

Experimental and Theoretical Studies of the Organization of Afferents to Single Orientation Columns in Visual Cortex

M.P. STRYKER, B. CHAPMAN, K.D. MILLER, AND K.R. ZAHS

Department of Physiology and Neuroscience Graduate Program, University of California, San Francisco, California 94143-0444

In the visual cortex, as in other neocortical areas in mammals, neuronal response properties are arranged in columns. Cortical columns were described in the earliest experiments of Hubel and Wiesel (1962), who demonstrated that all of the neurons within each radial column in the primary visual cortex respond selectively to elongated edges of a particular angle or orientation. Since then, a number of visual response properties, in addition to selectivity for stimulus orientation, have been found to be shared by the neurons within single cortical columns. 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 neurons in a particular column will tend to respond more strongly to one eye than to the other eye; and (in many species) for *on- or off-center type*, in that the neurons within a column will tend to respond better to bright stimuli than to dark stimuli, or vice versa. Neighboring columns differ from one another in a systematic fashion, generally in a manner that makes changes in response properties as gradual and progressive as possible as one proceeds from column to column in the tangential direction. Thus, the columns of the visual cortex are precisely organized both radially and tangentially with respect to three (or, in many species, all four) of the response properties noted above.

To understand how this organization arises in development, we must know something about the anatomical connections responsible for these columns. The structural basis for the organization of topography and ocular-dominance columns has been reasonably well understood for more than a decade (Hubel et al. 1977). Direct anatomical and physiological experiments have revealed that topography and ocular-dominance columns are not merely products of intracortical circuitry. Instead, the major afferent input to the visual cortex from the lateral geniculate nucleus is precisely ordered with respect to topography and ocular dominance. For the ocular dominance columns, at least, the progressive reorganization of this afferent pathway in development appears to be the mechanism by which the orderly arrangement of cortical columns is established. Relatively simple mechanisms of activity-dependent synapse rearrangement can account for the principal features of afferent organization with respect to

topography and ocular-dominance columns, and the plasticity exhibited by the developing visual cortex is consistent with the existence of such mechanisms (for review, see Miller and Stryker 1990).

Approaches to the Microcircuitry of Cortical Orientation Selectivity

The structural basis of the orientation columns has remained elusive and difficult to establish with confidence. The original model of 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. Figure 1 shows the circularly symmetric receptive field of an *on-center* geniculate neuron at the top left, with locations in the center giving *on* responses marked with closed plus signs and locations in the surround giving *off* responses marked with open minus signs. At the right are shown the overlapping receptive fields of four such geniculocortical afferents that are aligned at an angle of about 40° from the vertical. The hypothesis regarding the afferent convergence that produces simple-cell receptive fields is illustrated by the dotted axons of these four geniculate cells, terminating on a single stellate neuron in the visual cortex. The dashed rectangle indicates the size and position of an optimal bright-bar stimulus for the hypothesized cell. 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 (Creutzfeldt et al. 1974; Sillito 1975) 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 orientation columns, making them fundamentally different from the other types of cortical columns.

The Hubel and Wiesel (1962) model was supported by several lines of evidence. First, Hubel and Wiesel noted that the major geniculate input terminated most heavily in layer IV and, to a much lesser extent, in layer VI. These were precisely the layers in which cells with simple-type receptive fields were found. The structure of the simple-cell receptive field was readily explicable

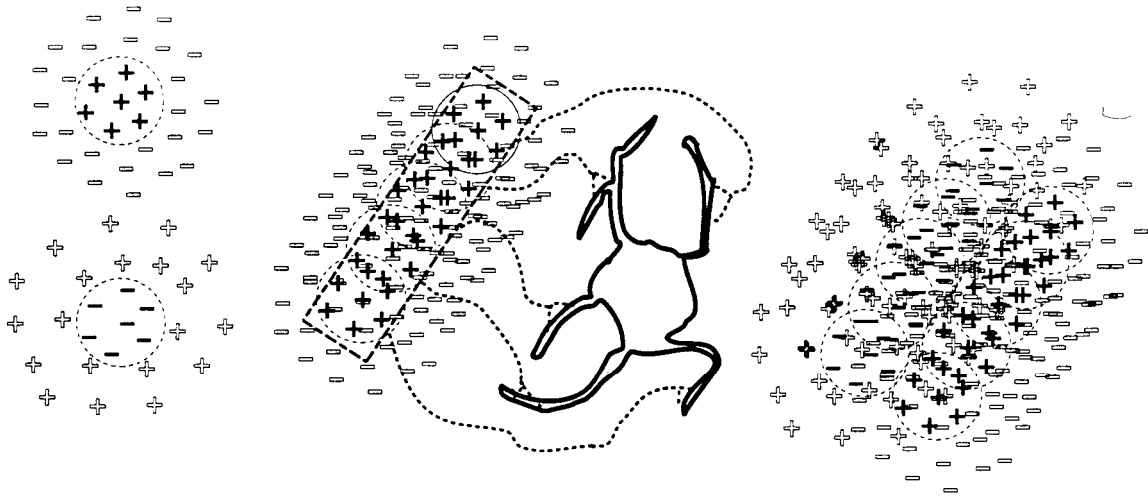


Figure 1. Original model for neuronal circuitry underlying cortical orientation selectivity redrawn with changes from Hubel and Wiesel (1962). (*Left*) Receptive fields of two lateral geniculate nucleus neurons, an *on*-center cell above and an *off*-center cell below. Responses of the cells' center mechanism are indicated with closed pluses or minuses; responses of the cells' surround mechanism are indicated with open pluses or minuses. Pluses indicate responses to light onset or to sustained local brightness; minuses indicate responses to light offset or to sustained local darkness. (*Center*) Proposed convergence of five geniculocortical afferents (the receptive fields are identical to those illustrated at left and are aligned in the visual field) onto a cortical simple cell to endow that cell with selective responses to bars or edges of light oriented at approximately 40° clockwise from the vertical. The optimum size for a light bar projected onto the simple-cell's receptive field is indicated by the dashed rectangle; the hypothesis is that this rectangle also activates the geniculocortical afferents in the manner illustrated, falling simultaneously on all their centers. Axons (dashed lines) of the geniculocortical afferents are hypothesized to make synaptic connections onto the cortical stellate cell shown in the right half of the center panel. Note the parallel arrangements of areas responsive to light onset or light offset in the cortical receptive field. (*Right*) A second kind of simple cell hypothesized to receive inputs from *on*- and *off*-center geniculocortical afferents that occupy parallel rows in the visual field.

by the hypothesis that it received convergent input from a collection of geniculocortical afferents whose receptive fields were aligned. The spatially separate *on* and *off* areas of simple-cell receptive fields would then correspond to the *on* and *off* areas of the receptive fields of their geniculate inputs. Responses to the separate *on* and *off* areas appeared to summate more or less linearly, so that the optimal *on* stimulus was one that filled all of the *on* regions simultaneously with minimal intrusion into the *off* regions, and vice versa for *off* stimuli. All of these findings were consistent with the Hubel and Wiesel model.

