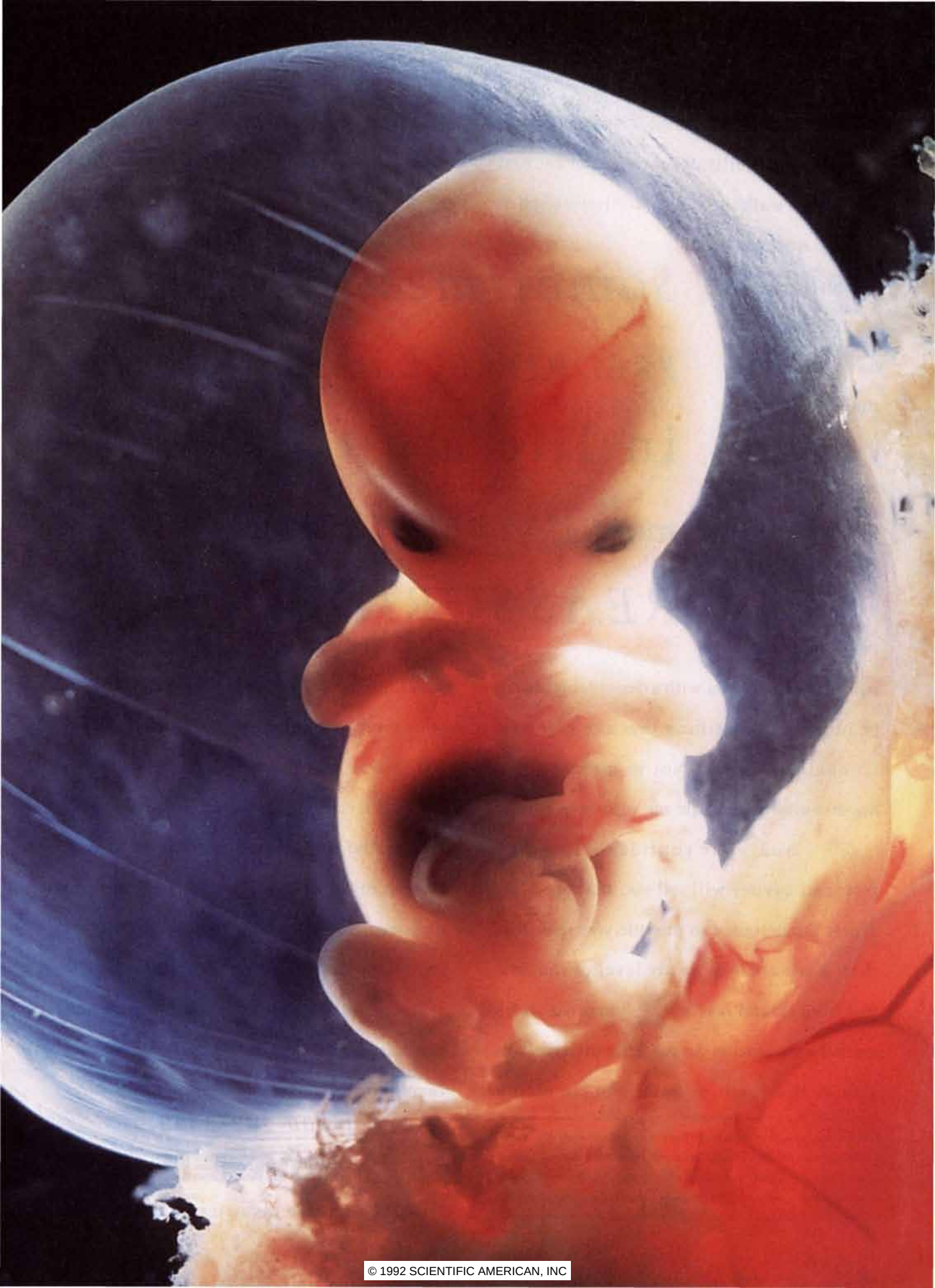

# The Developing Brain

*During fetal development, the foundations of the mind are laid as billions of neurons form appropriate connections and patterns. Neural activity and stimulation are crucial in completing this process*

by Carla J. Shatz

An adult human brain has more than 100 billion neurons. They are specifically and intricately connected with one another in ways that make possible memory, vision, learning, thought, consciousness and other properties of the mind. One of the most remarkable features of the adult nervous system is the precision of this wiring. No aspect of the complicated structure, it would appear, has been left to chance. The achievement of such complexity is even more astounding when one considers that during the first few weeks after fertilization many of the sense organs are not even connected to the embryonic processing centers of the brain. During fetal development, neurons must be generated in the right quantity and location. The axons that propagate from them must select the correct pathway to their target and finally make the right connection.

How do such precise neural links form? One idea holds that the brain wires itself as the fetus develops, in a manner analogous to the way a computer is manufactured: that is, the chips and components are assembled and connected according to a preset circuit diagram. According to this analogy, a flip of a biological switch at some point in prenatal life turns on the computer. This notion would imply that the brain's entire structure is recorded in a set of biological blueprints—presumably DNA—and that the organ begins to work only after the wiring is essentially complete.

Research during the past decade shows that the biology of brain development follows very different rules. The neural connections elaborate themselves from an immature pattern of wiring that only grossly approximates the adult pattern. Although humans are born with almost all the neurons they will ever have, the mass of the brain at birth is only about one fourth that of the adult brain. The brain becomes bigger because neurons grow in size, and the number of axons and dendrites as well as the extent of their connections increases.

Workers who have studied the development of the brain have found that to achieve the precision of the adult pattern, neural function is necessary: the brain must be stimulated in some fashion. Indeed, several observations during the past few decades have shown that babies who spent most of their first year of life lying in their cribs developed abnormally slowly. Some of these infants could not sit up at 21 months of age, and fewer than 15 percent could walk by about the age of three. Children must be stimulated—through touch, speech and images—to develop fully. Based in part on such observations, some people favor enriched environments for young children, in the hopes of enhancing development. Yet current studies provide no clear evidence that such extra stimulation is helpful.

