of infants raised in a nursing home attached to a women's prison. Both institutions were clean and both provided adequate food and medical care. The babies in the prison nursing home were all cared for by their mothers, who, although in prison and away from their families, tended to shower affection on their infants in the limited time allotted to them each day. In contrast, infants in the foundling home were cared for by nurses, each of whom was responsible for several babies. As a result, children in the foundling home had far less contact with other humans than did those in the prison's nursing home.

The two institutions also differed in another respect. In the prison nursing home, the cribs were open, so that the infants could readily watch other activities in the ward; they could see other babies play and observe the staff go about their business. In the foundling home, the bars of the cribs were covered by sheets that prevented the infants from seeing outside. In reality, the babies in the foundling home were living under conditions of severe sensory and social deprivation.

Infants at the two institutions were followed through their early years. At the end of the first 4 months, the infants in the foundling home fared better on several developmental tests than those in the prison nursing home, suggesting that intrinsic factors did not favor the infants in the prison nursing home. But by the end of the first year, the motor and intellectual performance of the children in the foundling home had fallen far below that of children in the prison nursing home. Many of the children in the foundling home had developed a syndrome that Spitz called *hospitalism* and is now sometimes called *anaclitic depression*. These children were withdrawn and displayed little curiosity or gaiety. Moreover, their defects extended beyond emotional and cognitive signs. They were especially prone to infection, implying that the brain exerts complex controls over the immune system as well as behavior. By their second and third years, children in the prison nursing home were similar to children raised in normal families at home—they were agile, had a vocabulary of hundreds of words, and spoke in sentences. In contrast, the development of children in the foundling home was still further delayed—many were unable to walk or to speak more than a few words.

More recent studies of other similarly deprived children have confirmed these conclusions and shown that the defects are long-lasting. Longitudinal studies of orphans who were raised for several years in large impersonal institutions with little or no personal care, then adopted by caring families, have been especially revealing. Despite every effort of the adoptive parents, many of the children were never able to develop appropriate, caring relationships with family members or peers (Figure 49–1A). More recent imaging studies have revealed defects in brain structure correlated with, and presumably due to, this deprivation (Figure 49–1B).

As compelling as these observations are, it is difficult to derive definitive conclusions from them. An influential set of studies that extended the analysis of social behavior to monkeys was carried out in the 1960s by two psychologists, Harry and Margaret Harlow. The Harlows reared newborn monkeys in isolation for 6 to 12 months, depriving them of contact with their mothers, other monkeys, or people. At the end of this period, the monkeys were physically healthy but behaviorally devastated. They crouched in a corner of their cage and rocked back and forth like autistic children (Figure 49–1C). They did not interact with other monkeys, nor did they fight, play, or show any sexual interest. Thus, a 6-month period of social isolation during the first 18 months of life produced persistent and serious disturbances in behavior. By comparison, isolation of an older animal for a comparable period was found to be without such drastic consequences. These results confirmed, under controlled conditions, the critical influence of early experience on later behavior. For ethical reasons, these studies would not be possible today.

Development of Visual Perception Requires Visual Experience

The dramatic dependence of the brain on experience and the ability of that experience to shape perception is evident in people born with cataracts. Cataracts are opacities of the lens that interfere with the optics of the eye but not directly with the nervous system; they are easily removed surgically. In the 1930s, it became apparent that patients who had congenital binocular cataracts removed after the age of 10 years experienced permanent deficits in visual acuity and had difficulties perceiving shape and form. In contrast, when cataracts that develop in adults are removed decades after they form, normal vision returns immediately.

Likewise, children with *strabismus* (crossed eyes) do not have normal depth perception (*stereopsis*), an ability that requires the two eyes to focus on the same location at the same time. They can acquire this ability if their eyes are aligned surgically during the first few years of life, but not if surgery occurs later in adolescence. As a result of these observations, congenital cataracts are now usually removed, and strabismus is corrected surgically, in early childhood. Over the