The orientation-selective cells that predominated in the other layers of the cortex had receptive fields that were termed complex because they could not easily be explained by convergent input from geniculate afferents. Although complex cells were orientation-selective, they commonly responded poorly to flashed lights, and they generally lacked separate *on* and *off* areas whose alignment could account for the preferred orientation. Even when complex cells responded to flashed lights, the optimal stimulus size could not be predicted from (and was usually much smaller than) the areas responsive to small, flashed lights. The properties of complex cells were, however, readily explained by the hypothesis that they received convergent inputs from a collection of simple cells in the same orientation column. This hypothesis accorded with the sparse or absent geniculocortical afferent inputs to the layers of cortex in which complex cells predominate. The struc-

ture of receptive fields, together with the anatomy of afferent pathways, was then seen to be consistent with a hierarchical arrangement in which geniculocortical afferents converge in their major zone of termination on simple cells that themselves provide convergent excitatory input to complex cells up and down the cortical column.

The emphasis in the Hubel and Wiesel (1962) hypothesis was on the pattern of convergence of excitatory inputs consistent with known anatomy that could explain the visual response properties of cortical neurons. An alternative hypothesis for explaining orientation selectivity emphasized the role of inhibitory inputs. The cross-orientation inhibition model assumed that excitatory thalamocortical inputs to cortical cells were not aligned in the visual field with the precision needed to make cortical cells orientation-selective. Instead, the cortical cells were hypothesized not to be selective or to be only weakly selective on the basis of their thalamocortical inputs, and intracortical inhibitory connections between neurons with orthogonal orientation preferences was hypothesized to account for cortical cell orientation specificity (Blakemore and Tobin 1972; Creutzfeldt et al. 1974). The orderly arrangement of cortical columns, with neighboring columns having similar preferred orientations and more distant columns generally having gradually increasing differences in preferred orientation, appeared to be consistent with a simple model in which local corticocortical excitation and more remote corticocortical inhibition would coop-

erate to create or refine orientation selectivity. Such a model is illustrated in Figure 2, which shows a hypothetical surface view of a 1.6-mm square of visual cortex. The bold lines and stippled figures indicate neuronal responses as a polar function of stimulus orientation in each of nine different cortical columns, four of which are selective for the same orientation as the central one and four of which are selective for the orthogonal orientation. The synaptic connections hypothesized in this model are illustrated as well; when the corticocortical inputs illustrated are active, orientation selectivity is made more precise. Orientation selectivity is minimal or absent without inhibitory inputs from columns representing orthogonal orientations (for details, see Fig. 2).

Experimental tests of the cross-orientation inhibition model have provided mixed results. The principal experimental finding in support of the cross-orientation inhibition model is the effect of reducing or eliminating

local γ -aminobutyric acid (GABA)-mediated inhibition. Treatment of visual cortex with bicuculline or other pharmacological agents designed to remove intracortical inhibition reduced or eliminated orientation selectivity in the majority of cortical cells (Tsumoto et al. 1979; Sillito et al. 1980; other studies revealed much smaller effects, Pettigrew and Daniels 1973; Albus and Baumfalk 1989; Eysel et al. 1989). In addition, the excitatory regions that were revealed by blocking or reducing corticocortical inhibition did not appear to be elongated parallel to the axis of preferred orientation. Both the reduction of orientation selectivity and the apparently circular excitatory receptive fields were surprising, if one accepts the Hubel and Wiesel (1962) model.

It has not been possible directly to confirm or deny the Hubel and Wiesel and cross-orientation inhibition hypotheses. Each of these hypotheses deals with mi-

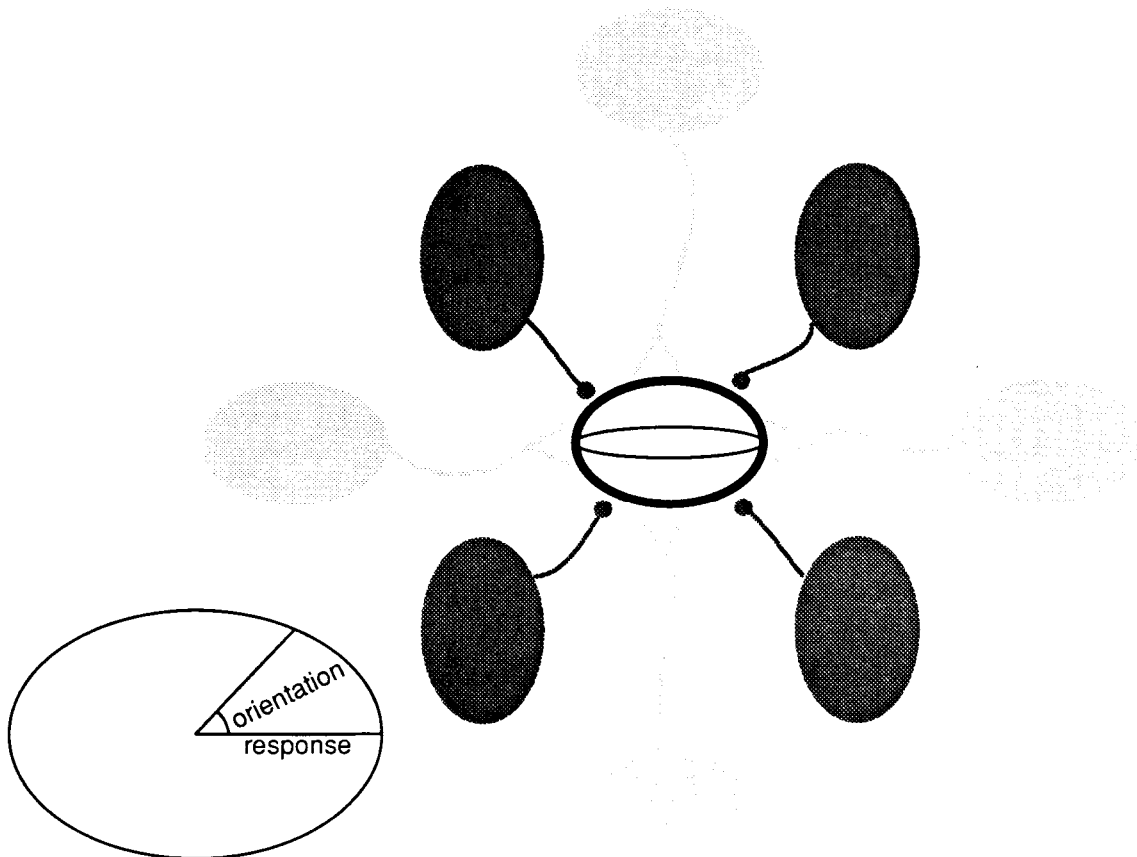


Figure 2. Model for the establishment or refinement of orientation selectivity by an intracortical network. Each oval indicated the weak selectivity for stimulus orientation that would be present in a central region of the cortex and eight neighboring regions if they did not have orientation-selective excitatory and inhibitory corticocortical synaptic connections. The perimeters of the ovals indicate in polar coordinates the response expected from each region as a function of stimulus orientation. The four regions with identical orientation preferences (light stippling, horizontal elongation) are hypothesized to make mutually excitatory connections. The four regions with orthogonal orientation preference (dark stippling, vertical elongation) are hypothesized to make inhibitory connections with neurons in the central region. The very eccentric thin oval in the central region indicates the precise orientation selectivity expected under the assumptions of this model when the corticocortical connections are active and effective. The initial selectivity may be hypothesized to result from asymmetric convergence of *on*- and *off*-center thalamocortical inputs (Heggelund 1986), or it may be hypothesized to be vanishingly small (and perhaps a consequence of the ellipsoidal nature of afferent receptive fields, as proposed by Vidyasagar and Urbas [1982], and Shou and Leventhal [1989]), so that the network bootstraps itself over the course of a few seconds through stages of increasing selectivity.

cat (Law et al. 1988). In intact cortex, one can rarely record isolated electrical signals of more than one or two geniculocortical afferents in a single vertical penetration through cortical layer IV. As originally pointed out by Helen Sherk (University of Washington), the factor that prevents isolation of 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 with the intrinsic electrical noise of the microelectrode, since the microelectrode noise can be as little as $5 \mu\text{V}$, whereas afferent spikes are $10\text{--}100 \mu\text{V}$. Instead, it is the ongoing discharge of cortical cells that produces spikes of some hundreds of microvolts that prevents recognition of most of the signals from afferents. We applied drugs to silence the cortical cell discharge and thereby made it routine to record and plot $10\text{--}40$ afferent receptive fields on a single vertical penetration through the visual cortex.

