

- Antarctic O₃ changes were published in the November 1986 supplementary issue of vol. 13 of *Geophysical Research Letters*.
14. S. Solomon, R. R. Garcia, F. S. Rowland, D. J. Wuebbles, *Nature (London)* 321, 755 (1986); M. B. McElroy, R. J. Salawitch, S. C. Wofsy, J. A. Logan, *ibid.*, p. 759; O. B. Toon, P. Hamill, R. P. Turco, J. Pinto, *Geophys. Res. Lett.* 13, 1284 (1986); P. J. Crutzen and F. Arnold, *Nature (London)* 324, 651 (1986).
 15. R. E. Dickinson and R. J. Cicerone, *Nature (London)* 319, 109 (1986); V. Ramanathan, R. J. Cicerone, H. B. Singh, J. P. Kichl, *J. Geophys. Res.* 90, 5547 (1985).
 16. R. Gammon *et al.*, *Atmospheric Ozone 1985* (World Meteorological Organization, Geneva, 1986), chap. 3.
 17. R. F. Weiss, *J. Geophys. Res.* 86, 7185 (1981).
 18. J. D. Mahlman, H. Levy, W. J. Moxim, *ibid.* 91, 2687 (1986).
 19. H. S. Johnston, G. Whitten, J. Birks, *ibid.* 78, 6107 (1973).
 20. H. S. Johnston, *Science* 173, 517 (1971); P. J. Crutzen, *J. Geophys. Res.* 76, 7311 (1971); *Environmental Impact of Stratospheric Flight* (National Academy of Sciences, Washington, DC, 1975).
 21. P. J. Crutzen, I. S. A. Isaksen, G. C. Reid, *Science* 189, 457 (1975).
 22. P. J. Crutzen, *Ambio* 3, 201 (1974); M. B. McElroy, J. W. Elkins, S. C. Wofsy, Y. L. Yung, *Rev. Geophys. Space Phys.* 14, 143 (1976); S. C. Liu, R. J. Cicerone, T. M. Donahue, W. L. Chameides, *Tellus* 29, 251 (1977).
 23. M. J. Molina and F. S. Rowland, *Nature (London)* 249, 810 (1974); *Stratospheric Ozone Depletion by Halocarbons: Chemistry and Transport* (National Academy of Sciences, Washington, DC, 1979).
 24. R. S. Stolarski and R. J. Cicerone, *Can. J. Chem.* 52, 1610 (1974).
 25. D. F. Heath, A. J. Krueger, P. J. Crutzen, *Science* 197, 886 (1977).
 26. I. S. A. Isaksen and F. Stordal, *J. Geophys. Res.* 91, 5249 (1986).
 27. See *Atmospheric Ozone 1985* (World Meteorological Organization, Geneva, 1986), especially chaps. 12–14.
 28. M. P. McCormick, H. M. Steele, P. Hamill, W. P. Chu, T. J. Swisler, *J. Atmos. Sci.* 39, 1387 (1982).
 29. J. D. Mahlman and S. B. Fels, *Geophys. Res. Lett.* 13, 1316 (1986).
 30. J. M. Rodriguez, M. K. W. Ko, N. D. Sze, *ibid.*, p. 1292.
 31. L. T. Molina and M. J. Molina, *J. Phys. Chem.* 91, 433 (1987).
 32. S. Solomon, G. H. Mount, R. W. Sanders, A. L. Schmeltekopf, *J. Geophys. Res.*, in press.
 33. A. J. Hills, R. J. Cicerone, J. G. Calvert, J. W. Birks, *Nature (London)*, in press.
 34. R. L. McKenzie and P. V. Johnston, *Geophys. Res. Lett.* 11, 73 (1986); G. Mount, R. Sanders, A. Schmeltekopf, S. Solomon, *J. Geophys. Res.*, in press.
 35. B. G. Gardiner and J. D. Shanklin, *Geophys. Res. Lett.* 13, 1199 (1986).
 36. A. J. Krueger, M. R. Schoeberl, R. S. Stolarski, *ibid.* 14, 527 (1987).
 37. The National Center for Atmospheric Research is sponsored by the National Science Foundation. I thank R. S. Stolarski, J. D. Mahlman, and B. A. Ridley for helpful discussions and the NASA HALOE Satellite Science Team for support.

A Physiological Basis for a Theory of Synapse Modification

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The functional organization of the cerebral cortex is modified dramatically by sensory experience during early postnatal life. The basis for these modifications is a type of synaptic plasticity that may also contribute to some forms of adult learning. The question of how synapses modify according to experience has been approached by determining theoretically what is required of a modification mechanism to account for the available experimental data in the developing visual cortex. The resulting theory states precisely how certain variables might influence synaptic modifications. This insight has led to the development of a biologically plausible molecular model for synapse modification in the cerebral cortex.

ALTHOUGH ARISTOTLE IDENTIFIED HEART AS THE SEAT OF intellect, reserving for brain the function of cooling the head, it is now generally believed that it is brain that is the source of thought, the location of memory, the physical basis of mind, consciousness, and self-awareness: all that make us distinct and human. In recent years it has become increasingly fashionable to treat this complex system as a neural network: an assembly of neurons connected to one another by synaptic junctions that serve to transmit information and possibly to store memory.

Since the contents of memory must depend to some extent on experience, the neural network and, in particular, the synapses between neurons cannot be completely determined genetically. This evident reasoning has led to much discussion about possible modification of synapses between neurons as the physiological basis of learning and memory storage. To properly function, neural network models require that vast arrays of synapses have the proper strengths. A basic problem becomes how these synapses adjust their

weights so that the resulting neural network shows the desired properties of memory storage and cognitive behavior.

The problem can be divided into two parts. First, what type of modification is required so that in the course of actual experience the neural network arrives at the desired state? The answer to this question can be illuminated by mathematical analysis of the evolution of neural networks by means of various learning hypotheses. The second part of this problem is to find experimental justification for any proposed modification algorithm. A question of extraordinary interest is: What are the biological mechanisms that underlie the nervous system modification that results in learning, memory storage, and eventually cognitive behavior?