**SEVEN-WEEK-OLD HUMAN FETUS is about an inch long. Eyes and limbs are visible, and the emerging brain is apparent. Stimulation is needed to complete development, a process that for many neural systems continues into neonatal life.**

Much research remains to be done before anyone can conclusively determine the types of sensory input that encourage the formation of particular neural connections in newborns. As a first step toward understanding the process, neurobiologists have focused on the development of the visual system in other animals, especially during the neonatal stages. It is easy under the conditions that prevail at that stage to control visual experience and observe behavioral response to small changes. Furthermore, the mammalian eye differs little from species to species. Another physiological fact makes the visual system a productive object of study: its neurons are essentially the same as neurons in other parts of the brain. For these reasons, the results of such studies are very likely to be applicable to the human nervous system as well.

But perhaps the most important advantage is that in the visual system, investigators can accurately correlate function with structure and identify the pathway from external stimulus to physiological response. The response begins when the rods and cones of the retina transform light into neural signals. These cells send the signals to the retinal interneurons, which relay them to the output neurons of the retina, called the retinal ganglion cells. The axons of the retinal ganglion cells (which make up the optic nerve) connect to a relay structure within the brain known as the lateral geniculate nucleus. The cells of the lateral geniculate nucleus then send the visual information to specific neurons located in what is called layer 4 of the (six-layer) primary visual cortex. This cortical region occupies the occipital lobe in each cerebral hemisphere [*see illustration on next page*].

Within the lateral geniculate nucleus, retinal ganglion cell axons from each eye are strictly segregated: the axons of one eye alternate with those from the other and thus form a se-

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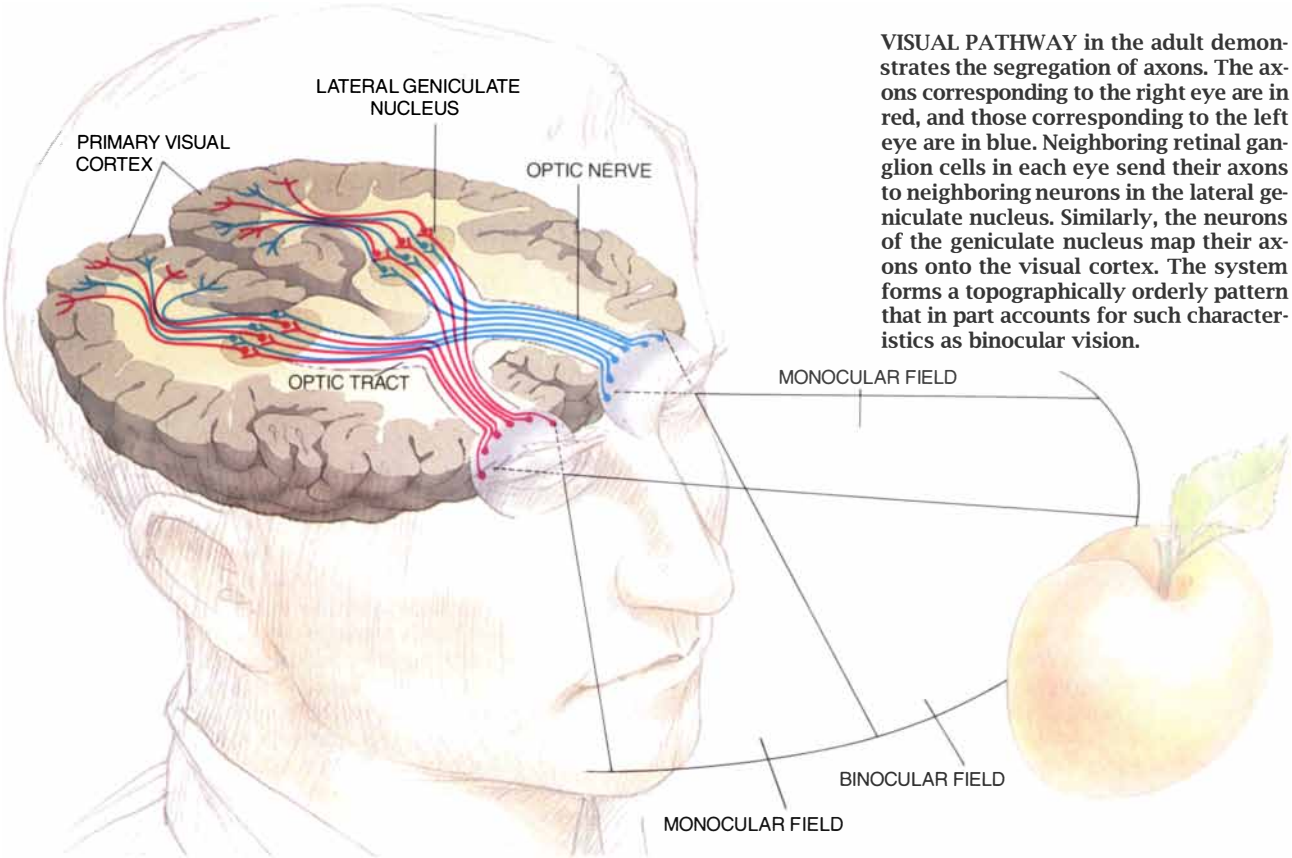
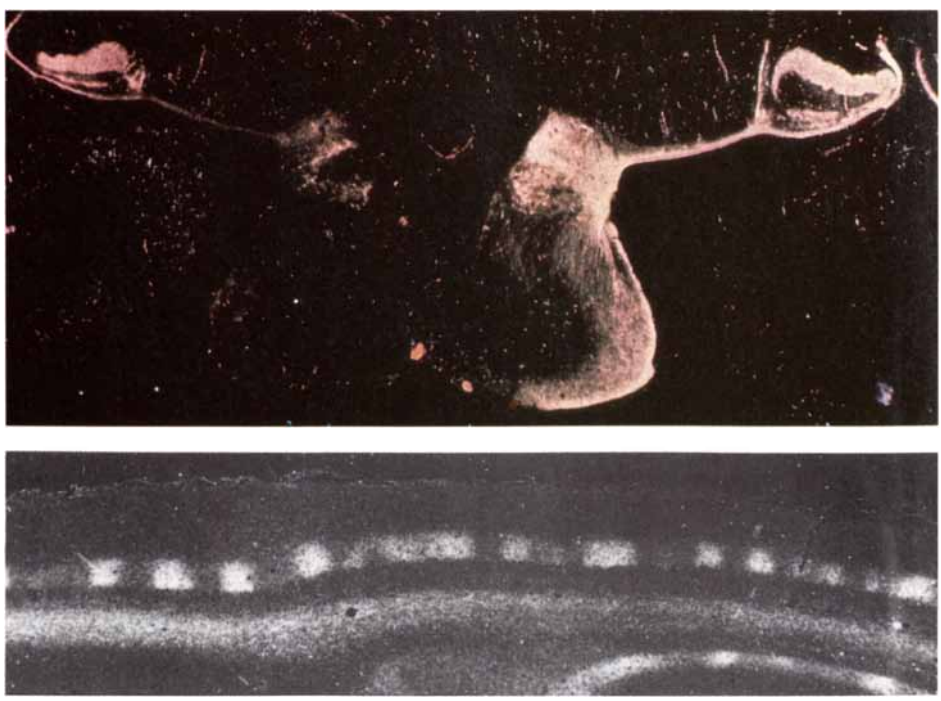



