like those of Hess, Negishi, and Creutzfeldt (1976), which plot the effect, as a function of distance, of pharmacologically exciting a group of distant neurons on the visual responses of a local neuron. Miller and Stryker (1990) and Miller (1990) discuss the rather good agreement between the column spacings observed experimentally and the current experimental estimates of the values of the model parameters.

The mathematical model was formulated to incorporate a generic Hebb rule synapse, in which the correlation between the electrical activities of

the presynaptic terminal and the postsynaptic cortical cell controlled changes in synaptic efficacy. The agreement between the predictions of the model and the results of a wide variety of experiments on the normal and experimentally perturbed development of ocular dominance columns led us to ask whether such a mechanism was the only one that could work so satisfactorily. Could other proposed mechanisms of plasticity be excluded on the grounds that they would necessarily fail to reproduce the biological phenomena of interest? Miller's analysis showed that all of the biologically plausible mechanisms of synaptic plasticity that we knew had been proposed in this system could be described in the same mathematical framework that we had used to analyze the Hebb synapse model. As one extreme example, the model was applied to a hypothetical mechanism in which the afferent terminals interact with one another through diffusible trophic or trophic substances and the postsynaptic cells just sit there like potatoes (Miller et al. 1989). If one assumes such a non-Hebbian mechanism, the activity of postsynaptic cells plays no role whatever in synaptic plasticity. None of the mathematical behavior differed as our model was applied to different biological mechanisms; what did differ was the biological interpretation of the model parameters. For example, in the original model, the corticocortical interaction function I represented the net synaptic interaction among cortical cells as a function of their separation. In the mathematically identical presynaptic trophic substance model, the I function represented the release, diffusion, degradation, and uptake of the hypothetical trophic factor or factors. In either case, the mathematical model tells us what the spatial extent of the net interactions between synapses on different cells had to be in order to produce ocular dominance columns of the experimentally observed spacing. But it does not tell us the biological mechanism by which such interactions are effected.

The *quantitative* answer given by the mathematical model is, however, enormously helpful to the biologist engaged in the search for the answer to the normal *qualitative* question of what mechanism of synaptic plasticity is responsible for some feature of development, for the model allows one to use measurements of, for example, the diffusion constant of a hypothetical trophic substance, to completely exclude it as an explanation for the phenomenon. If one puts forward a number of alternative hypotheses about the biological mechanisms involved in ocular dominance column formation, one can then measure the real values of the biological features that correspond to the model parameters under the assumptions implicit in each mechanism. If a proposed mechanism is not operative, it is unlikely that the measured values would agree with the ones required by the model except by chance, and if they do not agree, the mechanism simply cannot be the correct one. It is thus true that, with appropriate choices of values for the parameters, very many biological mechanisms could produce the same behavior in the model, and the eager modelers could produce computer pictures that beautifully mimic real development

under the assumption of whichever mechanisms they chose. The model does not tell us the answer—it is no substitute for doing biology. But the model does tell us what to measure to see whether a proposed mechanism is consistent with the phenomenon it hopes to explain.

For the reasons above, biologists and modelers should not be satisfied by computer pictures that merely resemble real development. Given the different backgrounds of most modelers and most biologists, such pictures may constitute the only language common to the two camps, and the model certainly should be capable of producing such pictures, but more is needed. For productive interaction with biology, it is necessary in addition that the elements of a model correspond in some fairly direct way to the elements of the biological system, and the model parameters must, at least in principle, be susceptible of straightforward measurement from the biological system. Only then can one test the model, make quantitative predictions, and refine it to account for further features of the biology.

DOES CORTICAL ACTIVITY PLAY A ROLE IN THE FORMATION OF OCULAR DOMINANCE COLUMNS?