One experimental model that appears to be well suited for the purpose of determining how neural networks modify is the visual cortex of the cat. The modification of visual cortical organization by sensory experience is recognized to be an important component of early postnatal development (1). Although much modifiability disappears after the first few months of life, some of the underlying mechanisms are likely to be conserved in adulthood to provide a basis for learning and memory. We have approached the problem of experience-dependent synaptic modification by determining theoretically what is required of a mechanism in order to account for the experimental observations in visual cortex. This process has led to the formulation of hypotheses, many of which are testable with currently available techniques. In this article we illustrate how the interaction between theory and experiment has suggested a possible

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molecular mechanism for the experience-dependent modifications of functional circuitry in the mammalian visual cortex.

The Experimental Model

Neurons in the primary visual cortex, area 17, of normal adult cats are sharply tuned for the orientation of an elongated slit of light and most are activated by stimulation of either eye (2). Both of these properties—orientation selectivity and binocularity—depend on the type of visual environment experienced during a critical period of early postnatal development. We believe that the mechanisms underlying the experience-dependent modification of both receptive field properties are likely to be identical. However, for the sake of clarity, we concentrate primarily on the modification of binocular connections in striate cortex.

The majority of binocular neurons in the striate cortex of a normal adult cat do not respond with equal vigor to stimulation of either eye; instead they typically display an eye preference. To quantify this impression Hubel and Wiesel (2) originally separated the population of recorded neurons into seven ocular dominance (OD) categories (Fig. 1). The OD distribution in a normal kitten or adult cat shows a broad peak at group 4, which reflects a high percentage of binocular neurons in area 17 (Fig. 1A). This physiological assay of OD has proved to be an effective measure of the state of functional binocularity in the visual cortex.

Monocular deprivation (MD) during the critical period [extending from approximately 3 weeks to 3 months of age in the cat (3)] has profound and reproducible effects on the functional connectivity of striate cortex. Brief periods of MD will result in a dramatic shift in the OD of cortical neurons such that most will be responsive exclusively to the open eye (Fig. 1B). The OD shift after MD is the best known and most intensively studied type of visual cortical plasticity.

When the MD is begun early in the critical period, the OD shift can be correlated with anatomically demonstrable differences in the geniculocortical axonal arbors of the two eyes (4, 5). However, MD initiated late in the critical period (6) or after a period of rearing in the dark (7) will induce clear changes in cortical OD without a corresponding anatomic change in the geniculocortical projection. Long-term recordings from awake animals also indicate that OD changes can be detected within a few hours of monocular experience (8), which seems too rapid to be explained by the formation or elimination of axon terminals. Moreover, deprived-eye responses in visual cortex may be restored within minutes under some conditions

Table 1. Parameters identified as crucial variables for synapse modification.

Parameter	Possible measures	Symbolic notation
Presynaptic activity of the j th synapse*	Firing rate; transmitter release (millisecond time base [†])	d_j
Postsynaptic activity	Firing rate; dendritic depolarization (millisecond time base [†])	c
Time-averaged postsynaptic activity	Firing rate; dendritic depolarization (minute to hour time base [†])	\bar{c}
Synaptic transfer function of the j th synapse*	$\Delta c/\Delta d_j$	m_j
"Global" modulation	Dendritic field potentials; second messenger activity	X, Y, Z

*The notation we use for the input activity of a single LGN fiber and its synaptic weight is d_j and m_j , respectively. When we refer to the total input activity and synaptic weight of an array of fibers, we use vector notation, d and m . [†]Time bases can be inferred from experimental results. In this article, d and c are averages over approximately 500 msec, \bar{c} is average over several hours.

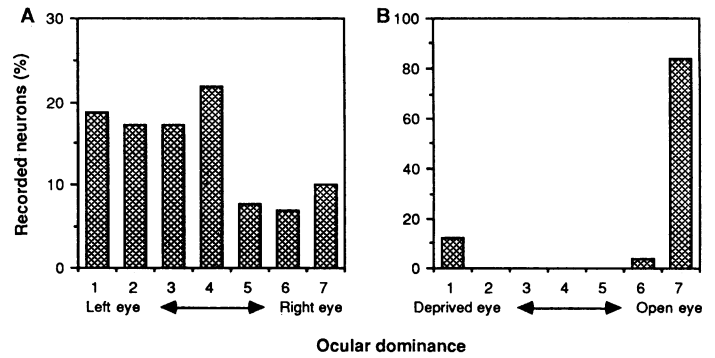


Fig. 1. Representative histograms of OD data (5) obtained from the striate cortex of (A) normal cats and (B) cats that were monocularly deprived early in life. The bars show the percentage of neurons in each of the seven OD categories. Cells in groups 1 and 7 are activated by stimulation of either the contralateral eye or the ipsilateral eye, respectively, but not both. Cells in group 4 are activated equally well by either eye. Cells in groups 2 and 3, and 5 and 6 are binocularly activated, but show a preference for either the contralateral eye or the ipsilateral eye, respectively. The histogram in (A) reveals that the majority of neurons in the visual cortex of a normal animal are driven binocularly. The histogram in (B) shows that a period of monocular deprivation leaves few neurons responsive to the deprived eye. Fewer than 1 percent of the recorded neurons were classified in groups 2, 3, 4, and 5.)

[such as during intracortical bicuculline administration (9)], which suggests that synapses deemed functionally “disconnected” are nonetheless physically present. Therefore it is reasonable to assume that changes in functional binocularity are explained not only by adjustments of the terminal arbors of geniculocortical axons but also by changes in the efficacy of individual cortical synapses.

The consequences of binocular deprivation (BD) on visual cortex stand in striking contrast to those observed after MD. Although 7 days of MD during the second postnatal month leave few neurons in striate cortex responsive to stimulation of the deprived eye, most cells remain responsive to visual stimulation through either eye after a comparable period of BD (10). Thus, it is not merely the absence of patterned activity in the deprived geniculocortical projection that causes the decrease in synaptic efficacy after MD.