**VISUAL PATHWAY** in the adult demonstrates the segregation of axons. The axons corresponding to the right eye are in red, and those corresponding to the left eye are in blue. Neighboring retinal ganglion cells in each eye send their axons to neighboring neurons in the lateral geniculate nucleus. Similarly, the neurons of the geniculate nucleus map their axons onto the visual cortex. The system forms a topographically orderly pattern that in part accounts for such characteristics as binocular vision.

ries of eye-specific layers. The axons from the lateral geniculate nucleus in turn terminate in restricted patches within cortical layer 4. The patches corresponding to each eye interdigitate with one another to form structures termed ocular dominance columns.

To establish such a network during development, axons must grow long distances, because the target structures form in different regions. The retinal ganglion cells are generated within the eye. The lateral geniculate neurons take shape in an embryonic structure known as the diencephalon, which will form the thalamus and hypothalamus. The layer 4 cells are created in another protoorgan called the telencephalon, which later develops into the cerebral cortex. From the beginning of fetal development, these three structures are many cell-body diameters distant from one another. Yet after identifying one or the other of these targets, the axons reach it and array themselves in the correct topographic fashion—that is, cells located near one another in one structure map their axons to the correct neighboring cells within the target.

This developmental process can be compared with the problem of stringing telephone lines between particu-



**NEURAL DEVELOPMENT** of the visual system is revealed here by a radioactive tracer injected into the vitreous humor of the left eye. The images correspond to a top view of the visual system of a cat. Only areas receiving input from the injected eye become labeled (*white areas*). In the lateral geniculate nucleus (*top left*), most of the left eye's input ends in layers in the right nucleus, although the wiring of the visual pathway places some label in the left nucleus. Similar segregation is seen in the ocular dominance columns in layer 4 of the visual cortex (*bottom left*); the gaps represent regions corresponding to axons from the uninjected eye. The adult patterns are in distinct contrast to their immature forms, shown to the right. The immature axons have yet to segregate: the label is uniformly distributed.

lar homes located within specific cities. For instance, to string wires between Boston and New York, one must bypass several cities, including Providence, Hartford, New Haven and Stamford. Once in New York, the lines must be directed to the correct borough (target) and then to the correct street address (topographic location).

Corey Goodman of the University of California at Berkeley and Thomas Jessel of Columbia University have demonstrated that in most instances, axons immediately recognize and grow along the correct pathway and select the correct target in a highly precise manner. A kind of "molecular sensing" is thought to guide growing axons. The axons have specialized tips, called growth cones, that can recognize the proper pathways. They do so by sensing a variety of specific molecules laid out on the surface of, or even released from, cells located along the pathway. The target itself may also release the necessary molecular cues. Removing these cues (by genetic or surgical manipulation) can cause the axons to grow aimlessly. But once axons have arrived at their targets, they still need to select the correct address. Unlike pathway and target selection, address selection is not direct. In fact, it involves the correction of many initial errors.

The first hint that address selection is not precise came from experiments using radioactive tracers. Injections of these tracers at successively later times in fetal development outline the course and pattern of axonal projections. Such studies have also shown that structures emerge at different times in development, which can further complicate address selection.

For instance, Pasko Rakic of Yale University has shown that in the visual pathway in monkeys, the connections between the retina and the lateral geniculate nucleus appear first, followed by those between the lateral geniculate nucleus and layer 4 of the visual cortex. Other studies found that in cats and primates (including humans), the lateral geniculate nucleus layers develop during the prenatal period, before the rods and cones of the retina have formed (and thus before vision is even possible). When Simon LeVay, Michael P. Stryker and I were postdoctoral fellows at Harvard Medical School, we found that at birth, layer 4 columns in cats do not even exist in the visual cortex [*see illustrations below*]. I subsequently determined that even earlier, in fetal life, the cat has no layers in the lateral geniculate nucleus. These important visual structures emerge only gradually and at separate stages.