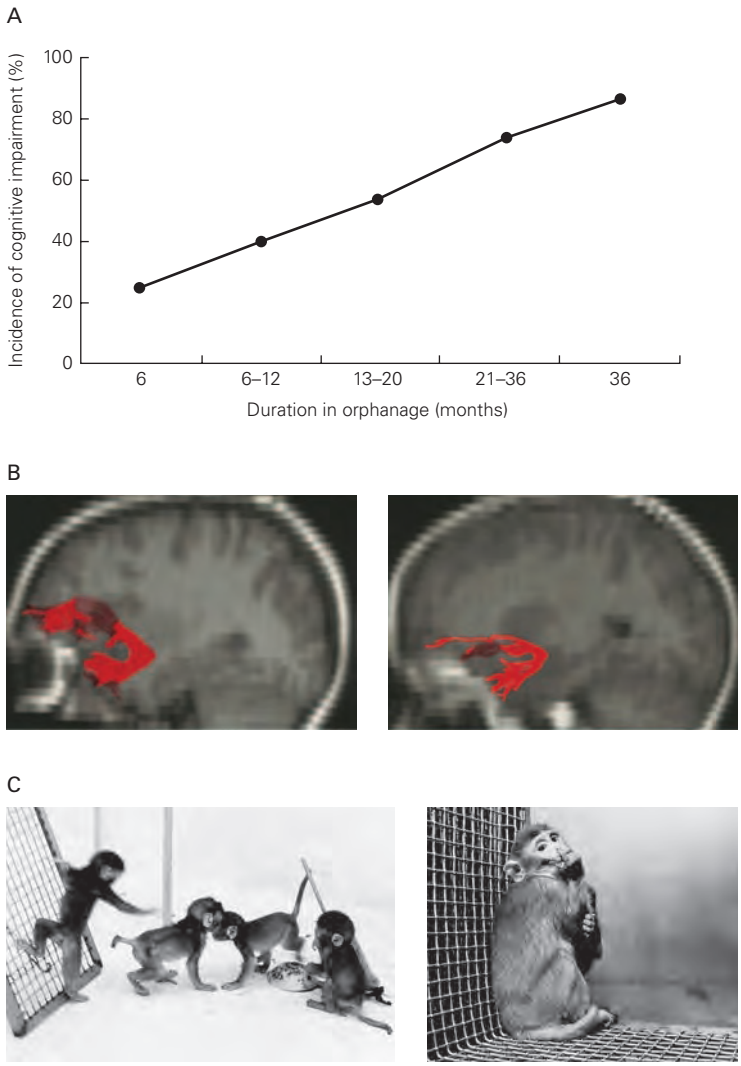

Figure 49–1 Early social deprivation has a profound impact on later brain structure and behavior.

A. Neurocognitive dysfunction is evident in children raised under conditions of social deprivation in orphanages. The incidence of cognitive impairment increases with the duration of stay in the orphanage. (Adapted from Behen et al. 2008.)

B. Diffusion tensor magnetic resonance imaging (MRI) scans show a well-developed and robust uncinate fasciculus (**red region**) in a normal child (*left*), whereas in a socially deprived child (*right*), it is thin and poorly organized. (Reproduced, with permission, from Eluvathingal et al. 2006. Copyright © 2006 by the AAP.)

C. Early social interactions impact later social behavior patterns. Monkeys reared in the presence of their siblings acquire social skills that permit effective interactions in later life (*left*). A monkey reared in isolation never acquires the capacity to interact with others and remains secluded and isolated in later life (*right*). (Source: Harry F. Harlow. Used with permission.)

past five decades, researchers have elucidated structural and physiological underpinnings of these critical periods.

Development of Binocular Circuits in the Visual Cortex Depends on Postnatal Activity

Because sensory experience of the world is transformed into patterns of electrical activity in the brain, one might imagine that electrical signals in neural circuits affect the brain's circuitry. But is this true? And if it is true, what changes occur, and how does activity trigger them?

Our most detailed understanding of these links comes from studies of the neural circuits that mediate binocular vision. The key figures in the early phases of this work were David Hubel and Torsten Wiesel. Following their pioneering studies on the structural and functional organization of the visual cortex in cats and monkeys (Chapter 23), they undertook another set of studies on how experience affects the circuits they had delineated.