Stent (11) suggested that the crucial difference between MD and BD is that only in the former instance are cortical neurons active. This idea was put to the test in an ingenious series of experiments by Singer and colleagues in which kittens were presented with visual stimuli that created an imbalance in the presynaptic geniculocortical fiber activity from the two eyes, but that were believed to be ineffective in driving cortical neurons (12, 13). Under these conditions, there was no shift in cortical OD. Thus, on a purely descriptive level, it appeared that postsynaptic activation was a necessary condition for synaptic modifications to occur in the visual cortex. This simple rule resembles Hebb’s postulate of learning (14), which states that synaptic efficacy should increase only when the pre- and postsynaptic elements are concurrently active. To account for the effects of MD in striate cortex, Stent added the complementary statement that postsynaptic activity is also a necessary condition for the weakening of inactive synapses. According to this idea, postsynaptic activation is necessary for all synaptic modifications and the sign of the change (positive or negative) is dependent on the amount of presynaptic activity.

Subsequent work has suggested, however, that the generation of action potentials in a cortical neuron does not ensure that OD modifications will occur after MD (15). This has led to the idea that there is a critical level of postsynaptic activation that must be reached before experience-dependent modifications will occur, and that this threshold is higher than the depolarization required for soma-spikes (16). Singer (17) has recently proposed a tentative mechanism that

could account for this type of modification scheme. Experience-dependent modifications do not normally occur in the visual cortex of anesthetized kittens (18). However, shifts of OD can be induced under anesthesia when cortical excitability is raised by pairing monocular visual stimulation with electrical stimulation of the midbrain reticular formation (19). Only under these conditions can visual stimulation evoke decreases in the extracellular calcium ion concentration as measured with ion-sensitive electrodes (20). These findings led Singer to suggest that the threshold level of postsynaptic activation required for synaptic modification is related to voltage-dependent calcium entry into cortical dendrites. According to this hypothesis, free calcium in the dendrite acts as a second messenger to trigger the molecular changes required for a modification of synaptic efficacy to occur.

This idea that synaptic change is dependent on some suprathreshold output of the postsynaptic neuron can account for many of the observed results in striate cortex after different types of visual deprivation. However, there are several examples of synapse modification in visual cortex that will occur with little or no evoked activity in cortical neurons. For instance, if after a brief period of MD the deprived eye is allowed to see and the experienced eye is sutured closed (known as a reverse suture experiment), then there is a robust OD shift back to the newly opened eye (4, 13, 21). This shift occurs despite the fact that, at the time of the reversal, the unsutured eye was functionally disconnected from the striate cortex. Moreover, if impulse activity from one eye is completely silenced with intraocular tetrodotoxin and the other eye is sutured closed, then an OD shift can sometimes occur in favor of the sutured eye even though this eye is deprived of the visual patterns required to drive cortical neurons

(22). Finally, the OD shift produced by a period of MD will disappear, as will orientation selectivity, if the animal is subsequently binocularly deprived (23). This change in selectivity occurs under conditions where visual cortical neurons are presumably inactive. Hence, it is clear that relative postsynaptic inactivity does not preclude synapse modifications under all conditions. Thus, the Hebb-Stent hypothesis cannot account for the observed data unless further assumptions are made.

Work over the past several years has led to an alternative theoretical solution to the problem of visual cortical plasticity (24). According to Cooper *et al.* (25), when a cortical neuron is depolarized beyond a "modification threshold," θ_M , then synaptic efficacies change along lines envisaged by Hebb (14). However, when the level of postsynaptic activity falls below θ_M , then synaptic strengths decrease. Thus, in this model the sign of a synaptic change is a function primarily of the level of postsynaptic activity. Analysis by Cooper *et al.* confirmed that such a modification scheme could lead to the development of selectivity that is appropriate for the input environment. However, these researchers also noted that a fixed modification threshold leads to certain technical problems. For instance, if the postsynaptic response to all patterns of input activity slipped below θ_M (as might occur during binocular deprivation), then the efficacy of all synapses would decrease to zero. Bienenstock *et al.* (26) solved this problem by allowing the modification threshold to float as a function of the averaged activity of the cell. With this feature, the theory can successfully account for virtually all the types of modification that have been observed in kitten striate cortex over the past 20 years. This theory is outlined in more detail in the next section; then we shall return to the question of possible mechanisms.

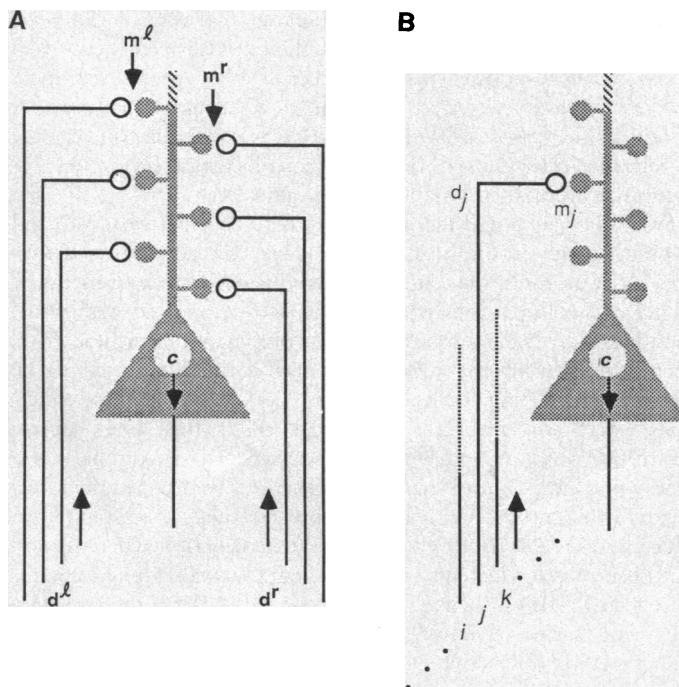


Fig. 2. Illustrated schematically are pyramidal-shaped cortical neurons and the proximal segments of their apical dendrites. The shaded circles attached to the dendrites represent dendritic spines. In the first stage of the theoretical analysis we consider only the inputs to the cell from the LGN (A). The signals conveyed along these afferents arise either from the left retina (d^l) or the right retina (d^r) and are transferred to the cortical neuron by the synaptic junctions m^l and m^r . The output of the cortical neuron, as measured by the firing rate or the dendritic depolarization, is represented as c , which is the sum of $m^l \cdot d^l$ and $m^r \cdot d^r$. The central question is how one of these afferent synapses, m_j , modifies in time as a function of both its level of presynaptic activity d_j and the level of postsynaptic depolarization (B).