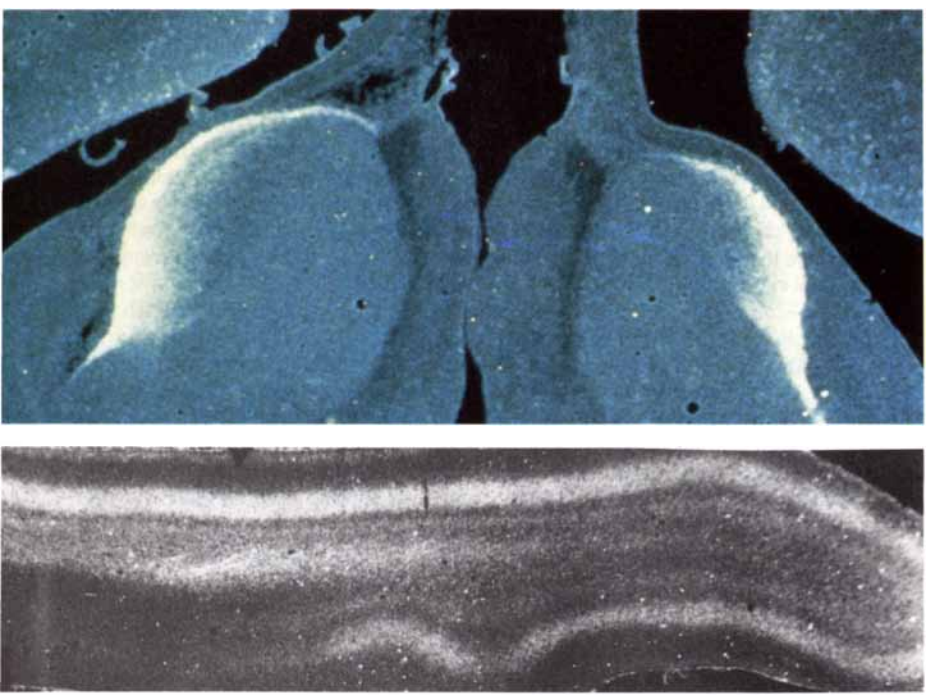
The functional properties of neurons, like their structural architecture, do not attain their specificity until later in life. Microelectrode recordings from the visual cortex of newborn cats and monkeys reveal that the majority of layer 4 neurons respond equally well to visual stimulation of either eye. In the adult, each neuron in layer 4 responds primarily if not exclusively to stimulation of one eye only. This finding implies that during the process of address selection, the axons must correct their early "mistakes" by removing the inputs from the "inappropriate" eye.

In 1983 my colleague Peter A. Kirkwood and I found further evidence that axons must fine-tune their connections. It came from our work on the brains of six-week-old cat fetuses (the gestation period of the cat is about nine weeks). We removed a significant portion of the visual pathway—from the ganglion cells in both eyes to the lateral geniculate nucleus—and placed it in vitro in a special life-support chamber. (Inserting microelectrodes in a fetus is extremely difficult.) The device kept the cells alive for about 24 hours. Next we applied electrical pulses to the two optic nerves to stimulate the ganglion cell axons and make them fire action potentials, or nerve signals. We found that neurons in the lateral geniculate nucleus responded to the ganglion cells and, indeed, received inputs from both eyes. In the adult the layers respond only to stimulation of the appropriate eye.

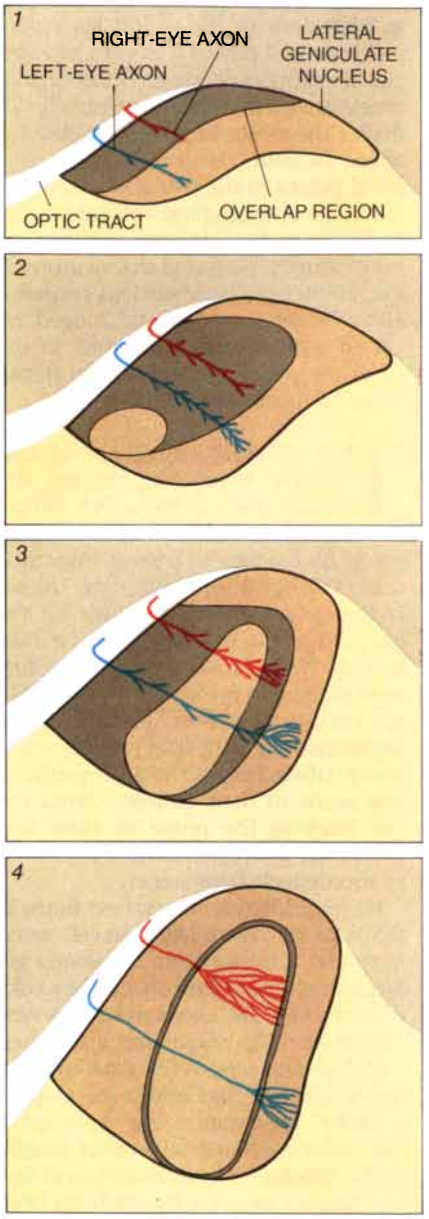
The eventual emergence of discretely functioning neural domains (such as the layers and ocular dominance columns) indicates that axons do manage to correct their mistakes during address selection. The selection process itself depends on the branching pattern of individual axons. In 1986 David W. Sretavan, then a doctoral student in my laboratory, was able to examine the process in some detail. Experimenting with fetal cats, he selectively labeled single retinal ganglion cell axons in their entirety—from the cell body in the retina to their tips within the lateral geniculate nucleus—at successively later stages.

He found that at the earliest times in development, when ganglion cell axons have just arrived within the lateral geniculate nucleus (after about five weeks of gestation), the axons assume a very simple sticklike shape and are tipped with a growth cone. A few days later the axons arising from both eyes acquire a "hairy" appearance: they have short side branches along their entire length.

The presence of side branches at this age implies that the inputs from both eyes mix with one another. In other words, the neural regions have yet to take on the adult structure, in which each eye has its own specific regions. As development continues, the axons sprout elaborate terminal branches and lose their side branches. Soon individual axons from each eye have highly branched terminals that are restricted to the appropriate layer. Axons from one eye that traverse territory belonging to those from the other eye are smooth and unbranched [*see illustration on next page*].