Visual Experience Affects the Structure and Function of the Visual Cortex

In one influential study, Hubel and Wiesel raised a monkey from birth to 6 months of age with one eyelid sutured shut, thus depriving the animal of vision in that eye. When the sutures were removed, it became clear that the animal was blind in the deprived eye, a condition called *amblyopia*. They then performed electrophysiological recordings from cells along the visual

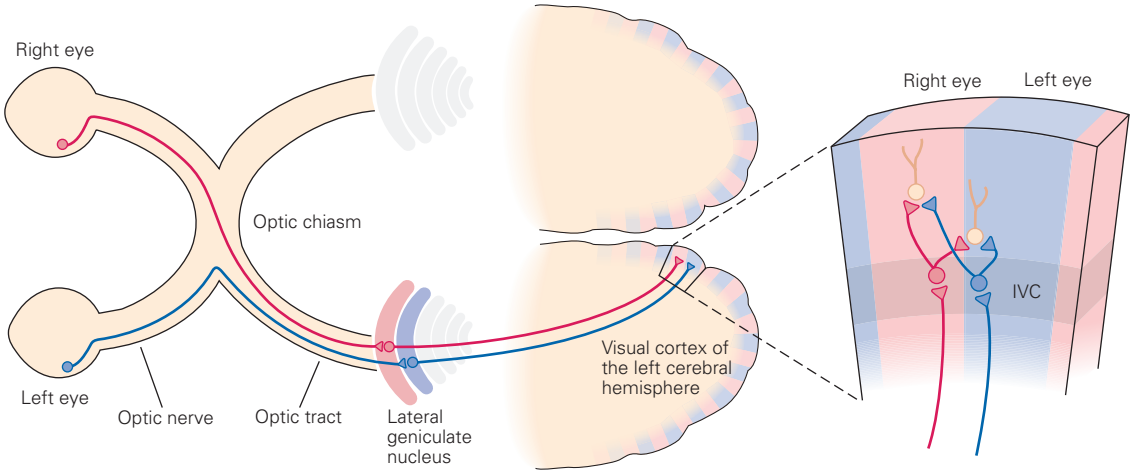

Figure 49–2 Afferent pathways from the two eyes project to discrete columns of neurons in the visual cortex. Retinal ganglion neurons from each eye send axons to separate layers of the lateral geniculate nucleus. The axons of neurons in this nucleus project to neurons in layer IVC of the primary visual cortex, which is organized in alternating sets of ocular dominance columns; each column receives input from only one eye. The axons of the neurons in layer IVC project to neurons in adjacent columns as well as to neurons in the upper and lower layers of the same column. As a result, most neurons in the upper and lower layers of the cortex receive information from both eyes.

pathway to determine where the defect arose (Figure 49–2). They found that retinal ganglion cells in the deprived eye, as well as neurons in the lateral geniculate nucleus that receive input from the deprived eye, responded well to visual stimuli and had essentially normal receptive fields.

In contrast, cells in the visual cortex were fundamentally altered. In the cortex of normal animals, most neurons are responsive to binocular input. In animals that had been monocularly deprived for the first 6 months, most cortical neurons did not respond to signals from the deprived eye (Figure 49–3). The few cortical cells that were responsive were not sufficient for visual perception. Not only had the deprived eye lost its ability to drive most cortical neurons, but little recovery ever occurred: The loss was permanent and irreversible.

Hubel and Wiesel went on to test the effects of visual deprivation imposed for shorter periods and at different ages. They obtained three types of results, depending on the timing and duration of the deprivation. First, monocular deprivation for a few weeks shortly after birth led to loss of cortical responses from the deprived eye that was reversible after the eye had been opened, especially if the opposite eye was then closed to encourage use of the initially deprived eye. Second, monocular deprivation for a few weeks during the next several weeks also resulted in a substantial loss of cortical responsiveness to signals from the deprived eye, but in this case, the effects were irreversible. Finally, deprivation in adults, even for periods of many months, had no effect on the responses of cortical cells to signals from the deprived eye or on visual perception. These results demonstrated that the cortical connections that control visual perception are established within a critical period of early development.

Are there anatomical correlates of these functional defects? To address this question, we need to recall three basic facts about the anatomy of the visual cortex (Figure 49–2). First, inputs from the two eyes remain segregated in the lateral geniculate nucleus. Second, the geniculate inputs carrying information from the two eyes to the cortex terminate in alternating columns, termed *ocular dominance columns*. Third, lateral geniculate axons terminate on neurons in layer IVC of the primary visual cortex; convergence of input from the two eyes on a common target cell occurs at the next stage of the pathway, in cells above and below layer IVC.

