Mechanisms of Plasticity in the Visual Cortex

The Friedenwald Lecture

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Plasticity in the visual cortex underlies amblyopia, which may result from strabismus, anisometropia, astigmatism, form deprivation from cataract, or other optical defects in the eyes. This is sensory-dependent or experience-dependent plasticity, in which optical or motor changes lead to an abnormal pattern of signals that reach the visual cortex. The abnormal pattern of signals in turn leads to changes in the connections within the cortex. There is a critical period during which the connections in the cortex are particularly susceptible to these changes.

The fundamental mechanisms are there for normal as well as abnormal development. During the first few months and years of life, the eyes grow larger, the distance between the eyes increases, and the fovea matures. The connections in the visual cortex are fine-tuned to accompany these changes that occur in the eye. Moreover, binocular vision is not fully developed at birth. Depth perception depends on cues other than stereopsis. Coordination of eye movements is immature. There is less need for the eyes to fixate in a coordinated fashion because acuity is poor. Ability for accurate vergence movements does not develop until the need is there.

Abnormal optical input leads to fine tuning of the connections in the visual cortex in an abnormal way. In most cases, this is to avoid double vision. Either the connections of one eye to the cortex are blurred or reduced (amblyopia), and/or the image in one eye is suppressed, and/or the mapping of the retina onto the cortex is distorted or altered (abnormal retinal correspondence).

This subject is an important one from several points of view. From the clinical point of view, strabismus, anisometropia, cataract, astigmatism, and other optical deficits that put people at risk for amblyopia affect between 2% and 4% of the population. This is more than all other forms of blindness put together. From the philosophical point of view, arguments about nature versus nurture have long been discussed in relation to the visual system. Molyneux's question (whether a man born blind, on having his sight restored, can distinguish a cube from a sphere) is one example. From the historical point of view, Hippocrates described strabismus and its genetic component, and operations for cataract were well known among the Arabs in the 8th century. From the perspective of neurobiology, the visual system has become the model for the understanding of plasticity because it is the one system where work at the behavioral, anatomic, and physiological levels can be correlated to lead to a study of the basic mechanisms involved.

In this paper, I will summarize my work on the subject and relate it to the work of some of the other people who have made substantial and important contributions to the subject in the last 30 years.

DIFFERENT CRITICAL PERIODS AT DIFFERENT LEVELS OF THE VISUAL SYSTEM

My first experiment on this subject occurred when Harry Wyatt was in the laboratory in the early 1970s. We wanted to study synaptic mechanisms underlying plasticity. It seemed to us that synaptic mechanisms were more clearly understood in the retina than in the cortex and that we should try to find a form of visual deprivation that had an effect on the retina.

At that time, Wiesel and Hubel had shown that the effects of visual deprivation in the cortex are accentuated by competition. Cells in the cortex of animals with monocular deprivation were driven almost entirely by the normal eye. Few cells could be driven by the deprived eye. On the other hand, binocular deprivation was not simply the sum of two monocular deprivations. One third of the cells in animals with binocular deprivation were normal and could be driven by both eyes, one third could be driven by...
both eyes with abnormal responses, and only one third could not be driven by either eye. The conclusion was that strong input from the normal eye competed with weak input from the deprived eye in monocularly deprived animals in such a way that the connections from the deprived eye decayed.

Monocular deprivation is obviously not a competitive stimulus for the retina or for the lateral geniculate where the input from the two eyes is kept largely separate. Wiesel and Hubel did not find any effects of monocular deprivation on the retina, and the effects that they found on the cells in the lateral geniculate could be accounted for by competition between the terminals of those cells in the cortex.

We thought that rearing animals in an environment continually moving in one direction might provide a competitive stimulus for cells in the retina for an animal that has a lot of directionally selective cells in the retina, such as the rabbit. However, when we reared rabbits in a drum with vertical stripes continually moving in one direction, the result was negative: The percentage of cells preferring movement to the right, compared to the percentage preferring movement left, was normal.

The curve for direction-selective changes passes through the normal ratio (60%) before 4 weeks of age, and the curve for ocular dominance changes passes through the normal ratio (43%) after 7 weeks of age. Reprinted with permission from Daw NW, Wyatt HJ. J Physiol. 1976;257:155–170.

FIGURE 1. Distribution of preferred directions of direction-selective cells in the cortex of normal animals (left) and in the cortex of animals reared for 2 hours per day in a drum continually moving to the right from \(3\frac{1}{2}\) weeks to 7 weeks of age. Reprinted with permission from Daw NW, Wyatt HJ. J Physiol. 1976;257:155–170.