The sequence of developmental changes in the branching patterns shows that the adult pattern of connections emerges as axons remodel by the selective withdrawal and growth of different branches. Axons apparently grow to many different addresses within their target structures and then somehow eliminate addressing errors.




**AXONAL REMODELING in the lateral geniculate nucleus occurs largely before birth. At the earliest times in development (*1*), the axons from the left eye and right eye are simple and tipped with growth cones. The shaded region represents the intermixing of inputs from both eyes. After further development (*2*), the axons grow many side branches. The axons soon begin to lose some side branches and start to extend elaborate terminal branches (*3*). Eventually these branches occupy the appropriate territory to form eye-specific layers (*4*).**

One possible explanation for axonal remodeling is that specific molecular cues are arrayed on the surface of the target cells. Although this idea might seem conceptually attractive, it has very little experimental support. An alternative explanation appears to be stronger. It holds that all target neurons are fair game. Then, some kind of competition between inputs would lead to formation of specific functional areas.

An important clue concerning the nature of the competitive interactions between axons for target neurons has come from the experiments of David H. Hubel of Harvard Medical School and Torsten N. Wiesel of the Rockefeller University. In the 1970s, when both workers were at Harvard, they studied the formation of childhood cataracts. Clinical observations indicated that if the condition is not treated promptly, it can lead to permanent blindness in the obstructed eye. To emulate the effect, Hubel and Wiesel closed the eyelids of newborn cats. They discovered that even a week of sightlessness can alter the formation of ocular dominance columns. The axons from the lateral geniculate nucleus representing the closed eye occupy smaller than normal patches within layer 4 of the cortex. The axons of the open eye occupy larger than normal patches.

The workers also showed that the effects are restricted to a critical period. Cataracts, when they occur in adulthood and are subsequently corrected by surgery, do not cause lasting blindness. Apparently the critical period has ended long ago, and so the brain's wiring cannot be affected.

These observations suggest that the ocular dominance columns form as a consequence of use. The axons of the lateral geniculate nucleus from each eye somehow compete for common territory in layer 4. When use is equal, the columns in the two eyes are identical; unequal use leads to unequal allotment of territory claimed in layer 4.

How is use translated into these lasting anatomic consequences? In the visual system, use consists of the action potentials generated each time a visual stimulus is converted into a neural signal and is carried by the ganglion cell axons into the brain. Perhaps the effects of eye closure on the development of ocular dominance columns occur because there are fewer action potentials coming from the closed eye. If that is the case, blockage of all action potentials during the critical period of postnatal life should prevent axons from both eyes from fashioning the correct patterns and lead to abnormal development in the visual cortex. Stryker and William Harris, then a postdoctoral fellow at Harvard, obtained this result when they used the drug tetrodotoxin to block retinal ganglion cell action potentials. They found that the ocular dominance columns in layer 4 failed to appear (the layers in the lateral geniculate nucleus were unaffected because they had already formed in utero).

Nevertheless, action potentials by themselves are not sufficient to create the segregated patterns in the cortex. Neural activity cannot be random. Instead it must be defined, both temporally and spatially, and must occur in the presence of special kinds of synapses. Stryker and his associate Sheri Strickland, who are both at the University of California at San Francisco, have shown that simultaneous, artificial stimulation of all the axons in the optic nerves can prevent the segregation of axons from the lateral geniculate nucleus into ocular dominance columns within layer 4. Although this result resembles that achieved with tetrodotoxin, an important difference exists. Here ganglion cell action potentials are present—but all at the same time. Segregation to form the columns in the visual cortex, on the other hand, proceeds when the two nerves are stimulated asynchronously.

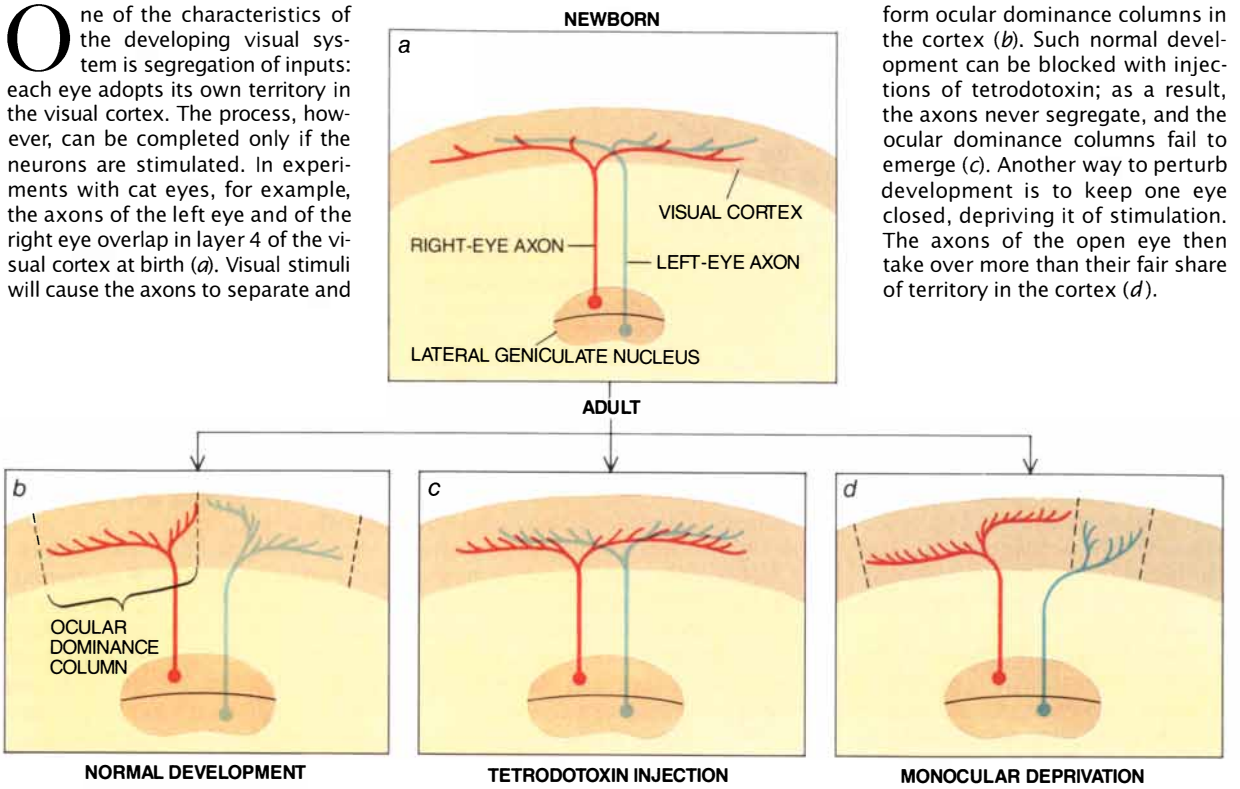
In a sense, then, cells that fire together wire together. The timing of action-potential activity is critical in determining which synaptic connections are strengthened and retained and which are weakened and eliminated. Under normal circumstances, vision itself acts to correlate the activity of neighboring retinal ganglion cells, because the cells receive inputs from the same parts of the visual world.