The design of our experiment is illustrated in Figure 3. The procedure was to align a microelectrode so that

it passed down a single orientation column in the primary visual cortex of the ferret. Recordings were made at a series of cortical depths to guarantee this alignment by observing that preferred orientation was the same (or nearly so) throughout all the layers of the cortex. Plots of neuronal response as a function of stimulus orientation, like those shown at the right side of the figure, allowed us accurately to determine the preferred orientation of the cortical cells. In the earlier experiments, the electrode was withdrawn from the cortex, and cortical cells were then silenced by killing them, using superfusion of the excitotoxin kainic acid (Zahs and Stryker 1988). In the later experiments, the electrode was withdrawn to a position in layer III just above the major input to layer IV; the cortical cells were then silenced more quickly and with less damage by superfusing them with muscimol, a potent analog of the inhibitory neurotransmitter, GABA, that acts on the postsynaptic GABA_A receptors to inhibit all cortical neurons. Once the cortical cells were silent, the microelectrode was advanced again slowly into and through layer IV, where the action potentials of many

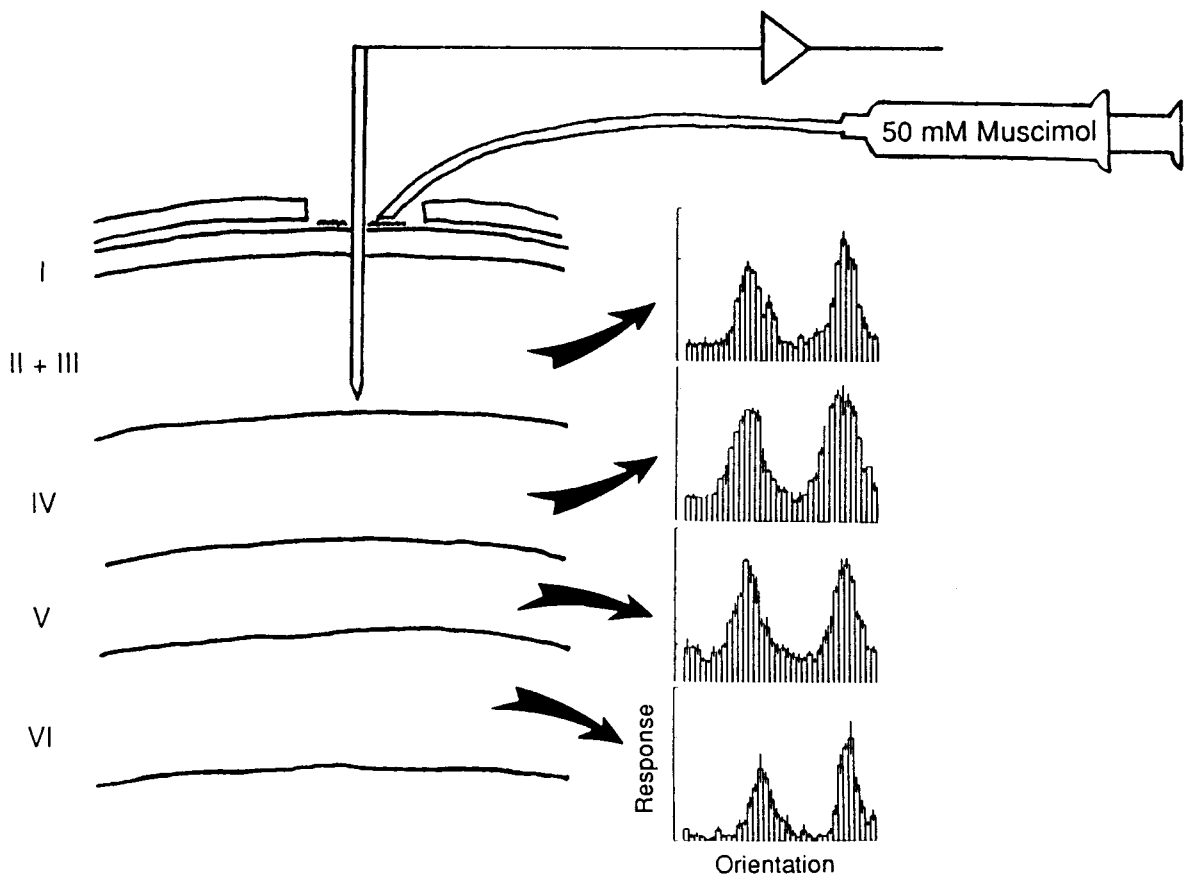


Figure 3. Experimental setup for study of Chapman et al. (1991) illustrating cortical cell orientation-tuning histograms. A radial microelectrode penetration through the depth of cortical area 17 is shown. Orientation-tuning histograms for four single-unit recordings from cells located at the end of the arrow's tails are shown on the right. Each histogram shows the mean response in spikes per second to three presentations of 36 randomly interleaved orientations of moving light bars swept across the cell's receptive field. Orientation conventions are the same as those described in Fig. 2. After these recordings were made, the electrode was withdrawn to approximately the depth shown, just above layer IV. Muscimol (50 mM) was then superfused onto gelfoam surrounding the electrode for several hours to silence cortical cell activity prior to advancing the electrode again down through layer IV to record the responses of geniculocortical afferents.

afferent single units were individually discriminable. These units had visual response properties identical to those of the 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 4 shows the results of this experiment for three cases. In the cases illustrated, the afferent receptive fields, shown as ellipses, occupied 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. We can examine the degree of elongation of geniculocortical afferent input to a typical orientation column by plotting the entire collection of geniculocortical afferent receptive field centers from the 18 such experiments that we performed, after rotating the sample from each penetration by an angle that puts the preferred orientation of the cortical cells at the horizontal. This universe of geniculocortical input, shown in Figure 5, gives our best estimate of the coverage of the visual field by the inputs to a single orientation column (plotted as if it were a column selective for the horizontal orientation). The number of geniculate inputs illustrated is of the same order as Martin's (1988) estimate of the true number of geniculocortical afferents that terminate around a single thin column in the cat's visual cortex. In any one experiment, of course, we saw only about 5–10% of the number illustrated, and our analysis depends on the assumption that the sample obtained in this experiment is a random sample from the larger universe of afferent inputs.