FIGURE 2. Comparison of sensitive periods for direction-selective changes and ocular dominance changes. Points plot the percentage of cells preferring the direction seen second and the eye open second after reversals at various different ages. The curve for direction-selective changes passes through the normal ratio (60%) before 4 weeks of age, and the curve for ocular dominance changes passes through the normal ratio (43%) after 7 weeks of age. Reprinted with permission from Daw NW, Wyatt HJ. J Physiol. 1976;257:155–170.

FIGURE 3. Comparison of the onset of stereopsis in the cat with the sensitive period for direction and ocular dominance changes. Stereopsis does not start until the sensitive period for direction-selective changes is largely complete. On the other hand, there is substantial capability for ocular dominance changes after stereoscopic acuity is close to adult levels. Ability to reverse direction selectivity and ocular dominance from Figure 2: development of stereoscopic acuity plotted against left axis.
As a control for our procedures, we then reared kittens in the drum and recorded from cells in the visual cortex. In that case, the result was positive: When the drum was continually moved to the right, a large majority of direction-selective cells in the cortex preferred movement to the right as opposed to movement to the left (Fig. 1).9

There were two ways to interpret these two experiments. One was to say that the cat is plastic and the rabbit is not. The second was to say that the cortex is plastic and the retina is not. In fact, monocular deprivation leads to ocular dominance shifts in the rabbit, although they are small,10 and there was little evidence that visual deprivation leads to any changes in the cat retina.11 The best general statement, therefore, seemed to be that the cortex is plastic and the retina is not.

Consequently, we thought of our experiments, privately, in terms of the general hypothesis that plasticity increases and remains for a longer period of time as one goes higher within the visual system. The retina is not plastic, the lateral geniculate has limited plasticity, the visual cortex is plastic for a limited period of time, and there are areas of temporal cortex dealing with memory12 which, together with the hippocampus, are plastic forever.

Within this general framework, we decided to compare the critical periods for direction-selective changes and ocular-dominance changes in cat primary visual cortex. We used a reversal paradigm. Animals were reared in a drum moving to the left starting at 2 weeks of age, then the direction of movement was switched to the right at a time that varied from animal to animal, until 12 weeks of age.9 When the switch was made early, the majority of cells preferred movement to the right. When the switch was made late, the majority of cells preferred movement to the left. Plotting the percentage of cells preferring the movement seen second against the age of the switch gave a curve that passed through the normal ratio (60% right, 40% left for the left visual cortex) just before 4 weeks of age (Fig. 2). A similar experiment performed by Blakemore and Van Sluyters13 with reverse eye suture showed a curve that passed through the normal ratio at 7 weeks of age. This result was confirmed by rearing animals with reversals of direction at 5 weeks, in which the majority of cells preferred the direction seen first, and animals with reversal of eye suture at 5 weeks, in which the majority of cells were dominated by the eye open second.14 When the two forms of deprivation were combined with each other, the majority of direction-selective cells preferred the direction seen first at the same time that they were dominated by the eye that opened second.15 Clearly, the critical period for changes in direction selectivity ends earlier than the critical period for ocular dominance changes.

At the time, we were puzzled by this result. Put-
ments, it was known that a high percentage of simple cells, which are found at the first level of processing in the visual cortex in layer IV, are direction selective, but the segregation of ocular dominance columns in layer IV had not been described. Now, it is clear that direction selectivity is a property of cells within layer IV, whereas signals from the two eyes are somewhat separate in layer IV and become combined at higher levels of the system. The result that the critical period for direction selectivity ends earlier than the critical period for binocularity therefore fits in with the general rule that the critical period ends later for functions dealt with at higher levels of the system.

Now, following the work of Held and his colleagues on the onset of stereopsis, we can present a hypothesis about the teleology. This is that direction selectivity, which is related to the orientation of the stimulus, needs to be coordinated for the two eyes early on, so that disparity-sensitive cells receive similar input from the two eyes. Held has pointed out that stereopsis occurs suddenly and that the period during which stereoscopic acuity improves from zero to near adult levels is similar to the period during which ocular dominance columns segregate, although there may be some improvement in disparity selectivity before this. This is true for cat, macaque, and human. Presumably, direction and orientation selectivity get coordinated for the two eyes in the prestereoscopic period, when the cells in layer IV are still binocular. Only after coordination and fine tuning has taken place is the system ready to create cells for disparity. It would be hard to create stereopsis with an acuity that is an order of magnitude greater than grating acuity if the inputs from the two eyes to the disparity-sensitive cells were not finely tuned and well coordinated.