What is the synaptic mechanism that strengthens or weakens the connections? As long ago as 1949, Donald O. Hebb of McGill University proposed the existence of special synapses that could execute the task. The signal strength in such synapses would increase whenever activities in a presynaptic cell (the cell supplying the synaptic input) and in a postsynaptic cell (the cell receiving the input) coincide. Clear evidence showing that such "Hebb synapses" exist comes from studies of the phenomenon of long-term potentiation in the hippocampus. Researchers found that the pairing of presynaptic and postsynaptic activity in the hippocampus can cause incremental increases in the strength of synaptic transmission between the paired cells. The strengthened state can last from hours to days.

Such synapses are now thought to be

## Development and Neural Function

One of the characteristics of the developing visual system is segregation of inputs: each eye adopts its own territory in the visual cortex. The process, however, can be completed only if the neurons are stimulated. In experiments with cat eyes, for example, the axons of the left eye and of the right eye overlap in layer 4 of the visual cortex at birth (*a*). Visual stimuli will cause the axons to separate and form ocular dominance columns in the cortex (*b*). Such normal development can be blocked with injections of tetrodotoxin; as a result, the axons never segregate, and the ocular dominance columns fail to emerge (*c*). Another way to perturb development is to keep one eye closed, depriving it of stimulation. The axons of the open eye then take over more than their fair share of territory in the cortex (*d*).




essential in memory and learning [see "The Biological Basis of Learning and Individuality," by Eric R. Kandel and Robert D. Hawkins, page 78]. Studies by Wolf Singer and his colleagues at the Max Planck Institute for Brain Research in Frankfurt and by Yves Fregnac and his colleagues at the University of Paris also suggest that Hebb synapses are present in the visual cortex during the critical period, although their properties are not well understood.

Just how coincident activity causes long-lasting changes in transmission is not known. There is general agreement among researchers that the postsynaptic cell must somehow detect the coincidence in the incoming presynaptic activity and in turn send a signal back to all concurrently active presynaptic inputs. But this cannot be the whole story. During the formation of the ocular dominance columns, inputs that are not active at the same time are weakened and eliminated.

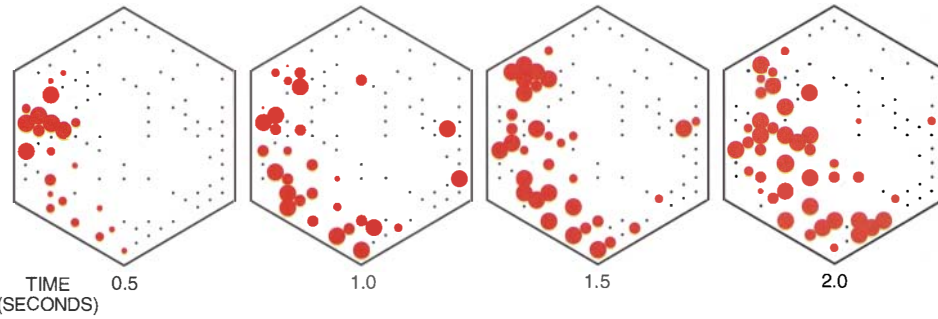
Consequently, one must also propose the existence of a mechanism for activity-dependent synaptic weakening. This weakening—a kind of long-term depression—would occur when presynaptic action potentials do not accompany postsynaptic activity. Synapses that have this special property (opposite to that of Hebb synapses) have been found in the hippocampus and cerebellum. The results of the Stryker and Strickland experiments suggest that such synapses are very likely to exist in the visual cortex as well.

A strongly similar process of axonal remodeling operates as motor neurons in the spinal cord connect with their target muscles. In the adult, each muscle fiber receives input from only one motor neuron. But after motor neurons make the first contacts with the muscle fibers, each muscle fiber receives inputs from many motor neurons. Then, just as in the visual system, some inputs are eliminated, giving rise to the adult pattern of connectivity. Studies have shown that the process of elimination requires specific temporal patterns of action-potential activity generated by the motor neurons.

The requirement for specific spatial and temporal patterns of neuronal activity might be likened to a process whereby telephone calls are placed from addresses in one city (the lateral geniculate nucleus in the visual system) to those in the next city (the visual cortex) to verify that connections have been made at the correct locations. When two near neighbors in the lateral geniculate nucleus simultaneously call neighboring addresses in the cortex, the telephones in both those homes will ring. The concurrent ringing verifies that relations between neighbors have been preserved during the wiring process.

If, however, one of the neighbors in the lateral geniculate nucleus mistakenly makes connections with very distant parts of layer 4 or with parts that receive input from the other eye, the called telephone will rarely if ever ring simultaneously with those of its neighbors. This dissonance would lead to the weakening and ultimate removal of that connection.