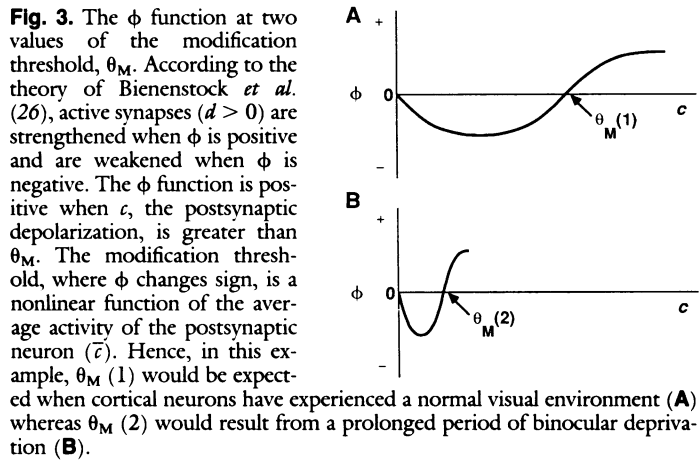
Theoretical Analysis

Cortical neurons receive synaptic inputs from many sources. In layer IV of visual cortex the principal afferents are those from the lateral geniculate nucleus (LGN) and from other cortical neurons. This leads to a complex network that has been analyzed in several stages. In the first stage, consider a single neuron with inputs from both eyes (Fig. 2A). Here d represents the level of presynaptic geniculocortical axon activity, m the synaptic transfer function ("synaptic strength" or "weight"), and c the level of postsynaptic activity of the cortical neuron. These parameters, their symbolic notation, and their possible physiological measures are shown in Table 1. The output of this neuron (in the linear region) can be written:

$$c = m^l \cdot d^l + m^r \cdot d^r \quad (1)$$

which means that the neuron firing rate (or dendritic depolarization) is the sum of the inputs from the left eye multiplied by the left-eye synaptic weights plus the inputs from the right eye multiplied by the right-eye synaptic weights. Thus, the signals from the left and right eyes are integrated by the cortical neuron and determine its level of depolarization (output) at any instant.

The crucial question becomes: How does m change in time according to experience? According to the theory of Bienenstock *et al.* (26), m modifies as a function of local, quasi-local, and global variables. Consider the synaptic weight of the j th synapse on a neuron, m_j (Fig. 2B). This synapse is affected by local variables in the form of information available only through the j th synapse, such as the presynaptic activity levels (d_j) and the efficacy of the synapse at a given instant in time [$m_j(t)$]. Quasi-local variables represent information that is available to the j th synapse through intracellular communication within the same cell. These include the instantaneous firing rate (or dendritic depolarization) of the cell (c), the



time-averaged firing rate (\bar{c}), and the potentials generated at neighboring synaptic junctions [$(dm)_{k,l,m} \dots$]. Finally, global variables (designated X , Y , and Z in Table 1) represent information that is available to a large number of cortical neurons, including the neuron receiving the j th synapse. These variables might include the presence or absence of modulatory neurotransmitters such as acetylcholine and norepinephrine (15) or the averaged activity of large numbers of cortical cells (16).

We can delay consideration of the global variables by assuming that they act to render cortical synapses modifiable or nonmodifiable by experience. In the “plastic state,” the Bienenstock *et al.* (26) algorithm for synaptic modification is written:

$$dm_j/dt = \phi(c, \bar{c})d_j \quad (2)$$

so that the strength of the j th synaptic junction, m_j , changes its value in time as a function, ϕ , of the quasi-local states, c and \bar{c} , and as a linear function of the local variable d_j . The crucial function, ϕ , is shown in Fig. 3.

One significant feature of this model is the change of sign of ϕ at the modification threshold, θ_M . When the input activity of the j th synapse (d_j) and ϕ are both concurrently greater than zero (27), then the sign of the synaptic modification is positive and the strength of the synapse increases. The ϕ function is positive when the output of the cell exceeds the modification threshold (this type of synaptic modification is “Hebbian”). When d_j is positive and ϕ is less than zero, then the synaptic efficacy weakens; $\phi < 0$ when $c < \theta_M$. Thus, “effective” synapses will be strengthened and “ineffective” synapses will be weakened, where synaptic effectiveness is determined by whether or not the presynaptic pattern of activity is accompanied by the simultaneous depolarization of the target dendrite beyond θ_M . Since the depolarization of the target cell beyond θ_M normally requires the synchronous activation of converging excitatory synapses, this type of modification will “associate” those synapses that are concurrently active by increasing their effectiveness together.

Another significant feature of this model is that the value of θ_M is not fixed but instead varies as a nonlinear function of the average output of the cell (\bar{c}). In a simple situation

$$\theta_M = \bar{c}^2 \quad (3)$$

By allowing θ_M to vary with the average response in a faster-than-linear fashion, the response characteristics of a neuron evolve to maximum selectivity starting at any level within the range of the input environment. It is also this feature that provides the stability properties of the model so that, for instance, simultaneous pre- and postsynaptic activity at a continued high level do not continue to increase the synaptic strength.

Now consider the situation of reverse suture where the right, formerly open eye is closed and the left, formerly sutured eye is reopened. The output of a cortical neuron in area 17 approaches zero just after the reversal since its only source of patterned input is through the eye whose synapses had been functionally disconnected as a consequence of the prior MD. However, as \bar{c} diminishes, so does the value of θ_M . Eventually, the modification threshold attains a value below the small output that is evoked by the stimulation of the synapses of the weak left eye. Now the efficacy of these “functionally disconnected” synapses will begin to increase, because even their low response values exceed θ_M . As these synapses strengthen and the average output of the cell increases, θ_M again slides out until it overtakes the new left-eye response values. At the same time, the efficacy of the right-eye synapses continually decreases because their response values remain below the modification threshold. In its final stable state, the neuron is responsive only to the newly opened eye, and the maximum output to stimulation of this eye equals θ_M .