A quantitative Monte-Carlo analysis of the individual penetrations showed that the afferent receptive fields were significantly elongated with better than 90% confi-

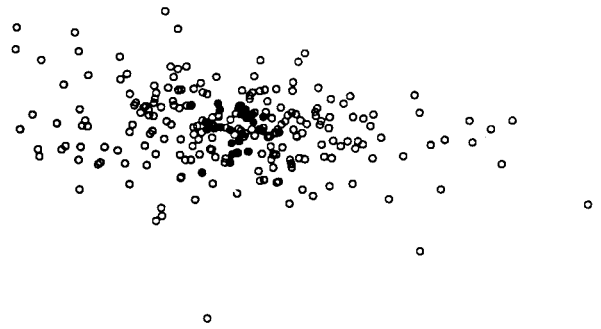


Figure 5. A universe of afferent receptive field positions was constructed from the 18 afferent receptive field arrays obtained in Chapman et al. (1991). Afferent receptive field locations were normalized for magnification factor by calculating the mean radius of the receptive fields encountered in each penetration and then multiplying the distance of each receptive field center from the center of the array by the average mean radius for all penetrations divided by the mean radius for that particular penetration. All the arrays were placed in register so that their geometric centers were superimposed, and they were individually rotated by an amount that rotated the preferred orientation of their associated cortical cell to the horizontal orientation. Afferent receptive field centers (not the whole fields) are shown. (○) Receptive field centers from 16 penetrations in which afferents were significantly aligned; (●) unaligned afferent arrays that were not significantly aligned (encountered in two penetrations). This universe represents our best estimate of the extent of afferent input to a single orientation column. Note the similarity to the central simple cell shown in Fig. 1.

dence in 16 of the 18 experiments 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 illustrated for these 16 cases in Figure 6. Although there are three cases of mismatches by as much as 25°, overall, the matches are good, as indicated by the proximity of the data points to the line of the

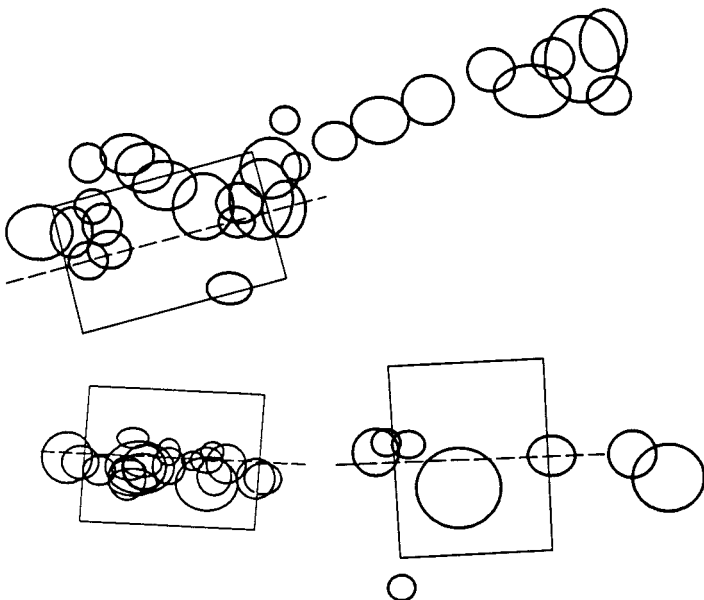


Figure 4. Receptive fields of cortical cells and geniculocortical afferents recorded in three microelectrode penetrations using the techniques illustrated in Fig. 3. On-center afferents are shown as solid ovals. For each penetration, the receptive field of a cortical cell recorded at the top of layer IV is shown (rectangle), with its preferred orientation, determined from its orientation-tuning histogram (dashed line). Note the alignment of the collection of afferent receptive fields in each case with the preferred orientation of the cortical neuron.

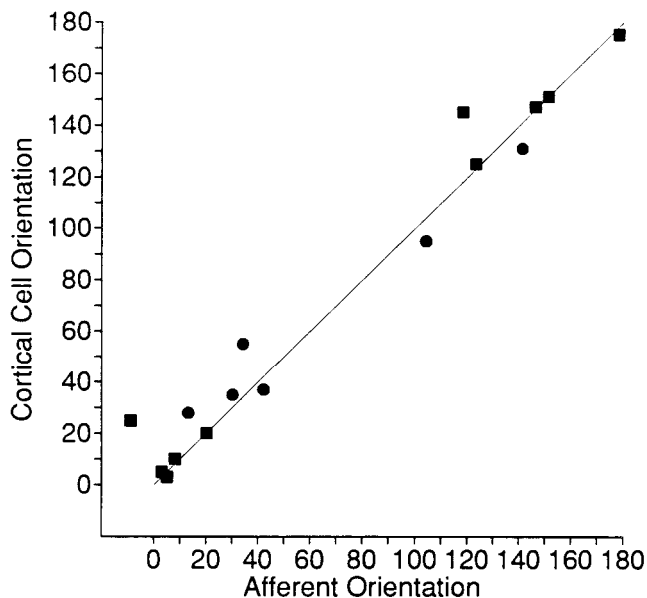


Figure 6. Correspondence between the cortical cell orientation preference and the angle of the principal axis of afferent receptive field arrays. Orientations are plotted following the normal mathematical conventions for angles: Zero degrees represents horizontal, with other orientations measured counterclockwise from the horizontal orientation. (■) Data collected under the blind protocol; (●) data collected when the experimenter plotting afferent receptive fields knew the orientation preference of the cortical cells at that site. The diagonal line ($x = y$) indicates the predicted result if cortical and afferent best orientations matched perfectly. (Data from Chapman et al. 1991.)

prediction of perfect agreement between the orientation of the collection of 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 purely by 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 early in development by some intracortical mechanism, after which afferent terminals were allowed to refine or stabilize in a manner that depends on the correlation between cortical and afferent activity. This possibility is consistent with the early emergence of periodic patchy corticocortical connections reminiscent of those that in adults connect columns of like orientation selectivity (Luhmann et al. 1986; Gilbert and Wiesel 1989; Callaway and Katz 1990). Thus, the finding of orientation specificity in the array of geniculocortical afferent input to a single orientation column in adult animals does 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.

Mechanisms of Geniculocortical Afferent Organization in Development

The earliest features of central nervous system organization, including 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, all appear to be governed by molecular mechanisms of specificity, and all take place normally in the absence of neuronal activity (for review, see Harris and Holt 1990). Thalamocortical organization does not appear to violate these general rules, insofar as they are understood. A special feature of thalamocortical organization is the subplate zone of the cortex, which contains many neurons that normally die at later stages of development. At least a coarse topographic specificity appears to be present when the afferent arbors finally grow 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). Neurons in the subplate make and receive synaptic connections very early and have been hypothesized to play a pioneer role in the development of corticofugal and corticopetal pathways (McConnell et al. 1989; Ghosh et al. 1990).

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. These phenomena have been studied most intensively in the case of the ocular-dominance columns. 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 (Hubel et al. 1977; Rakic 1977; LeVay et al. 1978, 1980). Ocular-dominance patches then develop by the progressive segregation of these initially overlapping inputs (LeVay and Stryker 1979).

The development of the ocular-dominance columns proceeds abnormally if the normal patterns of neural activity are disrupted. These abnormalities were first evident physiologically. 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 de-

prived 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 the visual cortex, appeared to be nearly normal (Wiesel and Hubel 1963b). Thus, neonatal monocular visual deprivation produces a rapid and powerful 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. These changes are produced most powerfully during a sensitive period in early life at and slightly after the time that major rearrangements of geniculocortical afferent arbors would be taking place in normal development. Studies of binocular visual deprivation and discordant binocular inputs suggest that the plasticity is a result of a competitive interaction between the geniculocortical afferents serving the two eyes that depends on patterns of neural activity (for review, see Stryker 1990). The plasticity produced by various visual deprivation procedures may thus represent the outcome of normal developmental mechanisms in the presence of abnormal patterns of activity.