When one compares our results on the sensitive period for direction selectivity with the results of Blakemore and van Sluyters, and the results from Timney on the onset of stereopsis in kittens, the sequence of events is clear (Fig. 3). Direction selectivity is largely set in place before stereopsis starts. There is a large capability for ocular dominance changes during the week or two in which stereoscopic acuity is improving dramatically, and there is still some capability for ocular dominance changes after stereoscopic acuity has reached adult levels.

MECHANISMS UNDERLYING PLASTICITY IN THE VISUAL CORTEX

Our more recent work has related to the mechanisms underlying plasticity. The changes in connections that occur in the visual cortex include changes in the terminals of geniculocortical axons, changes in intracortical connections, and synaptic changes.
There are also a number of dendritic changes that occur during normal development, and most likely these also can be altered by visual deprivation. How do the sensory signals cause all these anatomic and related physiological alterations? The sensory signals are carried from retina to cortex by electrical activity, so blockade of this activity by tetrodotoxin abolishes plasticity, but what happens after that?

The animal model that has been used for nearly all experiments on mechanisms is monocular deprivation. This corresponds to unilateral cataract in man, which is fairly rare. However, animal models of strabismus and anisometropia, which are much more common in man, do not give results that are as clear and consistent as monocular deprivation.

There are a large number of substances that have been shown to reduce or abolish the ocular dominance changes that usually occur after monocular deprivation. Apart from those that abolish activity in afferent fibers, like tetrodotoxin, the list includes substances that modulate activity in the cortex, hormones, growth factors, and general depressants of activity. Clearly, this is an inclusive criterion rather than an exclusive one. For substances that are critically involved in plasticity—that is substances that allow plasticity in the young animal by their presence—and are absent in the adult, other criteria are needed.

A further criterion is that the substance should follow the critical period. It should be high at the peak of the critical period and fall after that. For ocular dominance changes in the cat, the critical period starts at 3 weeks of age, peaks at 4 to 6 weeks, declines from then until around 5 months, then has a plateau of reduced plasticity until it finally ends between 9 months and 1 year of age (Fig. 4).

The critical period varies with layer, and a substance that is closely tied to plasticity should show corresponding variations with layer. For ocular dominance shifts, plasticity is different in layer IV than it is in other layers. In the monkey, it seems that the critical period ends earlier in layer IV. In the cat, this may also be true, although there may be some residual plasticity in layer IV at 9 months of age, in which case it would be more correct to say that the effects of monocular deprivation are smaller in layer IV than in other layers at all ages (Fig. 5).

Another criterion is that procedures that change the time course of the critical period should also change substances that are crucially involved in plasticity. The main procedure is rearing in the dark, which is known to prolong the end of the critical period and to delay the start.

Over the years, we have tested a variety of substances by these three criteria. One was the growth-associated protein, GAP-43. This protein, also known as F-I, has been implicated in long-term potentiation in the hippocampus. Helen McIntosh created an antibody to the cat version of GAP-43 and measured its concentration in cat visual cortex as a function of age. We found that the concentration is highest soon after birth, before the critical period starts, and drops substantially between then and 4 to 6 weeks of age, when the peak of the critical period occurs (Fig. 6). GAP-43 is known to be associated with growth cones. This suggests that the prime function of this protein has to do with axons finding their way to their targets.
ROLE OF NMDA RECEPTORS IN PLASTICITY IN THE VISUAL CORTEX

The one substance we tested that fulfills all three of the criteria discussed above is the N-methyl-D-aspartate (NMDA) receptor. This line of experiments rather than with sensory-dependent alterations of synapses, which occurs after the growth cones have found their targets and synaptogenesis is complete.

Because the critical period comes to an end just before puberty, we also wondered if the hormonal changes that occur with puberty could play a role. We discovered that the hormone cortisol, which rises in the human during adrenarche a little before puberty, reduces ocular dominance shifts. However, we also discovered that plasma levels of cortisol do not rise in the cat at approximately 1 year of age sufficiently to account for the end of the critical period. It is possible that there are changes in steroid receptors that occur during this period—large enough to reduce the effectiveness of the circulating levels of steroids substantially—but this has not yet been tested.