To examine whether the architecture of ocular dominance columns depends on visual experience early in postnatal life, Hubel and Wiesel deprived newborn animals of vision in one eye and then injected a labeled amino acid into the normal eye. The injected label was incorporated into proteins in retinal ganglion cell bodies, transported along the retinal axons to the lateral geniculate nucleus, transferred to geniculate neurons, and then transported to the synaptic terminals of these axons in the primary visual cortex. After closure of one eye, the columnar array of synaptic terminals relaying input from the deprived eye was reduced, whereas the columnar array of terminals relaying input from the

normal eye was expanded (Figure 49–4). Thus, sensory deprivation early in life alters the structure of the cerebral cortex.

How are these striking anatomical changes brought about? Does sensory deprivation alter ocular dominance columns after they have been established, or does it interfere with their formation? A columnar organization of the visual cortex is already evident by birth in monkeys, although the mature pattern is not achieved until several weeks after birth (Figure 49–5). Only at this time do the terminals of fibers from the lateral geniculate nucleus become completely segregated in the cortex. Because the inputs are partially but not completely segregated at the time visual deprivation exerts its effects, we can conclude that the deprivation perturbs the ability of the inputs to acquire their mature pattern. We shall return to the question of what leads to the initial, experience-independent phases of segregation in a later section of this chapter.

Patterns of Electrical Activity Organize Binocular Circuits

How does activity lead to maturation of ocular dominance columns? The crucial factor may be the

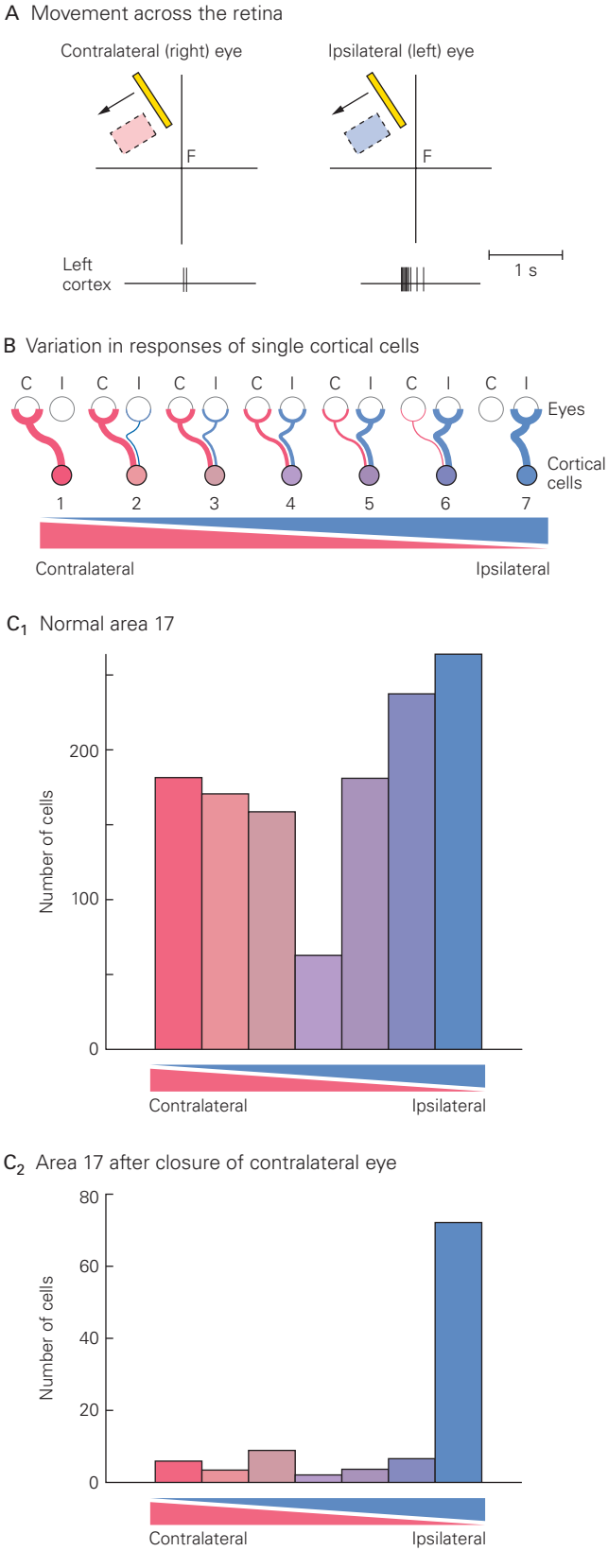

Figure 49–3 (Right) Responses of neurons in the primary visual cortex of a monkey to visual stimuli. (Adapted from Hubel and Wiesel 1977.)