Consistent with this notion is the fact that ocular-dominance columns do not form at all when neural activity is blocked (Stryker and Harris 1986). Instead of segregating, geniculocortical afferents appear to remain in their infantile state of complete overlap. 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 et al. 1980) and in cats raised 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. Even in darkness, however, there is information in the pattern of maintained activity of retinal ganglion and geniculate cells. Neighboring ganglion cells of the same center type tend to fire together over time periods of a millisecond to a few tens of milliseconds in adult cats (Mastrorade 1983), and activity is also correlated over longer time scales (Levick and Williams 1964; Rodieck and Smith 1966). 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-Resta 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.

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. Such a rule could also explain the effects of early monocular and binocular visual deprivation, discordant binocular inputs, and the effects of binocular activity blockade.

A number of experiments were designed to test crucial assumptions of the Hebb synapse mechanism. A difference between the neural activity in the two eyes, but not necessarily vision, was found to be necessary for ocular-dominance plasticity (Chapman et al. 1986), 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 were controlled by the timing of neural activity. Reiter et al. (1986) then showed that blocking both pre- and postsynaptic activity in the cortex completely prevented plasticity, thereby confirming the cortex as the crucial locus of the changes in development. To investigate whether presynaptic geniculocortical afferent activity, postsynaptic cortical activity, or both (as postulated by a Hebb synapse mechanism) are important in ocular-dominance plasticity, Reiter and Stryker (1988) selectively blocked postsynaptic activity during a period of monocular deprivation by pharmacologically inhibiting the cortical cells. In the region of cortex in which postsynaptic action potentials were blocked 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, exactly as predicted by a Hebb synapse model, since 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. The role of the postsynaptic cells appears therefore to be crucial because identical patterns of afferent activity produced opposite types of plasticity, depending on whether the postsynaptic cortical cells were able to respond to their inputs.

Mathematical Model of Ocular-dominance Columns

By explaining, at a qualitative level, how a simple neural mechanism could produce precise patterns of connections in development, the Hebb rule was tre-

mendously 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 would be necessary, what pattern of initial connections was possible, and what the role of intracortical interconnections would be in the process. Finally, a genuine model of development should allow one to predict the widths of the ocular-dominance columns from the input parameters.

Miller et al. (1989) constructed and analyzed a mathematical model of the development of ocular-dominance columns capable of addressing such quantitative questions. The model incorporates a minimal set of features consistent with the experiments above: (1) two sets of afferents, corresponding to the two eyes or to the layers of the LGN that serve the two eyes, that initially make widespread overlapping connections, some of which become ineffective or are removed in development; (2) correlated activity among afferents serving one eye, and the absence of correlation between the two eyes; and (3) postsynaptic activity in the cortex that is communicated via intracortical synaptic connections. These features are described by model parameters A (for the geniculocortical afferent terminal *arbor*), C (for *correlations* in the patterns of discharge activity), and I (corticocortical *interaction*). The strength *S* of each synaptic connection between the afferents and the cortical cells was hypothesized to change by a Hebb rule, and the model was carried forward in time from its initial state of coarsely topographic but otherwise random and near-uniform connections.

This model was analyzed mathematically, and the evolution of its neural connections was simulated in the computer. The model robustly reproduces many of the biological phenomena described above. Ocular-dominance columns indistinguishable in form from real ones were reproduced 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 were 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 such as that of the developing visual cortex can, at least in principle, account for the rich structure of ocular-dominance patches observed biologically. Mathematical analysis revealed 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 for a spacing that was too large, 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 was 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.

Each of the three parameters A, C, and I of the model can be, and has been to a limited extent, measured by straightforward anatomical and physiological experiments. The ocular-dominance column spacings observed experimentally fall well within the range of the spacing predicted by the model from our best experimental estimates of these three model parameters (for discussion, see Miller 1990a; Miller and Stryker 1990).

One surprising finding from the mathematical analysis was that the same mathematics could be used to model development under any of a wide range of biological mechanisms of synaptic plasticity. In fact, all of the biologically plausible mechanisms of synaptic plasticity that, to our knowledge, had been proposed to underlie ocular dominance plasticity could be described in the same mathematical framework that we had used to analyze the Hebb synapse model. Therefore all of the mechanisms could with appropriate values of the parameters equally well mimic biological development. 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 play no role in synaptic plasticity (Miller et al. 1989b). The difference between the model's treatment of the various hypotheses is 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 to produce ocular-dominance columns of the experimentally observed spacing. However, it does not tell us the biological mechanism by which such interactions are effected. The *quantitative* description obtained from the mathematical model allows one to measure experimentally the value of the model parameters under different assumptions about biological mechanisms of plasticity and to rule out most proposed mechanisms on the basis that they would not predict ocular-dominance patches of the observed spacing. If a proposed mechanism of synaptic plasticity does not operate in development, it is unlikely that the measured values of the model parameters 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.

Model of the Development of Orientation Columns

Our studies of the ocular-dominance columns indicate that a quite general mechanism of synaptic plasticity

ty in conjunction with the known architecture of the developing cortex and initially rather diffuse patterns of neural connections that are only statistically regular can give rise to eye-specific patterns of geniculocortical afferent connections such as those observed biologically. What sort of explanation could then be offered for the other aspects of afferent and cortical organization, such as the refinement of topographic maps, the formation in some species of *on/off* patches, and the organization of orientation columns? Perhaps surprisingly, it now appears that all of these phenomena could be produced by the same mechanisms of plasticity, responding to changing patterns of neural activity and connections as development proceeds. von der Malsburg (1979), Fraser (1980), and other investigators have modeled map refinement and binocular segregation in the retinotectal system using similar principles, and the experiments from the Constantine-Paton and Udin laboratories, among others (for review, see Constantine-Paton et al. 1990), provide strong support for the operation of similar principles in that system.

Miller (1989, 1990b, and in prep.) has recently proposed a model for the development of orientation columns in which the pattern of activity in *on*-center and *off*-center geniculocortical afferents, together with corticocortical interactions and arbor functions such as those in the ocular-dominance column model, can give rise to an arrangement of orientation columns and a partial segregation of *on* and *off* afferents such as that observed experimentally. This model is illustrated in Figure 7. The model is nearly identical formally to the ocular-dominance column model described above with one major exception, the correlation structure of *on*-center and *off*-center geniculocortical afferent activity. The hypothesis is that the activities of afferents of the same center type are highly correlated when their receptive fields are very near, but as the separation of receptive field centers increases, they become anticorrelated with one another. This is illustrated for two *on*-center afferents in the middle panel of Figure 8. When the receptive fields of the afferents are close to one another, the two centers overlap, and they will be driven in near synchrony by the same visual stimulus or spontaneous retinal input. When the receptive fields of the two afferents are separated by a greater distance, note that the *off*-surround of each afferent lies on top of the *on*-center of the other. In this situation, the afferent activities will then be anticorrelated, since any visual stimulus or localized spontaneous retinal activity that excited one of the afferents would inhibit the other. At greater distances still, the afferents would be uncorrelated. Note further what happens with two afferents of opposite center type, illustrated in the lower panel of Figure 8. When the receptive field centers of *on* and *off* afferents overlies one another, their activities will, of course, be anticorrelated. However, when the two receptive fields of opposite center type are separated by one center-diameter, the *on*-center of the one afferent lies on the *on*-surround of the other, and the *off*-surround of the one afferent is superimposed on the