<table>
<thead>
<tr>
<th>Ocular Dominance Group</th>
<th>MD Controls</th>
<th>MD With MK801</th>
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<tr>
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<td>1</td>
<td>2</td>
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<tr>
<td>Percentage of cells</td>
<td>50</td>
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FIGURE 7. Ocular dominance histograms from three animals given monocular deprivation after injections of MK801 compared to histograms from control animals deprived at the same age for the same period of time. Single cells assayed for eye dominance and put into seven ocular dominance groups: 1, driven by contralateral eye only; 7, driven by ipsilateral eye only; 4 driven equally by both eyes; 2 and 6, strongly dominated by one eye; 3 and 5, weakly dominated by one eye). Contralateral eye closed in all cases. Control animals showed an ocular dominance histogram dominated by the ipsilateral eye. Animals treated with MK-801 showed a significantly flatter ocular dominance histogram.

<table>
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<tr>
<th>Receptive field properties</th>
<th>MK801</th>
<th>Control</th>
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<tr>
<td>UD</td>
<td>BD</td>
<td>WT</td>
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<tr>
<td>Percentage of cells</td>
<td>60</td>
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FIGURE 8. Receptive field properties for animals injected with MK801 and given monocular deprivation, compared to receptive field properties of animals given monocular deprivation alone. Unidirectional (UD) cells with a substantial response in one direction compared to all others; bidirectional (BD) cells with a substantial response for movement along one axis compared to the perpendicular axis; widely tuned (WT) bidirectional cells responding over an angle greater than 90° and unidirectional cells responding over an angle greater than 180°; omnidirectional (OD) cells with a substantial response to all directions of movement; hard to drive (HTD) cells with little visual response.
FIGURE 9. Effect of injections of MK801 on activity of cells in the visual cortex. Cells were stimulated with a bar of light of the preferred length, width, orientation, velocity, and direction of movement, and response was measured as the total number of action potentials as the stimulus swept through the receptive field of the cell. Histograms show responses before and for a period after injection of MK-801.

started when Kevin Fox and Hiromichi Sato joined the laboratory in 1987. Glutamate is the excitatory transmitter in the visual cortex, and it acts on NMDA, AMPA-kainate, and metabotropic receptors. The NMDA receptor is of particular interest because it has voltage-dependent properties due to block of the channel by Mg$^{++}$, and it is required for long-term potentiation in the hippocampus. When one infuses the NMDA antagonist, 2-amino-5-phosphonovaleric acid (APV) into the visual cortex, as first shown by Kleinschmidt, Bear, and Singer, this abolishes the ocular dominance shifts that normally result from monocular deprivation. APV also affects the development of receptive-field properties, such as orientation and direction selectivity. We could interpret this by saying that APV abolishes the afferent signals, as TTX does (Stryker, private communication). Consequently, we repeated the experiment with a different technique to evaluate this point (Gordon and Daw, unpublished data).

We injected the NMDA channel blocker, MK-801, which crosses the blood–brain barrier, into the muscles of kittens (1 to 2 mg/kg body weight). The eyelids of one eye were sutured shut, and then the animals were kept in the dark for 16 hours a day. They were given one injection at 8 AM, brought into the light, given another injection at noon, and returned to the dark room at 4 PM. After 5 days of this treatment, cells were recorded from the visual cortex with our usual protocol, and an ocular dominance histogram was constructed. Comparison of the ocular dominance histogram from treated animals with the ocular

FIGURE 10. Total number of binding sites ($B_{max}$) for binding of $^3$H-MK801 to NMDA channels in cat visual cortex as a function of age, compared to the critical period for monocular deprivation (MD). Binding sites expressed as pmoles of $^3$H-MK801 bound per milligram of protein, from the intercept on a Scatchard plot. Critical period from Figure 4.