Despite the success of the Hebb synapse model in reproducing the development of ocular dominance columns, we have seen above the need to gather more evidence that such a mechanism is actually operative in normal development. Meaningful or behaviorally significant vision was found not to be necessary for ocular dominance plasticity (Chapman, Jacobson, Reiter, and Stryker 1986); this is consistent with a Hebb synapse explanation of development, in which the statistics of neural activity are sufficient to account for ocular dominance plasticity. By introducing controlled patterns of activity into the two optic nerves using electrical stimulation, Stryker (1986) showed that ocular dominance columns did not form when activity in the two eyes was simultaneous but that an equal amount of activity delivered alternately to the two eyes did allow ocular dominance segregation. These experiments were consistent with the Hebb synapse prediction that development and plasticity was controlled by the timing of neural activity. Another simple prediction of a Hebb synapse mechanism is that the neural activity relevant to ocular dominance development and plasticity is the activity in the cortex involving cortical cells and their geniculocortical afferent inputs. The experiments described above had all interfered with activity at earlier stages of the visual system as well. Reiter, Waitzman, and Stryker (1986) tested this prediction by infusing TTX into a region of cortex to block the discharge of cortical cells and their geniculocortical afferent terminals and then instituting a period of monocular deprivation to study whether the deprivation would cause a shift in ocular dominance. Consistent with the prediction of a Hebb synapse model, the cortical activity blockade completely prevented plasticity.

The experiments above have located the neural activity relevant to ocular dominance plasticity in the cortex, but they do not reveal whether it is

the presynaptic activity, the postsynaptic activity, or both (as postulated by a Hebb synapse mechanism) that are important. In many earlier experiments in which the responses of cortical cells were perturbed by substances infused into the cortex, ocular dominance plasticity was disrupted to a greater or lesser extent, consistent with a role for postsynaptic activity, but these substances appeared likely to have presynaptic effects on afferent terminals as well. Reiter and Stryker (1988) selectively blocked postsynaptic activity during a period of monocular deprivation by infusing the GABA_A agonist muscimol into the visual cortex, a substance that, as described in the first section of this paper, powerfully inhibits all cortical cells but appears to have no effect on activation of or synaptic release from afferent terminals. In the region of cortex in which cortical discharge was completely inhibited, not only was the normal synaptic plasticity prevented, but inputs from the less-active, occluded eye came to dominate over those from the more active, nondeprived eye, as shown in Figure 16-7. This form of synaptic plasticity in the reverse direction from normal is exactly what would be predicted by the Hebb synapse model. In this case, the activity of the less-active, occluded eye is better correlated with that of the inhibited postsynaptic cortical cells than is the activity of the more-active open eye. In adjacent regions of cortex, in which the cells were able to respond to their inputs, ocular dominance plasticity in the normal direction was evident. Since identical patterns of afferent activity produced opposite types of plasticity, depending on whether the postsynaptic cortical cells were able to respond to their inputs, the role of the postsynaptic cells is clearly crucial, as postulated by the Hebb synapse model. This experiment further suggests that a process coupled to postsynaptic membrane voltage or conductance controls the direction of synaptic plasticity, which favors more-active inputs when the postsynaptic cell can be depolarized by them but less-active inputs when the postsynaptic cell is inhibited. Finally, local responses rather than action potentials in the postsynaptic cells appear to be responsible at least for the reverse plasticity, since it took place while spikes were blocked in the cortical cells.

FUTURE DIRECTIONS

We have seen above that ocular dominance columns may result from activity-dependent reorganization of the geniculocortical afferents serving the left and right eyes using a mechanism involving Hebb rule synapses. To date, this hypothesis has passed all of the tests, several of them quite formidable, to which it has been subjected. Although we will not have conclusive evidence for this hypothesis until we understand the mechanisms of plasticity in more detail than we do at present, we may nevertheless design experiments that would be difficult to reconcile with other mechanisms. For example, if we could create ocular dominance columns with dramatically abnormal spacing by selectively perturbing corticocortical synaptic interactions, we would have compelling evidence that the