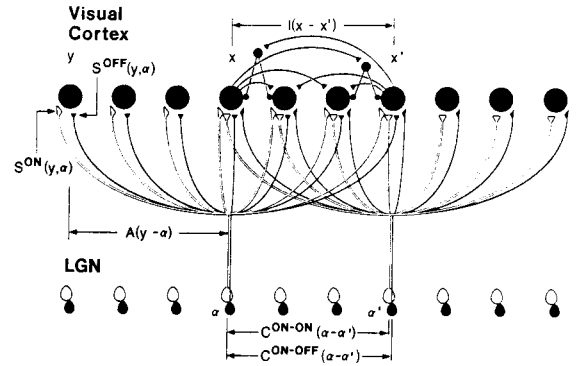


Figure 7. Elements of the model of Miller (1989, 1990, and in prep.) for the development of cortical orientation selectivity. (1) Afferents from the lateral geniculate nucleus (LGN) project to the visual cortex. *On*-center and *off*-center afferents (open and closed ellipses, respectively) make equivalent initial projections to the cortex. Synaptic interconnections among cortical cells (●) may be either excitatory (more local, direct connections) or inhibitory (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 α is given by the arbor function $A(y - \alpha)$, which is zero outside the arbor radius. (3) The degree of correlation in firing among incoming afferents from retinotopic positions α and α' is represented by the correlation functions $C^{\text{ON-OFF}}(\alpha - \alpha')$ and $C^{\text{ON-ON}}(\alpha - \alpha')$ ($C^{\text{OFF-OFF}}$ is present but is not illustrated), where $C^{\text{ON-OFF}}(\alpha - \alpha')$ gives the correlation between an *on*-center afferent from α and an *off*-center afferent from α' , etc. (4) Each synapse has a physiological strength that varies with time during development. This is illustrated by the functions $S^{\text{ON}}(y, \alpha)$ and $S^{\text{OFF}}(y, \alpha)$. (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 $I(x - x')$ that may be both excitatory and inhibitory at different distances. See text for discussion.

off-center of the other. The activities of the two opposite-type afferents will therefore be correlated with one another at this receptive-field separation, since a visual stimulus or spontaneous event in the retina would drive the two in synchrony.

The result of this peculiar correlation structure can be understood as favoring the development of traditional simple-cell receptive fields, such as that illustrated in Figure 1, with parallel rows of *on*-center and *off*-center afferents providing inputs to single cells. Computer simulations of the model with this correlation structure, starting from an initial state of diffuse, coarsely topographic connections without elongated patterns of afferent input or any organization of cortical orientation, produce patterns of tangential organization of orientation columns that resemble the ones observed in deoxyglucose or optical images of the orientation columns in monkeys and cats (Hubel and Wiesel 1963a; Hubel et al. 1978; Schoppman and Stryker 1981; Singer 1981; Blasdel and Salama 1986; Grinvald et al. 1986; Lowel et al. 1988; Redies et al. 1990). The model exhibits elongated collections of *on*- and *off*-center inputs to single orientation columns such

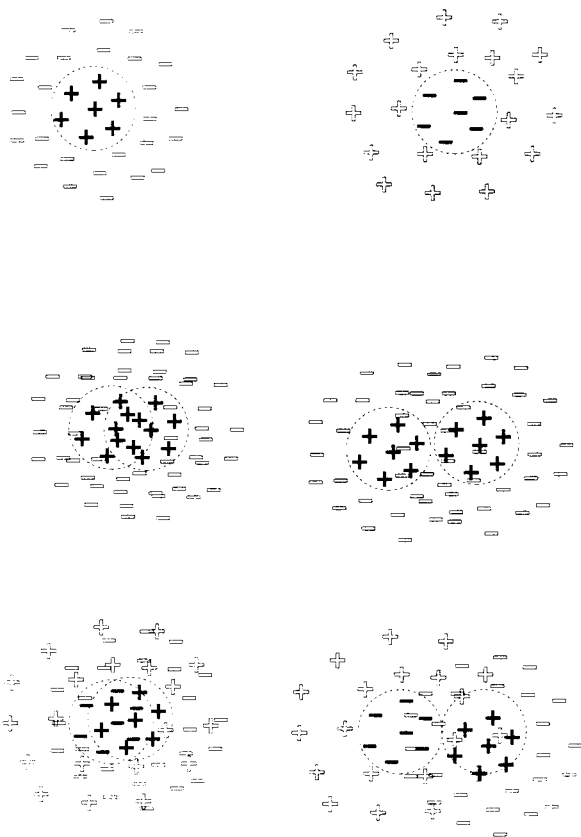


Figure 8. *On-* and *off-center* geniculocortical afferent receptive fields drawn individually (*top left* and *top right*) and with varying extents of superimposition (*below*). Conventions for symbols are the same as those in Fig. 1. (*Middle*) Two *on-center* receptive fields close together and at a separation of one receptive field center diameter. Note that cells will be activated simultaneously by light falling on their common center on the left-hand side of the figure but that they will rarely be activated together when their receptive fields are separated by the distance indicated on the right-hand side. (*Bottom*) One *off-center* and one *on-center* afferent at small separations to left and a separation of one receptive-field diameter at right. Note that these two cells will be driven in synchrony by visual stimuli when their receptive fields are disposed as indicated on the right-hand side of the bottom panel. This figure illustrates the synergistic action of opposite center types at appropriate receptive field separations. Note the similarity of the arrangement shown at the bottom right-hand side of this figure to the right-hand side simple cell illustrated in Fig. 1.

as those observed in Figure 4. The model also exhibits a patchy organization of regions dominated by *on-* and *off-center* inputs such as that described by Zahs and Stryker (1988) in ferret visual cortex.

In the orientation model, the periodicity of the pattern that develops depends on both the corticocortical interaction function I and the afferent correlation function C . In the ocular-dominance model, we noted above that the afferent correlation function C was merely permissive; as long as it was sufficiently broad, it played no role in setting the size of the ocular-dominance patches. This difference between the two outcomes is consistent with the different spacings ob-

served experimentally for orientation and ocular-dominance columns in the same cortex (Hubel et al. 1978; Blasdel and Salama 1986; Grinvald et al. 1986; Lowel et al. 1988).

This model has as yet little direct experimental support, but it is straightforward to test. Predictions of such a model are that orientation columns should not develop if activity of the cortex or of the afferents is blocked or if the correlation structure of the *on-* and *off-center* afferents is dramatically altered, for example, by chronic electrical stimulation that excites both kinds of afferents in synchrony. If these predictions are not borne out, the model must be wrong. As described above, the organization of the orientation columns in the visual cortex of the cat appears to be laid down by the time of the earliest microelectrode recordings made soon after birth and before ocular-dominance columns begin to form (Hubel and Wiesel 1963b). For this reason, we have begun to study the development of orientation columns in the ferret, which is born sufficiently early that one can record from its visual cortex and manipulate activity before orientation-selective responses are present. Orientation selectivity is clearly evident before the time of natural eye opening, and Chapman's preliminary findings suggest that neural activity is essential for the normal development of orientation selectivity. This activity takes place at a time in the animal's life when it would ordinarily live in a subterranean nest in total darkness, similar with respect to visual stimulation to the environment of animals still in utero (Sherk and Stryker 1976). Thus, the nonvisual maintained or "spontaneous" neural activity in the developing visual system may play a role for the cortex such as that suggested for prenatal activity in the formation of layers in the lateral geniculate nucleus (Shatz and Stryker 1988).