A. A diagonal bar of light is moved leftward across the visual field, traversing the receptive fields of a binocularly responsive cell in area 17 of visual cortex. Receptive fields measured through the right and left eye are drawn separately. The receptive fields of the two cells are similar in orientation, position, shape, and size, and respond to the same form of stimulus. Recordings (below) show that the cortical neuron responds more effectively to input from the ipsilateral eye. (Abbreviation: **F**, fixation point.)

B. The responses of individual cortical neurons in area 17 can be classified into seven groups. Neurons receiving input only from the contralateral eye (**C**) fall into group 1, whereas neurons that receive input only from the ipsilateral eye (**I**) fall into group 7. Other neurons receive inputs from both eyes, but the input from one eye may influence the neuron much more than the other (groups 2 and 6), or the differences may be slight (groups 3 and 5). Some neurons respond equally to input from both eyes (group 4). According to these criteria, the cortical neuron shown in part A falls into group 6.

C. Responsiveness of neurons in area 17 to stimulation of one or the other eye. **1.** The responses of more than 1,000 neurons in area 17 in the left hemisphere of normal adult and juvenile monkeys. Neurons in layer IV that normally receive only monocular input have been excluded. **2.** The responses of neurons in the left hemisphere of a monkey in which the contralateral (right) eye was closed from the age of 2 weeks to 18 months and then reopened. Most neurons respond only to stimulation of the ipsilateral eye.

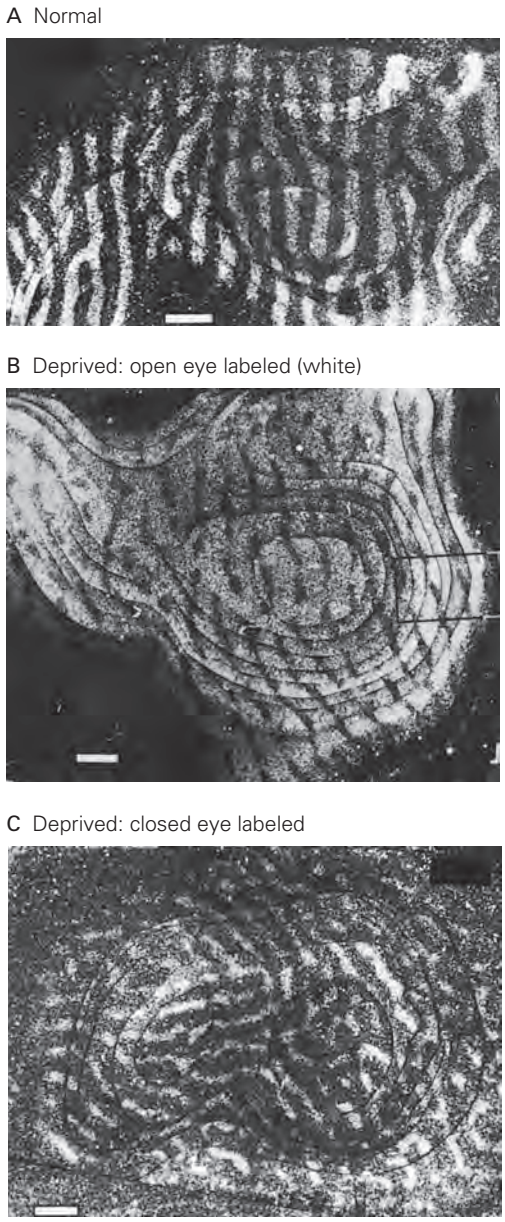

Figure 49–4 Visual deprivation of one eye during a critical period of development reduces the width of the ocular dominance columns for that eye. (Scale bars = 1 mm) (Adapted, with permission, from Hubel, Wiesel, and LeVay 1977.)

A. A tangential section through area 17 of the right hemisphere of a normal adult monkey, 10 days after one eye was injected with a radiolabeled amino acid. Radioactivity is localized in stripes (**white**) in layer IVC of the visual cortex, indicating sites of termination of the axons from the lateral geniculate nucleus that carry input from the injected eye. The alternating unlabeled (**dark**) stripes indicate sites of termination of the axons carrying signals from the uninjected eye. Labeled and unlabeled stripes are of equal width.