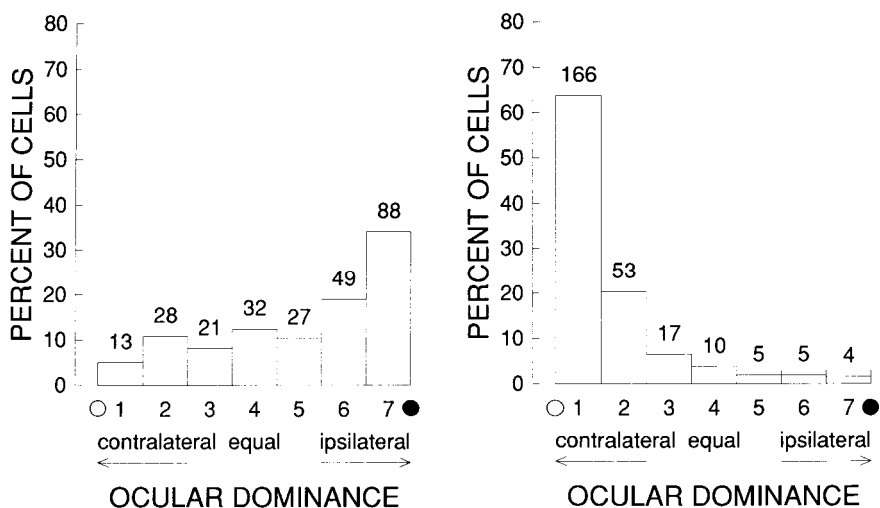


Figure 16-7. Ocular dominance histograms compiled from single unit responses in area 17. Monocular eyelid closures were performed in different animals either ipsilateral or contralateral to the muscimol-infused hemisphere. Results are plotted as if the eyelid sutured was always ipsilateral to the treated hemisphere and control recordings were obtained from unaffected regions of that hemisphere. That is, responses from single cells were plotted such that an ocular dominance of 1 indicates a cell driven exclusively by the open eye; 4, a cell driven equally by the two eyes; and 7, a cell driven exclusively by the occluded eye. All animals received intracortical muscimol infusions for 8 to 10 days and were monocularly deprived for 5 to 7 days beginning 3 days after the onset of the muscimol infusion. The direction of ocular dominance shift in favor of the occluded eye within the area blocked by the muscimol infusion was the same in all animals tested and opposite to the direction of shift in control areas outside of the blockade. Left: Ocular dominance distribution of 258 visually responsive units recorded within the region of cortex in which discharges had been blocked by muscimol infusion during the period of monocular deprivation. Right: Ocular dominance distribution of 260 visually responsive units recorded in regions of cortex outside of the muscimol-induced blockade, including contralateral control hemisphere as well as unblocked areas anterior to the blocked region. Data from experiments of Reiter and Stryker (1988).

columns did emerge by a self-organizing process like the one we have modeled.

Directly interfering, at a molecular level, with proposed mechanisms of plasticity is another approach of potentially great value. But it is an approach that is also fraught with difficulty because some of the molecular machinery responsible for plasticity may contribute significantly to neuronal activity as well, and alterations of activity may affect plasticity by any of a variety of mechanisms. Recent work on blocking the NMDA receptor (which currently appears to be the most likely molecular candidate for the correlation detector required by a Hebb synapse) has illustrated these difficulties (compare the interpretations of Kleinschmidt, Bear, and Singer 1987 with those of Miller, Chapman, and Stryker 1989). Ideally we should eventually have the molecular tools to interfere with plasticity at a stage beyond that involved with transmembrane currents; such tools could alter plasticity without affecting neural activity.

Could explanations along similar lines also account for aspects of afferent and cortical organization other than the ocular dominance columns? What about the refinement of topographic maps, the formation in some species of on/off patches, and the organization of ocular dominance columns? Malsburg (1979), Fraser (1980), and others have modeled map refinement and binocular segregation in the retinotectal system using similar principles, and the experiments of Constantine-Paton and her associates (reviewed in Constantine-Paton, Kline, and Debski 1990) provide strong support for the operation of similar principles in that system. In Miller's recent models (1989, and in preparation), interactions among cortical simple cells and between them and their *on*-center and *off*-center inputs can give rise to an arrangement of orientation columns and a partial segregation of *on* and *off* afferents similar to the arrangement observed experimentally. Finally, Shatz and Stryker (1988) have presented evidence that neural activity is essential for the segregation of the two eyes' inputs to form different layers of the lateral geniculate nucleus.

Each of these phenomena appears individually to be explicable in terms of an activity-dependent reorganization of afferents. One might well imagine that the different patterns of activity present at different stages of development could use similar mechanisms of synaptic plasticity to give rise to these different forms of organization, each building on organization generated previously or at prior stages of the visual system. At early stages, and certainly *in utero* and before eye-opening, only intrinsic activity would be present, but at later times, visual inputs might stimulate the patterns of activity relevant to normal development and plasticity. Such mechanisms might be widespread in the developing central nervous system. To devise and test a comprehensive explanation of how all of these sorts of reorganization take place in the same population of afferents is a challenge for the future.

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