CONCLUSIONS

We have seen that the geniculocortical afferent inputs to single-orientation columns mirror and may underlie the specificity of the cortical responses, just as the afferent inputs to the ocular-dominance columns do. Models of the development of specificity in afferent connections and cortical responses are consistent with a unifying notion that the same mechanisms of synaptic plasticity give rise to all four aspects of cortical organization discussed above: refined topography, ocular-dominance columns, *on/off* patches, and orientation columns. Although we will not have conclusive evidence for this hypothesis until we understand the cellular and molecular 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 columns with dramatically abnormal spacing by selectively perturbing corticocortical synaptic interactions, we would have compelling evidence that the columns did emerge by a self-organizing process such as the one we have modeled.

Directly interfering, at a molecular level, with proposed mechanisms of plasticity is another approach of potentially great value. However, 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 investigations on blocking the *N*-methyl-D-aspartate receptor (which currently appears to be the most promising molecular candidate for the correlation detector required by a Hebb synapse) have illustrated these difficulties (compare the interpretations of Kleinschmidt et al. 1987 with those of Miller et al. 1989a). Eventually, we should have the molecular tools to interfere with plasticity at a stage beyond that of blocking transmembrane currents. By altering plasticity without affecting neural activity, such tools will allow us to determine whether the same mechanisms of plasticity give rise to the various forms of afferent and cortical organization.

The combination of experimental studies of the development of cortical and afferent organization in vivo with theoretical studies of the classes of mechanisms that could account for such development has proved powerful. With the addition of these of molecular and cellular approaches in vitro, the future promises a genuine understanding of how the richness of cortical organization responsible for our perception and behavior arises.

ACKNOWLEDGMENTS

The studies reviewed here were carried out with the support of the National Eye Institute, the System Development Foundation, and the Human Frontiers Science Program.

REFERENCES

- Albus, K. and U. Baumfalk. 1989. Bicuculline induced changes in excitability and orientation selectivity of striate cortical neurones. *Soc. Neurosci. Abstr.* **15**: 324.
- Blakemore, C. and E.A. Tobin. 1972. Lateral inhibition between orientation detectors in the cats visual cortex. *Exp. Brain Res.* **15**: 439.
- Blasdel, G.G. and G. Salama. 1986. Voltage-sensitive dyes reveal a modular organization in monkey striate cortex. *Nature* **321**: 579.
- Callaway, E.M. and L.C. Katz. 1990. Emergence and refinement of clustered horizontal connections in cat striate cortex. *J. Neurosci.* **10**: 1134.
- Changeux, J.P. and A. Danchin. 1976. Selective stabilization of developing synapses as a mechanism for the specification of neuronal networks. *Nature* **264**: 705.
- Chapman, B., K.R. Zahs, and M.P. Stryker. 1989. Receptive fields of geniculocortical afferents tend to be aligned along preferred orientation of cortical cells. *Soc. Neurosci. Abstr.* **15**: 1055.
- . 1991. Relation of cortical cell orientation selectivity to alignment of receptive fields of geniculocortical afferents that arborize within a single orientation column in ferret visual cortex. *J. Neurosci.* **11**: (in press).
- Chapman, B., M.D. Jacobson, H.O. Reiter, and M.P. Stryker. 1986. Ocular dominance shift in kitten visual cortex caused by imbalance in retinal electrical activity. *Nature* **324**: 154.
- Constantine-Paton, M., H.T. Cline, and E. Debski. 1990. Patterned activity, synaptic convergence, and the NMDA receptor in developing visual pathways. *Annu. Rev. Neurosci.* **13**: 129.
- Creutzfeldt, O.D., U. Kuhnt, and L.A. Benevento. 1974. An intracellular analysis of visual cortical neurones response to moving stimuli: Response in cooperative neural network. *Exp. Brain Res.* **21**: 251.
- DesRosiers, M.H., O. Sakurada, T. Jehle, M. Shinohara, C. Kennedy, and L. Sokoloff. 1978. Demonstration of functional plasticity in the immature striate cortex of the monkey by means of [¹⁴C]-deoxyglucose method. *Science* **200**: 447.
- Eysel, U.T., J.M. Crook, and H.F. Machemer. 1989. Orientation tuning in cat striate cortex involves intracortical suppression of cross-orientation excitation. *Soc. Neurosci. Abstr.* **15**: 324.
- Ferster, D. 1986. Orientation selectivity of synaptic potentials in neurons of cat primary visual cortex. *J. Neurosci.* **6**: 1284.
- . 1987. Origin of orientation-selective EPSPs in simple cells of cat visual cortex. *J. Neurosci.* **7**: 1780.
- Fraser, S.E. 1980. Differential adhesion approach to the patterning of nerve connections. *Dev. Biol.* **79**: 453.
- Gilbert, C.D. and T.N. Wiesel. 1989. Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. *J. Neurosci.* **9**: 2432.
- Ghosh, A., A. Antonini, S.K. McConnell, and C.J. Shatz. 1990. Requirement for subplate neurons in the formation of thalamocortical connections. *Nature* **347**: 179.
- Grinvald, A., E. Lieke, R.D. Frostig, C.D. Gilbert, and T.N. Wiesel. 1986. Functional architecture of cortex revealed by optical imaging of intrinsic signals. *Nature* **324**: 361.
- Harris, W.A. and C.E. Holt. 1990. Early events in the embryogenesis of the vertebrate visual system: Cellular determination and pathfinding. *Annu. Rev. Neurosci.* **13**: 155.
- Hata, Y., T. Tsumoto, H. Sato, K. Hagihara, and H. Tamura. 1988. Inhibition contributes to orientation selectivity in visual cortex of cat. *Nature* **335**: 815.
- Hebb, D.O. 1949. *The organization of behaviour*. Wiley, New York.
- Heggelund, P. 1986. Quantitative studies of the discharge fields of single cells in cat striate cortex. *J. Physiol.* **373**: 277.
- Hubel, D.H. and T.N. Wiesel. 1962. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol.* **160**: 106.
- . 1963a. Shape and arrangement of columns in cat's striate cortex. *J. Physiol.* **165**: 559.
- . 1963b. Receptive fields of cells in striate cortex of very young, visually inexperienced kittens. *J. Neurophysiol.* **26**: 994.
- . 1970. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* **206**: 419.
- Hubel, D.H., T.N. Wiesel, and S. LeVay. 1977. Plasticity of ocular dominance columns in monkey striate cortex. *Philos. Trans. R. Soc. Lond. B* **278**: 377.
- Hubel, D.H., T.N. Wiesel, and M.P. Stryker. 1978. Anatomical demonstration of orientation columns in macaque monkey. *J. Comp. Neurol.* **177**: 361.
- Kleinschmidt, A., M.F. Bear, and W. Singer. 1987. Blockade of "NMDA" receptors disrupts experience-dependent plasticity of kitten striate cortex. *Science* **238**: 355.
- Law, M.I., K.R. Zahs, and M.P. Stryker. 1988. Organization of primary visual cortex (area 17) in the ferret. *J. Comp. Neurol.* **278**: 157.
- LeVay, S. and M.P. Stryker. 1979. The development of ocular dominance columns in the cat. In *Aspects of Developmental Neurobiology Society for Neuroscience Symposia* (ed.