B. A comparable section through the visual cortex of an 18-month-old monkey whose right eye had been surgically closed at 2 weeks of age. Label was injected into the left (open) eye. The wider (**white**) stripes are the labeled terminals of afferent axons carrying signals from the open eye; the narrow (**dark**) stripes are terminals of axons with input from the closed eye.

C. A section comparable to that in part B from an 18-month-old animal whose right eye had been shut at 2 weeks. Label was injected into the closed eye, giving rise to narrow (**white**) stripes of labeled axon terminals and wide (**dark**) stripes of unlabeled terminals.

differences in the proportion of inputs from each eye that converge on common target cells at birth. If by chance the fibers conveying input from one eye are initially more numerous in one local region of cortex, those axons may have an advantage, leading to further segregation.

How might this occur? An attractive idea, based on a theory first proposed in the 1940s by Donald Hebb, is that synaptic connections are strengthened when pre- and postsynaptic elements are active together. In the case of binocular interactions, neighboring axons from the same eye tend to fire in synchrony because they are activated by the same visual stimulus at any instant. The synchronization of their firing means that they cooperate in the depolarization and excitation of a target cell. This cooperative action maintains the viability of those synaptic contacts at the expense of the noncooperating synapses.

Cooperative activity could also promote branching of axons and thus create the opportunity for the formation of additional synaptic connections with cells in the target region. At the same time, the strengthening of synaptic contacts made by the axons of one eye will impede the growth of synaptic inputs from the opposite eye. In this sense, fibers from the two eyes may be said to compete for a target cell. Together,