So far, the discussion has been limited to an idealized single neuron whose inputs arise only from the LGN. The second stage of the theoretical analysis requires that relevant intracortical connections be incorporated into the model. Consider a simple network, illustrated in Fig. 4, in which inhibitory and excitatory cortical neurons receive input from the LGN and from each other. In a network generalization of Eq. 1, the integrated output of the i th neuron may be written:

$$c_i = m_i^e \cdot d^e + m_i^i \cdot d^i + \sum L_{ij}f_j \quad (4)$$

where the term $\sum L_{ij}f_j$ is the sum of the output from other cells in the network multiplied by the weight of their synapses on the i th cell.

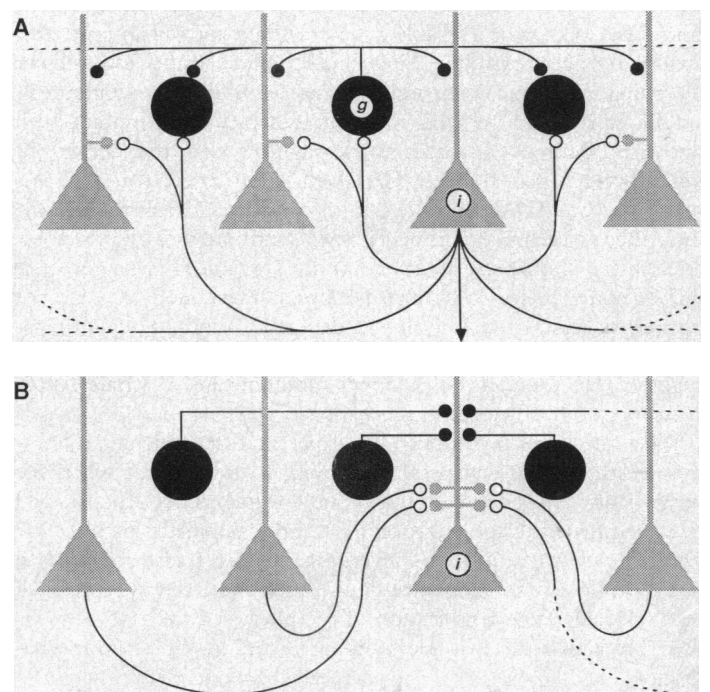


Fig. 4. In the second stage of the theoretical analysis, the neurons of Fig. 2 are placed in a cortical network in which the inhibitory and excitatory cells receive input from the LGN and from each other. (A) The efferent intracortical connections of two neurons in the network. The i th neuron is excitatory, the g th is inhibitory, and both synapse upon every other cell in the network. (B) The intracortical inputs to the i th neuron. Thus, in addition to the geniculate afferents (d^e and d^i , shown in Fig. 2A), each neuron in the network receives excitatory and inhibitory intracortical inputs. In a network generalization of Eq. 1, the integrated output of the i th neuron may be written as Eq. 4.

The influence of this network on the synaptic modifications of the i th neuron may be analyzed by using a mean field approximation (28). Assuming only that the net influence of the intracortical connections is inhibitory [$(\sum L_{ij} \epsilon_j) < 0$], this work has proven that a neuron will evolve to an asymptotically stable state that is appropriate for a given visual environment (in agreement with what has been observed experimentally). Importantly, this occurs without the need to assume any modification of the inhibitory synapses in the network.

There is an interesting consequence of assuming the neuron is under the influence of an inhibitory mean field network. Recall that according to the theory of Bienenstock *et al.* (26), MD leads to convergence of geniculocortical synapses to a state where stimulation of the deprived eye input results in an output that equals zero ($\epsilon = 0$). However, with average network inhibition, the evolution of the cell to this state does not require that the efficacy of deprived-eye synapses be driven completely to zero. Instead, these excitatory synapses will evolve to a state where their influence is exactly offset by intracortical inhibition. Thus, the removal of intracortical inhibition in this network would reveal responses from otherwise ineffective inputs. This result is in accordance with the experimental observation of “unmasking” of synapses when the inhibitory effects of γ -aminobutyric acid (GABA) are antagonized with the blocking agent bicuculline (9).

A Possible Physiological Mechanism

One of the consequences of the network theory discussed in the previous section is that the experimental results obtained in visual cortex over the last generation can be explained by modification of excitatory synapses, with minimal changes in intracortical inhibition. The balance of available experimental evidence supports this conclusion. For example, Singer (29) found using intracellular recording that geniculocortical synapses on inhibitory interneurons are more resistant to MD than are synapses on pyramidal cell dendrites. Moreover, recent work suggests that the density of inhibitory synapses that use GABA in kitten striate cortex is also unaffected by MD during the critical period (30). Taken together, these theoretical and experimental results indicate that the search for mechanism should be focused on the excitatory synapses that impinge on excitatory cells in visual cortex. Interestingly, this type of synapse is formed exclusively on dendritic spines, a feature that distinguishes it from other types of cortical synapse (31). This suggests that experience-dependent modifications in striate cortex occur primarily at axospinous synapses.

What mechanisms support the experience-dependent modification of axospinous synapses? According to the theory, when the postsynaptic cell is depolarized beyond θ_M , then active synapses will be strengthened. Depolarization beyond θ_M minimally requires the synchronous activation of converging excitatory afferents. When postsynaptic activity fails to reach θ_M , then the active synapses will be weakened. The identification of the physiological basis of θ_M is therefore central to an understanding of the modification mechanism.

Work on long-term potentiation (LTP) in the hippocampal slice preparation has provided an important insight into the nature of the modification threshold that may be applicable to the visual cortex. LTP is a long-lasting increase in the synaptic strength of excitatory afferents that have been tetanically stimulated (32). The induction of LTP depends on the coactivation of converging excitatory afferents [input cooperativity (33)], the depolarization of the postsynaptic neuron (34), the activation of *N*-methyl-D-aspartate (NMDA) receptors (35), and the postsynaptic entry of Ca^{2+} ions (36). A current

working hypothesis is that the synchronous tetanic activation of converging afferents depolarizes the target dendrite beyond the threshold for postsynaptic Ca^{2+} entry through gates linked to the NMDA receptor (37). Elevated dendritic calcium then triggers the intracellular changes that lead to enhanced synaptic efficacy (38).