- J.A. Ferrendelli), vol. 4, p. 83. Society for Neuroscience, Bethesda, Maryland.
- LeVay, S., M.P. Stryker, and C.J. Shatz. 1978. Ocular dominance columns and their development in layer IV of the cat's visual cortex: A quantitative study. *J. Comp. Neurol.* **179**: 223.
- LeVay, S., T.N. Wiesel, and D.H. Hubel. 1980. The development of ocular dominance columns in normal and visually deprived monkeys. *J. Comp. Neurol.* **191**: 1.
- Levick, W.R. and W.O. Williams. 1964. Maintained activity of lateral geniculate neurones in darkness. *J. Physiol.* **170**: 582.
- Lowe, S., H.J. Bischof, B. Leutenecker, and W. Singer. 1988. Topographic relations between ocular dominance and orientation columns in the cat striate cortex. *Exp. Brain Res.* **71**: 33.
- Luhmann, H.J., L. Martinez Millan, and W. Singer. 1986. Development of horizontal intrinsic connections in cat striate cortex. *Exp. Brain Res.* **63**: 443.
- Maffei, L. and L. Galli-Resta. 1990. Correlation in the discharges of neighboring rat retinal ganglion cells during prenatal life. *Proc. Natl. Acad. Sci.* **87**: 2861.
- Martin, K.A.C. 1988. The Wellcome prize lecture: From single cells to simple circuits in the cerebral cortex. *Quart. J. Exp. Physiol.* **73**: 637.
- Mastrorarde, D.N. 1983. Correlated firing of retinal ganglion cells I. Spontaneously active inputs to X and Y cells. *J. Neurophysiol.* **49**: 303.
- McConnell, S.K., A. Ghosh, and C.J. Shatz. 1989. Subplate neurons pioneer the first axon pathway from the cerebral cortex. *Science* **245**: 978.
- Miller, K.D. 1989. Orientation-selective cells can emerge from a hebbian mechanism through interactions between ON and OFF center inputs. *Soc. Neurosci. Abstr.* **15**: 794.
- . 1990a. Correlation-based models of neural development. In *Neuroscience and connectionist models* (ed. M.A. Gluck and D.E. Rumelhart), p. 267. Lawrence Erlbaum, Hillsdale, New Jersey.
- . 1990b. Cortical organization of orientation selectivity emerges from interactions between on- and off-center inputs. *Soc. Neurosci. Abstr.* **16**: 798.
- Miller, K.D. and M.P. Stryker. 1990. Development of ocular dominance columns: Mechanisms and models. In *Connectionist modeling and brain function: The developing interface* (ed. S.J. Hanson and C.R. Olson), p. 255. MIT Press, Cambridge, Massachusetts.
- Miller, K.D., B. Chapman, and M.P. Stryker. 1989a. Visual responses in adult cat visual cortex depend on N-methyl-D-aspartate receptors. *Proc. Natl. Acad. Sci.* **85**: 5183.
- Miller, K.D., J.B. Keller, and M.P. Stryker. 1989b. Ocular dominance column development: Analysis and simulation. *Science* **245**: 605.
- Pettigrew, J.D. and J.D. Daniels. 1973. GABA antagonism in visual cortex: Different effects on simple, complex, and hypercomplex neurons. *Science* **182**: 81.
- Rakic, P. 1977. Prenatal development of the visual system in the rhesus monkey. *Philos. Trans. Roy. Soc. Lond. B* **278**: 245.
- Redies, C., M. Diksic, and H. Rimpl. 1990. Functional organization in the ferret visual cortex: A double-label 2-deoxyglucose study. *J. Neurosci.* **10**: 2791.
- Reiter, H.O. and M.P. Stryker. 1988. Neural plasticity without postsynaptic action potentials: Less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited. *Proc. Natl. Acad. Sci.* **85**: 3623.
- Reiter, H.O., D.M. Waitzman, and M.P. Stryker. 1986. Cortical activity blockade prevents ocular dominance plasticity in the kitten visual cortex. *Exp. Brain Res.* **65**: 182.
- Rodieck, R.W. and P.S. Smith. 1966. Slow dark discharge rhythms of cat retinal ganglion cells. *J. Neurophysiol.* **29**: 942.
- Schoppmann, A. and M.P. Stryker. 1981. Physiological evidence that the 2-deoxyglucose method reveals orientation columns in cat visual cortex. *Nature* **293**: 574.
- Shatz, C.J. and M.B. Luskin. 1986. The relationship between the geniculocortical afferents and their cortical target cells during development of the cat's primary visual cortex. *J. Neurosci.* **6**: 3655.
- Shatz, C.J. and M.P. Stryker. 1988. Prenatal tetrodotoxin infusion blocks segregation of retinogeniculate afferents. *Science* **242**: 87.
- Sherk, H. and M.P. Stryker. 1976. Quantitative study of cortical orientation selectivity in visually inexperienced kitten. *J. Neurophysiol.* **39**: 63.
- Shou, T. and A.G. Leventhal. 1989. Organized arrangement of orientation-sensitive relay cells in the cat's dorsal lateral geniculate nucleus. *J. Neurosci.* **9**: 4287.
- Sillito, A.M. 1975. The contribution of inhibitory mechanisms to the receptive field properties of neurones in the striate cortex of the cat. *J. Physiol.* **250**: 305.
- Sillito, A.M., J.A. Kemp, J.A. Milson, and N. Berardi. 1980. A re-evaluation of the mechanisms underlying simple cell orientation selectivity. *Brain Res.* **194**: 517.
- Singer, W. 1981. Topographic organization of orientation columns in the cat visual cortex. *Exp. Brain Res.* **44**: 431.
- Stent, G.S. 1973. A physiological mechanism of Hebb's postulate of learning. *Proc. Natl. Acad. Sci.* **84**: 3936.
- Stryker, M.P. 1986. The role of neural activity in rearranging connections in the central visual system. In *The biology of change in otolaryngology* (ed. R.W. Ruben et al.), p. 211. Elsevier, Amsterdam.
- . 1990. Activity-dependent reorganization of afferents in the developing mammalian visual system. In *Development of the visual system* (ed. D.M.K. Lam and C.J. Shatz), p. 267. MIT Press, Cambridge, Massachusetts.
- Stryker, M.P. and W.A. Harris. 1986. Binocular impulse blockade prevents formation of ocular dominance columns in the cat's visual cortex. *J. Neurosci.* **6**: 2117.
- Tanaka, K. 1983. Cross-correlation analysis of geniculostriate neuronal relationships in cats. *J. Neurophysiol.* **49**: 1303.
- Toyama, K., M. Kimura, and K. Tanaka. 1981. Cross-correlation analysis of interneuronal activity in cat visual cortex. *J. Neurophys.* **46**: 191.
- T'so, D.Y., C.D. Gilbert, and T.N. Wiesel. 1986. Relationships between horizontal interactions and functional architecture as revealed by cross-correlation analysis. *J. Neurosci.* **6**: 1160.
- Tsumoto, T., W. Eckart, and O.D. Creutzfeldt. 1979. Modification of orientation sensitivity of cat visual cortex neurones by removal of GABA mediated inhibition. *Exp. Brain Res.* **34**: 351.
- von der Malsburg, C. 1979. Development of ocularity domains and growth behavior of axon terminals. *Biol. Cybernet.* **32**: 49.
- Wiesel, T.N. and D.H. Hubel. 1963a. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* **26**: 978.
- . 1963b. Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *J. Neurophysiol.* **26**: 978.
- Vidyasagar, T.R. and J.V. Urbas. 1982. Orientation sensitivity of cat LGN neurones with and without inputs from visual cortical areas 17 and 18. *Exp. Brain Res.* **46**: 157.
- Zahs, K.R. and M.P. Stryker. 1988. Segregation of ON and OFF afferents to ferret visual cortex. *J. Neurophysiol.* **59**: 1410.