The research cited thus far has explored the remodeling of connections after the animal can move or see. But what about earlier in development? Can mechanisms of axonal remodeling operate even before the brain can respond to stimulation from the external world? My colleagues and I thought the formation of layers in the lateral geniculate nucleus in the cat might be a good place to address this question. After all, during the relevant developmental period, rods and cones have not yet emerged. Can the layers




**RETINAL ACTIVITY, recorded frame by frame every 0.5 second by a hexagonal array of microelectrodes (*black spots*), is locally synchronized. Each diagram represents the pattern and intensity of action-potential firing (*red*) of individual ganglion cells. The wave of retinal activity sweeps across from the lower left to the top right of the retina.**

develop their specific territories for each eye even though vision cannot yet generate action-potential activity?

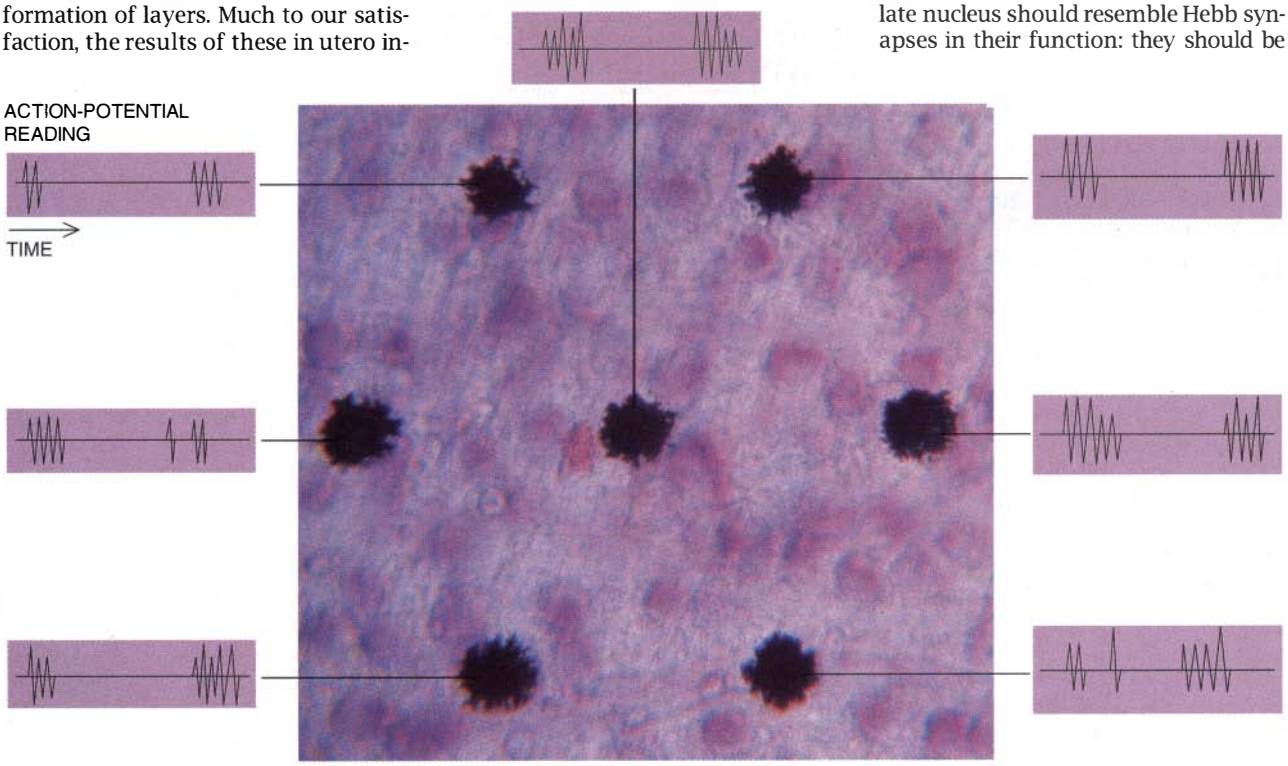
We reasoned that if activity is necessary at these early times, it must somehow be generated spontaneously within the retina, perhaps by the ganglion cells themselves. If so, the firing of retinal ganglion cells might be contributing to layer construction, because all the synaptic machinery necessary for competition is present. It should be possible to prevent the formation of the eye-specific layers by blocking action-potential activity from the eyes to the lateral geniculate nucleus.

To hinder activity during fetal development, Sretavan and I, in collaboration with Stryker, implanted special minipumps containing tetrodotoxin in utero just before the lateral geniculate nucleus layers normally begin to form in the cat (at about six weeks of fetal development). After two weeks of infusion, we assessed the effects on the formation of layers. Much to our satisfaction, the results of these in utero infusion experiments showed clearly that the eye-specific layers do not appear in the presence of tetrodotoxin. Moreover, by examining the branching patterns of individual ganglion cell axons after the treatment, we reassured ourselves that tetrodotoxin did not simply stunt normal growth.

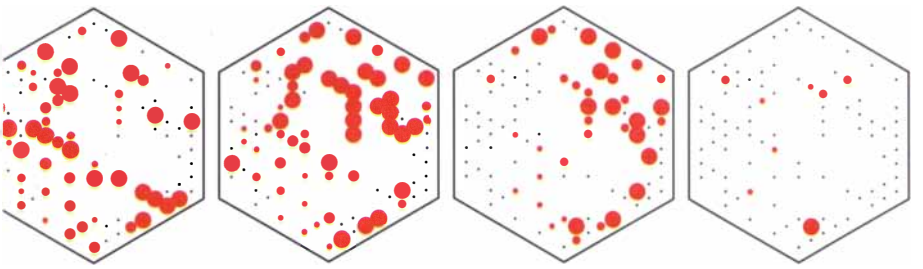
In fact, the branching patterns of these axons were very striking. Unlike normal axons at the comparable age, the tetrodotoxin-treated axons did not have highly restricted terminal branches. Rather they had many branches along the entire length of the axon. It was as if, without action-potential activity, the information necessary to withdraw side branches and elaborate the terminal branches was missing.