NMDA receptors are a subclass of excitatory amino acid receptor, and glutamic acid or a closely related substance is thought to be the transmitter of excitatory axospinous synapses at many locations in the forebrain (39). These receptors are widely distributed in the cerebral cortex, including the visual areas (40). It appears that NMDA receptors normally coexist postsynaptically with quisqualate or kainate receptors or both (41). The “non-NMDA” receptors are thought to mediate the classical excitatory postsynaptic potential that normally results from electrical stimulation of axospinous synapses (35). NMDA receptors, on the other hand, appear to be linked to a membrane channel that will pass Ca^{2+} ions. Dingleline (42) reported that activation of NMDA receptors leads to calcium flux only when the cell is concurrently depolarized. This voltage dependency is apparently due to a blockage of the NMDA channel by Mg^{2+} ions that is alleviated only when the membrane is depolarized sufficiently (43). Thus, calcium entry through channels linked to the NMDA receptor could specifically signal pre- and postsynaptic coactivation (44).

Recently Kleinschmidt *et al.* (45) have obtained results that suggest that NMDA receptor-mediated Ca^{2+} entry also contributes to the synapse modifications that underlie OD plasticity in striate cortex. Specifically, they have found that intracortical infusion of 2-amino-5-phosphonovaleric acid (APV), a selective antagonist of the NMDA receptor (46), prevents the OD shift that would normally occur after MD. Moreover, this pharmacological treatment also resulted in a striking loss of orientation selectivity and a decrease in visual responsiveness. These data support Singer’s hypothesis that dendritic calcium entry is a crucial variable for synaptic modifications in the striate cortex (17).

Our theoretical analyses lead us to suggest several refinements of the Singer hypothesis. Specifically, we propose the following: (i) θ_M is the membrane potential at which NMDA-receptor activation by sensory fiber activity results in dendritic calcium entry; (ii) increased calcium flux across the dendritic spine membrane results specifically in an increase in the synaptic gain; and (iii) activated synapses accompanied by no postsynaptic calcium signals will be weakened over time.

This physiological model is consistent with the theory of Bienenstock *et al.* (26). According to the model, the value and sign of ϕ are determined by the Ca^{2+} movement into dendritic spines. Synaptic efficacy will increase when presynaptic activity evokes a large postsynaptic calcium signal ($\phi > 0$). This will occur only when the membrane potential exceeds the level required to open the NMDA receptor-activated calcium channels ($\epsilon > \theta_M$). When the amplitude of the evoked Ca^{2+} signal falls below a certain critical level, corresponding to $\phi = 0$ and $\epsilon = \theta_M$, then active synapses will be weakened over time. Application of an NMDA-receptor blocker theoretically would increase the value of θ_M , such that it would take a greater level of depolarization to achieve the critical calcium flux. In accordance with the experimental observations of Kleinschmidt *et al.* (45), the theoretical consequence would be a loss of orientation selectivity, a prevention of OD plasticity, and a decrease in visual responsiveness.

Changes in synaptic efficacy that depend on postsynaptic calcium have been observed directly in *Hermisenda* (47). In this invertebrate, a classically conditioned response will result from the repeated pairing of light (the conditioned stimulus) with rotation of the animal (the unconditioned stimulus). The crucial modification occurs at the level of the “type B” photoreceptor, which is both

depolarized by light and synaptically activated by inputs from the vestibular system. The pairing of light with rotation depolarizes the cell beyond the threshold for Ca^{2+} entry. Elevated intracellular Ca^{2+} leads to a long-term change that leaves the cell more excitable to light than before conditioning. In this case, as in hippocampal LTP, postsynaptic calcium entry leads specifically to an increase in the efficacy of the active synapses.

Our physiological model makes no statement about the actual locus where the modification is stored. Calcium ion acts as an intracellular second messenger to activate a host of enzymes including protein kinases (48), phosphatases (49), and proteases (38). In *Herrnissenda* the synaptic efficacy appears to be increased by the covalent modification of potassium channels in the postsynaptic membrane (47). The essential modification that underlies LTP in the hippocampus is still controversial. The candidates range from alterations in the morphology of dendritic spines (38) to changes in the amount of transmitter released presynaptically (50). The weakening of synapses whose activity is not coincident with postsynaptic calcium entry could be explained by receptor desensitization (51). Any of these changes could contribute to the experience-dependent modification of neuronal response properties in visual cortex.

However, the model does make some explicit predictions about the regulation of the calcium messenger system that is linked to the NMDA receptors on cortical dendrites. Recall that θ_M depends on the average activity of the cell. If the average activity decreases, as during binocular deprivation, then θ_M decreases and it should take less dendritic depolarization to maintain synaptic efficacy. One way this could occur in our model would be to alter the voltage or transmitter sensitivity of the NMDA receptors with the result that less synaptic activity (depolarization) would be required to evoke the necessary calcium signal. It is well documented that receptor supersensitivity occurs as a consequence of postsynaptic inactivity at many locations in the nervous system (52). Alternatively, a weak calcium signal could be amplified at points further downstream, for example, by increasing the activity of calcium-activated enzymes.

Dendritic spines obviously play an important role in this model. We speculate that these postsynaptic structures are specialized to isolate high levels of intracellular calcium. The morphological organization of spines appears to be ideally suited for this task. Most mature spines are physically separated from the dendrite by a narrow neck, and in many cases contain an organelle called the "spine apparatus," which is thought to be a type of endoplasmic reticulum that can sequester free Ca^{2+} (53). The length of the spine neck may be constantly changing in the living brain (54), but electron microscopic examination has led repeatedly to the conclusion that in the fixed brain the longest spine necks on cortical pyramidal cells are found at the ends of apical dendrites, whereas the shortest spine necks are a consistent feature of the part of the dendrite near the cell body (55).

The unusual morphology of dendritic spines raises some interesting questions with regard to the nature of NMDA receptor-mediated Ca^{2+} influx. Numerous modeling studies have shown that the high electrical resistance of the spine neck should amplify the depolarization evoked by synaptic activity within the spine head (56). Consequently, NMDA-activated Ca^{2+} entry should occur more readily in spines with longer necks (higher resistance). Synapses on a spine with high neck resistance might even be capable of evoking significant Ca^{2+} entry without concurrent dendritic depolarization. This raises the possibility that the modifiability of axospinous synapses might depend on spine shape. In this context, we note that total light deprivation leads to the development in visual cortex of truncated spines without a constricted neck region (57). A period of rearing in the dark is also known to leave kitten striate cortex unusually modifiable by visual experience (7).