FIGURE 11. NMDA contribution to the visual response in different layers as a function of age, compared to ocular dominance segregation. NMDA contribution to the visual response was calculated by recording the response from a single cell, iontophoresing the NMDA antagonist APV, and observing the reduction in the visual response. This gives a fraction for the response during iontophoresis of APV as a percentage of the control response (vertical axis represents % control response). Percentages from a number of different single cells from particular layers at particular ages were averaged together to give the numbers plotted in the graph. Ocular dominance (OD) segregation index calculated from grain counts from $^3$H-proline transported from one eye to layer IV in the visual cortex. Grain counts were smoothed, and the area between grain counts and mean level was calculated then expressed as a fraction of a square wave going from minimum to maximum levels. This gives a fraction of no segregation and 1 for perfect segregation. Results are plotted in this figure as 100 (1 - segregation index), to use the same scale as NMDA contribution to the visual response. • = OD seg; □ = layers II and III; ○ = layer IV; ● = layers V and VI.
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FIGURE 12. Effect of dark rearing on the NMDA contribution to the visual response in layers IV, V, and VI. Dark rearing retains the NMDA contribution to the visual response at high levels for several months. If animals are dark reared until 6 weeks of age and then brought into the light, the change in the NMDA contribution to the visual response proceeds. Open symbols, light-reared animals; filled symbols, dark-reared animals; half-filled symbols, animals reared in the light until 6 weeks then brought into the light. Circles, layer IV; squares, layers V and VI. Reprinted with permission from Czepita D, Reid SNM, Daw NW. J Neurophysiol. 1994.

The dominance histogram from control animals (Fig. 7) showed that MK801 reduced the ocular dominance shift by about the same amount as infusion of APV directly into the visual cortex. In agreement with Kleinschmidt, Bear, and Singer and with Rauschecker, Egert, and Kossel, the percentage of cells specific for the orientation and direction of movement of the stimulus was also reduced (Fig. 8).

At the end of the physiological recordings, we injected MK801 into the muscle at the same dose that we had during the rearing procedure and followed the visual response to a stimulus of the preferred length, width, orientation, velocity, and direction of movement. In one case, the response dropped to 50% of control and came back to 75% of control after 45 minutes. In the other case, the response dropped to 25% of control and came back to 50% of control after an hour (Fig. 9). This showed that the response was at least 50% of control for three quarters of the time that the animals were in the light. Although these results are not water tight (injection of MK801 into the muscle could have peripheral effects that would affect ocular dominance shifts by an indirect route), they do suggest that ocular dominance shifts are reduced by doses of NMDA antagonists that do not act like TTX: The afferent activity is somewhat reduced but certainly not abolished.

The next question is: Do measures of the NMDA receptor change in synchrony with the critical period? Barbara Gordon measured binding of $^3$H-MK801 to cat visual cortex at various ages and found that the total number of binding sites ($B_{\text{max}}$) peaked with the critical period (Fig. 10), in agreement with results from other laboratories. NMDA receptors are still there in the adult ($B_{\text{max}}$ is half that at the peak of the critical period), concentrated in layers II and III. Presumably, these NMDA receptors are involved in some other function—either normal processing of visual information or plasticity for some function other than convergence of the signals from the two eyes.

We also observed the NMDA contribution to the visual response. This was measured by recording from a cell, iontophoresing the NMDA antagonist APV, and observing the reduction in the response of the cell. We discovered that the NMDA contribution to the visual response is high in layers II and III at all ages. However, the NMDA contribution to the visual response for cells in layers IV, V, and VI drops from approximately 50% at 3 weeks of age to 10% to 15% at 6 weeks of age. This measure represents the relative contributions of NMDA and AMPA–kainate receptors to the visual response, and not the absolute number of NMDA receptors. The period during which the drop occurs is the same period during which ocular dominance columns are segregating in layer IV (Fig. 11).

Rearing in the dark postpones this change in the NMDA contribution to the visual response that occurs in layer IV. We reared different animals in the dark to 6 weeks, 3 months, and 5 months of age; one animal was reared to 11 months of age. In all cases, the NMDA contribution to the visual response was substantially above that in light-reared animals (Fig. 12). When animals were reared in the dark to 6 weeks of age and then brought into the light, the change proceeded.

Rearing in the dark therefore has a similar effect on the NMDA receptors in layers IV, V, and VI as it does on segregation of ocular dominance columns. Both events are under the control of light.

The summary of this body of work, combining our results with the results from other laboratories, is that:
Two mechanisms have been discussed. One is that the NMDA receptor plays a role in strengthening synapses according to the mechanism proposed by Hebb. The second is that NMDA receptors let calcium into the cell, and this triggers second messenger systems. Hebb suggested that if presynaptic and postsynaptic cells fire together, the synapse between them is strengthened, with the corollary that if they do not fire together, the synapse is weakened. This has to be modified for the visual cortex to take account of the fact that there is input from two sources. One modification is shown in Figure 13 and is essentially that the postsynaptic cell fires if a certain number of inputs fire together, in this illustration 2. If input from both left eyes fire together without input from a right eye, the left eye input is strengthened and the right eye input is weakened, resulting in monocular deprivation. If left and right eye input never fires together, there will be a tendency for cells initially dominated by the left eye to lose their right eye input and for cells initially dominated by the right eye to lose their left eye input. Binocularity will be maintained only if left and right eye input fires synchronously.