In 1988, at about the same time these experiments were completed, Lucia Galli-Resta and Lamberto Maffei of the University of Pisa achieved the extraordinary technical feat of actually recording signals from fetal ganglion cells in utero. They demonstrated directly that retinal ganglion cells can indeed spontaneously generate bursts of action potentials in the darkness of the developing eye. This observation, taken together with our experiment, strongly suggests that action-potential activity is not only present but also necessary for the ganglion cell axons from the two eyes to segregate and form the eye-specific layers.

Still, there must be constraints on the spatial and temporal patterning of ganglion cell activity. If the cells fired randomly, the mechanism of correlation-based, activity-dependent sorting could not operate. Furthermore, neighboring ganglion cells in each eye somehow ought to fire in near synchrony with one another, and the firing of cells in the two eyes, taken together, should be asynchronous. In addition, the synapses between retinal ganglion cell axons and neurons of the lateral geniculate nucleus should resemble Hebb synapses in their function: they should be




**ACTION-POTENTIAL READINGS of the developing retina are recorded by microelectrodes (*black spots*). The electrodes detect the small, extracellular currents that flow when the ganglion cells (*stained purple*) fire. All the cells fire at about the same time and then become silent before firing again. The area shown represents about 3 percent of the entire retina.**




able to detect correlations in the firing of axons and strengthen accordingly.

We realized that to search for such patterns of spontaneous firing, it would be necessary to monitor simultaneously the action-potential activity of many ganglion cells in the developing retina. In addition, the observation had to take place as the eye-specific layers were developing. A major technical advance permitted us to achieve this goal. In 1988 Jerome Pine and his colleagues at the California Institute of Technology, among them doctoral student Markus Meister, invented a special multielectrode recording device. It consisted of 61 recording electrodes arranged as a flat, hexagonal array. Each electrode can detect action potentials generated in one to several cells. When Meister arrived at Stanford University to continue postdoctoral work with Denis Baylor, we began a collaboration to see whether the electrode array could be used to detect the spontaneous firing of fetal retinal ganglion cells.

In these experiments, it was necessary to remove the entire retina from the fetal eye and place it, ganglion-cell-side down, on the array. (It is technically impossible to put the electrode array itself into the eye in utero.) Rachel Wong, a postdoctoral fellow from Australia visiting my laboratory, succeeded in carefully dissecting the retinas and in tailoring special fluids necessary to maintain the living tissue for hours in a healthy condition.

When neonatal ferret retinas were placed on the multielectrode array, we simultaneously recorded the spontaneously generated action potentials of as many as 100 cells. The work confirmed the in vivo results of Galli-Resta and Maffei. All cells on the array fired within about five seconds of one another, in a predictable and rhythmic pattern. The bursts of action potentials lasted several seconds and were followed by long silent pauses that persisted from 30 seconds to two minutes. This observation showed that the activity of ganglion cells is indeed correlated. Further analysis demonstrated that the activity of neighboring cells is more highly correlated than that of distant cells on the array.

Even more remarkable, the spatial pattern of firing resembled a wave of activity that swept across the retina at about 100 microns per second (about one tenth to one hundredth the speed of an ordinary action potential). After the silent period, another wave was generated but in a completely different and random direction. We found that these spontaneously generated retinal waves are present throughout the period when eye-specific layers take shape. They disappear just before the onset of visual function.

From an engineering standpoint, these waves seem beautifully designed to provide the required correlations in the firing of neighboring ganglion cells. They also ensure a sufficient time delay, so that the synchronized firing of ganglion cells remains local and does not occur across the entire retina. Such a pattern of firing could help refine the topographic map conveyed by ganglion cell axons to each eye-specific layer. Moreover, the fact that wave direction appears to be entirely random implies that ganglion cells in the two eyes are highly unlikely ever to fire synchronously—a requirement for the formation of the layers.

Future experiments will disrupt the waves in order to determine whether they are truly involved in the development of connections. In addition, it will be important to determine whether the correlations in the firing of neighboring ganglion cells can be detected and used by the cells in the lateral geniculate nucleus to strengthen appropriate synapses and weaken inappropriate ones. This seems likely, since Richard D. Mooney, a postdoctoral fellow in my laboratory, in collaboration with Daniel Madison of Stanford, has shown that long-term potentiation of synaptic transmission between retinal ganglion cell axons and the lateral geniculate nucleus neurons is present during these early periods of development. Thus, at present, we can conclude that even before the onset of function, ganglion cells can spontaneously fire in the correct pattern to fashion the necessary connections.

Is the retina a special case, or might many regions of the nervous system generate their own endogenous activity patterns early in development? Preliminary studies by Michael O'Donovan of the National Institutes of Health suggest that the activity of motor neurons in the spinal cord may also be highly correlated very early in development. It would appear that activity-dependent sorting in this system as well might use spontaneously generated signals. Like those in the visual system, the signals would refine the initially diffuse connections within targets.

The necessity for neuronal activity to complete the development of the brain has distinct advantages. The first is that, within limits, the maturing nervous system can be modified and fine-tuned by experience itself, thereby providing a certain degree of adaptability. In higher vertebrates, this process of refinement can occupy a protracted period. It can begin in utero and, as in the primate visual system, continue well into neonatal life, where it plays an important role in coordinating inputs from the two eyes. The coordination is necessary for binocular vision and stereoscopic depth perception.

Neural activity confers another advantage in development. It is genetically conservative. The alternative—exactly specifying each neural connection using molecular markers—would require an extraordinary number of genes, given the thousands of connections that must be formed in the brain. Using the rules of activity-dependent remodeling described here is far more economical. A major challenge for the future will be to elucidate the cellular and molecular bases for such rules.

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