Conclusions

We have presented an algorithm for synaptic modification that reproduces classical experimental results in visual cortex. These include the relation of cell tuning and response to various visual environments experienced during the critical period: normal rearing, binocular deprivation, monocular deprivation, and reverse suture. A molecular model for this form of modification has been proposed based on the NMDA receptors. In this model θ_M as proposed by Bienenstock *et al.* (26) is identified with the voltage-dependent unblocking of the NMDA receptor channels. A consequence of this relation is that the membrane potential at which Ca^{2+} enters through NMDA channels should vary depending on the history of prior cell activity.

Stated in this language, many questions become of obvious interest. Among these are: How long does it take θ_M to adjust to a new average firing rate? What is the molecular basis for this adjustment? How do the putative global modulators of cortical plasticity, such as acetylcholine and norepinephrine, interact with the second-messenger systems linked to NMDA receptors on cortical dendrites? Can we provide direct evidence that those cells that modify are or are not those acted on by the modulators? Are the known morphological features of dendritic spines causally related to the modifiability of synaptic strength? Do the same rules apply to reorganization in adults as apply in the developmental period?

There has been much discussion in recent years about possible modification of synapses between neurons as the physiological basis of learning and memory storage. Molecular models for learning at the single-synapse level have been presented (11, 17, 38, 47, 58), various learning algorithms have been proposed that show some indication of appropriate behavior (14, 24–26, 59), and a mathematical structure for networks of neurons is rapidly evolving (60). A concerted effort to unite these approaches has begun, and the close interaction between theory and experiment has greatly enriched both endeavors. Theory has been anchored to experimental observations and experiments have been focused onto those issues most relevant to sorting out the various possible hypotheses. Further, this interaction has enabled us to pose new questions with precision and clarity.

REFERENCES AND NOTES

1. S. M. Sherman and P. D. Spear, *Physiol. Rev.* **62**, 738 (1982); Y. Frégnac and M. Imbert, *ibid.* **64**, 325 (1984).
2. D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **160**, 106 (1962).
3. ———, *ibid.* **206**, 419 (1970).
4. S. LeVay, T. N. Wiesel, D. H. Hubel, *J. Comp. Neurol.* **191**, 1 (1980).
5. C. J. Shatz and M. P. Stryker, *J. Physiol. (London)* **281**, 267 (1978).
6. J. Presson and B. Gordon, *Soc. Neurosci. Abstr.* **8**, 5.10 (1982).
7. G. D. Mower *et al.*, *J. Comp. Neurol.* **235**, 448 (1985).
8. L. Mioche and W. Singer, personal communication.
9. F. H. Duffy, S. R. Snodgrass, J. L. Burchfiel, J. L. Conway, *Nature (London)* **260**, 256 (1976).
10. T. N. Wiesel and D. H. Hubel, *J. Neurophysiol.* **28**, 1029 (1965).
11. G. S. Stent, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 997 (1973).
12. W. Singer, J. Rauschecker, R. Werth, *Brain Res.* **134**, 568 (1977).
13. J. P. Rauschecker and W. Singer, *Nature (London)* **280**, 58 (1979).
14. D. O. Hebb, *The Organization of Behavior* (Wiley, New York, 1949).
15. T. Kasamatsu and J. D. Pettigrew, *J. Comp. Neurol.* **185**, 139 (1979); R. D. Freeman and A. B. Bonds, *Science* **206**, 1093 (1979); P. Buisseret and W. Singer, *Exp. Brain Res.* **51**, 443 (1983); M. F. Bear and W. Singer, *Nature (London)* **320**, 172 (1986).
16. W. Singer, in *The Neurosciences Fourth Study Program*, F. O. Schmitt and F. G. Worden, Eds. (MIT Press, Cambridge, MA, 1979), pp. 1093–1109.
17. W. Singer, in *The Neural and Molecular Bases of Learning*, J.-P. Changeux and M. Konishi, Eds. (Dahlem Konferenzen, Wiley, New York, 1987), pp. 301–336.
18. It is possible, however to condition single neurons in anesthetized preparations by pairing visual stimulation with the iontophoretic application of K^+ or a cocktail of putative facilitatory transmitters. See: Y. Frégnac, S. Thorpe, D. Shulz, E. Bienenstock, *Soc. Neurosci. Abstr.* **10**, 314.5 (1984); J. Greuel, H. Luhman, W. Singer, in preparation.
19. W. Singer and J. Rauschecker, *Exp. Brain Res.* **47**, 223 (1982).
20. H. Geiger and W. Singer, *Int. J. Dev. Neurosci. Suppl.* **R328** (1984).
21. C. Blakemore, L. J. Garey, Z. B. Henderson, N. V. Swindale, F. Vital-Durand, *J. Physiol. (London)* **307**, 25P (1980).
22. M. D. Jacobson, H. O. Reiter, B. Chapman, M. P. Stryker, *Soc. Neurosci. Abstr.* **11**,