The NMDA receptor could play a role within this

1. Antagonists to NMDA receptors reduce ocular dominance plasticity and the refinement of receptive-field properties.
2. The overall concentration of NMDA receptors in the visual cortex peaks with the critical period for ocular dominance plasticity.
3. The NMDA contribution to the visual response drops in layers IV, V, and VI as ocular dominance columns segregate.
4. Rearing in the dark postpones these changes, as it does ocular dominance segregation and other events during the critical period.

Thus, NMDA receptors fulfill three of the criteria for a substance that is higher in young animals than in adults and is also along the pathway for plasticity. It is, therefore, a critical component in this pathway.

MECHANISM OF ACTION OF NMDA RECEPTORS

I would like to make one final comment about the mechanism of action of NMDA receptors in plasticity.

FIGURE 14. Effect of quisqualate and NMDA on contrast-response curves in the cat visual cortex. Response measured for a stimulus of the preferred length, width, orientation, velocity, and direction of movement. Contrast varied from approximately 0.16 to 16 times the background. Quisqualate moves the curve upward; NMDA increases the slope of the curve. Reprinted with permission from Fox D, Sato H, Daw NW. J Neurophysiol. 1990;64;1413–1428.

FIGURE 15. Modeling of the action of NMDA and quisqualate on contrast-response curves in the cat visual cortex. The model predicts that there will be explosive switch-like behavior with a high ratio of NMDA to non-NMDA receptors and a hyperbolic tangent curve with a moderate ratio. The hyperbolic tangent curve rather than the switch-like behavior is seen in the visual cortex. Reprinted with permission from Fox D and Daw NW. Neural Computation. 1992;4;59–83.
framework by making it more probable that the postsynaptic cell fires when the presynaptic cell fires. We observed contrast response curves in the visual cortex and discovered that iontophoresis of the AMPA-kainate agonist, quisqualate, moved the curve upward, whereas iontophoresis of NMDA increased the slope of the curve (Fig. 14). The implication is that AMPA-kainate receptors act on thefferent signals in an additive fashion, whereas NMDA receptors act on them in a multiplicative fashion. NMDA receptors, therefore, could definitely act to increase the probability that the postsynaptic cell will fire when the presynaptic cell fires.

However, the NMDA receptor did not seem to act as a switch, in the sense that it produced an explosive or an all-or-none response as the action potential does. We modeled the system using equations for the voltage dependency of the NMDA receptor and required that two molecules of glutamate needed to bind at the NMDA receptor but only one needed to bind at the AMPA-kainate receptor (the model could not be made to fit the results with a requirement for binding two molecules of glutamate at the AMPA-kainate receptor). The model suggested that switch-like behavior can occur if the ratio of NMDA to AMPA-kainate receptors is high enough (Fig. 15). Whether the ratio is high enough in the hippocampus is not known because experiments similar to ours in the visual cortex have not been performed in the hippocampus, but it does not seem to occur in the visual cortex, at least as far as can be measured from an electrode at the cell body.

NMDA receptors undoubtedly let calcium into cells in the visual cortex, and this is the next step along the pathway. Calcium entry is likely to be higher in animals at the peak of the critical period, as a result of the presence of more NMDA receptors and possibly of a change in the nature of the NMDA receptors. It is not clear that calcium entry can distinguish between activation of input from two left eyes at the same time and activation of left eye input and right eye input at the same time. Current evidence suggests that calcium entry is a step along the pathway, but, like electrical activity, it is not calcium entry that makes young animals plastic while adults are not.

CONCLUSION
Some of my earlier work on color vision, mechanisms of directional selectivity in the rabbit retina, and generalizations about the function of transmitters in the retina came to a more definite conclusion. This work on plasticity in the visual cortex is definitely in mainstream. There have to be several other steps along the pathway between sensory input and alteration of connections in the visual cortex. Some of them, like NMDA receptors, may be crucial steps that are reduced or lacking in the adult. Many of them will be steps that are found at all ages. I look forward to hearing future Friedenwald awardees who have identified the remaining steps and shown which of them allow plasticity in young animals.

Key Words
visual cortex, amblyopia, development, visual deprivation, NMDA receptors

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