- 31.8 (1985). However, see also, J. M. Greuel, H. J. Luhmann, W. Singer, *Dev. Brain Res.*, in press.
23. J. Rauschecker and W. Singer, *Dev. Brain Res.* **4**, 495 (1982).
 24. L. N Cooper, in *Proceedings of the Nobel Symposium on Collective Properties of Physical Systems*, B. Lindquist and S. Lindquist, Eds. (Academic Press, New York, 1973), vol. 24, pp. 252-264; M. M. Nass and L. N Cooper, *Biol. Cybern.* **19**, 1 (1975).
 25. L. N Cooper, F. Liberman, E. Oja, *Biol. Cybern.* **33**, 9 (1979).
 26. E. L. Bienenstock, L. N Cooper, P. W. Munro, *J. Neurosci.* **2**, 32 (1982).
 27. When presynaptic fiber is spontaneously active, $d = 0$.
 28. L. N Cooper and C. Scofield, in preparation.
 29. W. Singer, *Brain Res.* **134**, 508 (1977).
 30. M. F. Bear, D. M. Schmechel, F. F. Ebner, *J. Neurosci.* **5**, 1262 (1985); G. D. Mower, W. F. White, R. Rustad, *Brain Res.* **380**, 253 (1986).
 31. M. Colonnier, in *The Organization of the Cerebral Cortex*, F. O. Schmitt, F. G. Worden, G. Adelman, S. G. Dennis, Eds. (MIT Press, Cambridge, MA, 1981), pp. 125-152.
 32. T. Lomo, *Acta Physiol. Scand. Suppl.* **68**, 128 (1966); T. V. P. Bliss and T. Lomo, *J. Physiol. (London)* **232**, 331 (1973).
 33. B. L. McNaughton, R. M. Douglas, G. V. Goddard, *Brain Res.* **157**, 277 (1978).
 34. S. R. Kelso, A. H. Ganong, T. H. Brown, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 5326 (1986).
 35. G. L. Collingridge, S. L. Kehl, H. McLennan, *J. Physiol. (London)* **334**, 33 (1983); E. W. Harris, A. H. Ganong, C. W. Cotman, *Brain Res.* **323**, 132 (1984).
 36. G. Lynch, J. Larson, S. Kelso, G. Barrionuevo, F. Schottler, *Nature (London)* **305**, 719 (1983).
 37. H. Wigström and B. Gustafsson, *Acta Physiol. Scand.* **123**, 519 (1985); P. O. Andersen, in *The Neural and Molecular Bases of Learning*, J.-P. Changeux and M. Konishi, Eds. (Dahlem Konferenzen, Wiley, New York, 1987), pp. 239-262.
 38. G. Lynch and M. Baudry, *Science* **224**, 1057 (1984).
 39. C. W. Cotman, A. Foster, T. Lanthorn, in *Glutamate as a Neurotransmitter*, G. DiChiara and G. Gessa, Eds. (Raven, New York, 1981), pp. 1-27; D. G. Nicholls and T. S. Sihra, *Nature (London)* **321**, 772 (1986); T. P. Hicks, D. Lodge, H. McLennan, Eds., *Excitatory Amino Acid Transmission* (Liss, New York, 1987).
 40. D. T. Monaghan and C. W. Cotman, *J. Neurosci.* **5**, 2909 (1985).
 41. A. C. Foster and G. E. Fagg, *Brain Res. Rev.* **7**, 103 (1985). NMDA receptors are so named because of their high affinity for N-methyl-D-aspartate. Foster and Fagg have proposed a formal nomenclature for the acidic amino acid receptors: A1 for the "NMDA" receptor, A2 for the "quisqualate" receptor, and A3 for the "kainate" receptor. However, because this scheme has not yet been widely adopted, we use the term "NMDA receptor" in this article.
 42. R. Dingledine, *J. Physiol. (London)* **343**, 385 (1983).
 43. L. Nowak, P. Bregestovski, P. Ascher, A. Herbert, A. Prochiantz, *Nature (London)* **307**, 462 (1984).
 44. Recent work indicates that NMDA receptors contribute significantly to the response generated by trains of presynaptic action potentials. This contribution is probably due to the temporal summation of fast excitatory postsynaptic potentials, which leads to a postsynaptic depolarization sufficient to relieve the Mg^{2+} block of the ionophore. This contribution of the NMDA receptor-mediated Ca^{2+} current to "normal" synaptic transmission in no way diminishes the importance of its novel role as a signal of pre- and postsynaptic coactivation. See: T. E. Salt, *Nature (London)* **322**, 263 (1986); C. E. Herron, R. A. J. Lester, E. J. Coan, G. L. Collingridge, *ibid.*, p. 265.
 45. A. Kleinschmidt, M. F. Bear, W. Singer, *Neurosci. Lett. Suppl.* **26**, S58 (1986); in preparation.
 46. J. C. Watkins and R. H. Evans, *Annu. Rev. Pharmacol. Toxicol.* **21**, 165 (1981).
 47. D. L. Alkon, *Science* **226**, 1037 (1984).
 48. E. J. Nestler, S. I. Walaas, P. Greengard, *ibid.* **225**, 1357 (1984).
 49. A. A. Stewart, T. S. Ingebritsen, A. Manalan, C. B. Klee, P. Cohen, *FEBS Lett.* **137**, 80 (1982).
 50. A. C. Dolphin, M. L. Errington, T. V. P. Bliss, *Nature (London)* **297**, 496 (1982); D. V. Agoston and U. Kuhnt, *Exp. Brain Res.* **62**, 663 (1986).
 51. T. Heidmann and J.-P. Changeux, *C. R. Acad. Sci. Ser. C* **285**, 665 (1982).
 52. W. B. Cannon and A. Rosenblueth, *The Supersensitivity of Denervated Structures* (Macmillan, New York, 1949); J. R. Sporn, B. B. Wolfe, T. R. Harden, T. Kendall, P. B. Molinof, *Mol. Pharmacol.* **13**, 1170 (1977).
 53. F. Joó, A. Mihály, A. Párducz, *Curr. Top. Res. Synapses* **1**, 119 (1984); E. Fifkova, J. A. Markham, R. J. Delay, *Brain Res.* **266**, 163 (1983).
 54. F. Crick, *Trends Neurosci.* **5**, 44 (1982).
 55. E. G. Jones and T. P. S. Powell, *J. Cell Sci.* **5**, 509 (1969); R. H. Laatsch and W. M. Cowan, *J. Comp. Neurol.* **128**, 359 (1966); F. F. Ebner and M. Colonnier, *ibid.* **160**, 51 (1975).
 56. R. G. Coss and D. H. Perkel, *Behav. Neural Biol.* **44**, 151 (1985).
 57. M. Friere, *J. Anat.* **126**, 193 (1978).
 58. E. R. Kandel and J. H. Schwartz, *Science* **218**, 433 (1982).
 59. C. Von der Marlsburg, *Kybernetik* **14**, 85 (1973); H. Frohn, H. Geiger, W. Singer, *Biol. Cybern.* **55**, 333 (1987).
 60. T. Kohonen, *Associative Memory: A System Theoretical Approach* (Springer-Verlag, Berlin, 1977); J. J. Hopfield and D. W. Tank, *Science* **233**, 625 (1986).
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