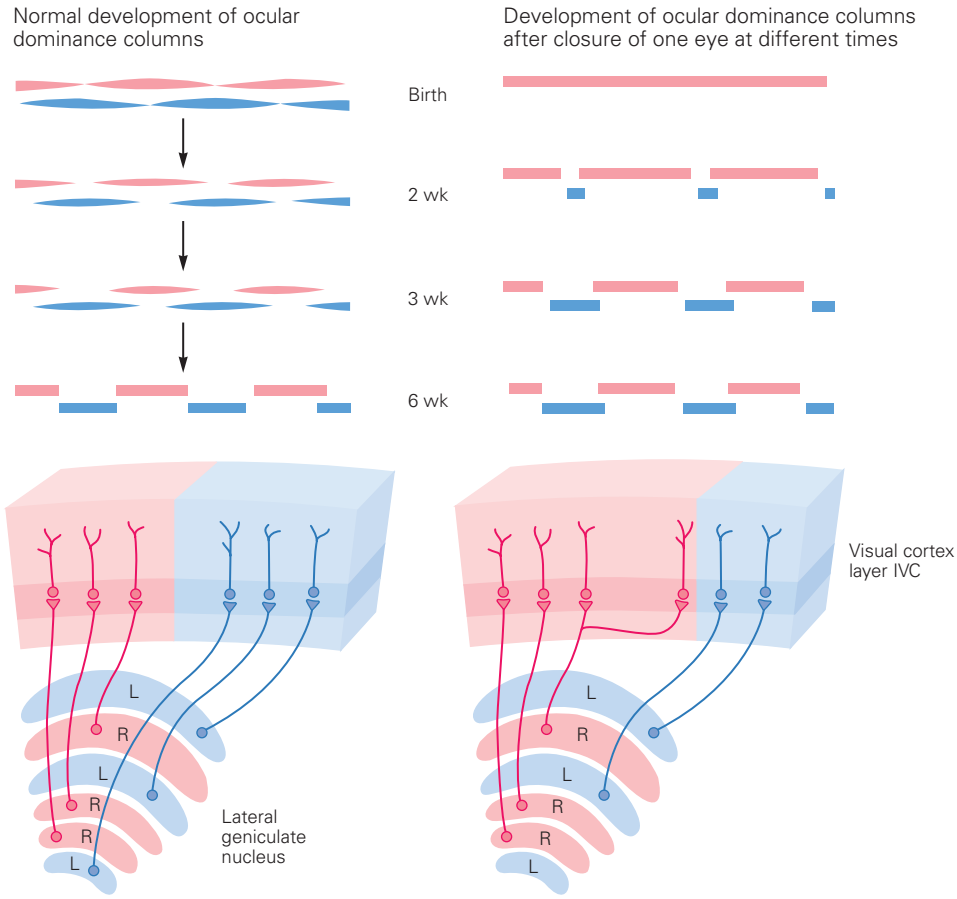

Figure 49–5 The effects of eye closure on the formation of ocular dominance columns. The top diagrams show the gradual segregation of the terminals of lateral geniculate afferents in layer IVC of the visual cortex under normal conditions (*left*) and when one eye is deprived of stimulation (*right*). **Blue domains** represent the areas of termination of inputs from one eye, **red domains** those of the other eye. The lengths of the domains represent the density of the terminals at each point along layer IVC. For clarity, the columns are shown here as one above the other, whereas in reality, they are side by side in the cortex. During normal development, layer IVC is gradually divided into alternating sites of input from each eye. The consequences of depriving sight in one eye depend on the timing of eye closure. Closure at birth leads to dominance by the open eye (**red**) because at this point little segregation has occurred. Closure at 2, 3, and 6 weeks has a progressively weaker effect on the formation of ocular dominance columns because the columns become more segregated with time. (Abbreviations: **L**, left; **R**, right.) (Adapted, with permission, from Hubel, Wiesel, and LeVay 1977.)

cooperation and competition between axons ensure that two populations of afferent fibers will eventually innervate distinct regions of the primary visual cortex with little local overlap.

Competition and cooperation are not simply the outcome of neural activity per se or of differences in absolute levels of activity among axons. Instead, they appear to depend on precise temporal patterns of activity in the competing (or cooperating) axons. The principle was dramatically illustrated by Hubel and Wiesel in a set of studies that examined stereoscopic vision—the perception of depth. The brain normally computes depth perception by comparing the disparity in retinal images between the two eyes. When the eyes are improperly aligned, this comparison cannot be made and stereoscopy is impossible. Such misalignments occur in children who are "cross-eyed," or strabismic. As noted above, this condition can be surgically repaired, but unless the surgery occurs during the first few years of life, the children forever remain incapable of stereoscopy.

Hubel and Wiesel examined the impact of strabismus on the organization of the visual system in cats. To render cats strabismic, the tendon of an extraocular muscle was severed in kittens. Both eyes remained fully functional but misaligned. Inputs from the two eyes that converged on a binocular cell in the visual cortex now carried information about different stimuli

in slightly different parts of the visual field. As a result, cortical cells became monocular, driven by input from one eye or the other but not both (Figure 49–6). Conversely, cortical neurons remained binocularly responsive following binocular visual deprivation, leading to a decrease but not an imbalance in activity arising from the two eyes. These findings suggested to Hubel and Wiesel that disruption of the synchrony of inputs led to competition rather than cooperation, so that cortical cells came to be dominated by one eye, presumably the one that had dominated at the outset.

These physiological studies led investigators to test whether pharmacological blockade of electrical activity in retinal ganglion cells could affect neural connectivity in the visual system. Activity was blocked by injecting both eyes with tetrodotoxin, a toxin that selectively blocks voltage-sensitive Na^+ channels. Signals from the two eyes were generated separately by direct electric stimulation of the bilateral optic nerves. In kittens, ocular dominance columns are not established if activity in retinal ganglion neurons is blocked before the critical period of development. When the two optic nerves were stimulated synchronously, ocular dominance columns still failed to form. Only when the optic nerves were stimulated asynchronously were ocular dominance columns established.

If the development of ocular dominance columns indeed depends on competition between fibers from the two eyes, might it be possible to induce the formation of columns where they normally are not present, simply by establishing competition between two sets of axons? This radical possibility was tested in frogs, where retinal ganglion neurons from each eye project only to the contralateral side of the brain. In normal frogs, afferent fibers from the two eyes do not compete for the same cells, so there is no columnar segregation of afferent inputs. To generate competition, a third eye was transplanted early in larval development into a region of the frog's head near one of the normal eyes. The retinal ganglion neurons of the extra eye extended axons to the contralateral optic tectum. Remarkably, axon terminals from the transplanted and normal eyes segregated, generating a pattern of alternating columns (Figure 49–7).

This finding provided dramatic support for the idea that competition between afferent axons for the same population of target neurons drives their segregation into distinct target territories. The columnar segregation of retinal inputs in the frog brain is dependent on synaptic activity, presumably at the synapses between retinal axons and tectal neurons. Thus, neural activity has powerful roles in fine-tuning visual circuits.

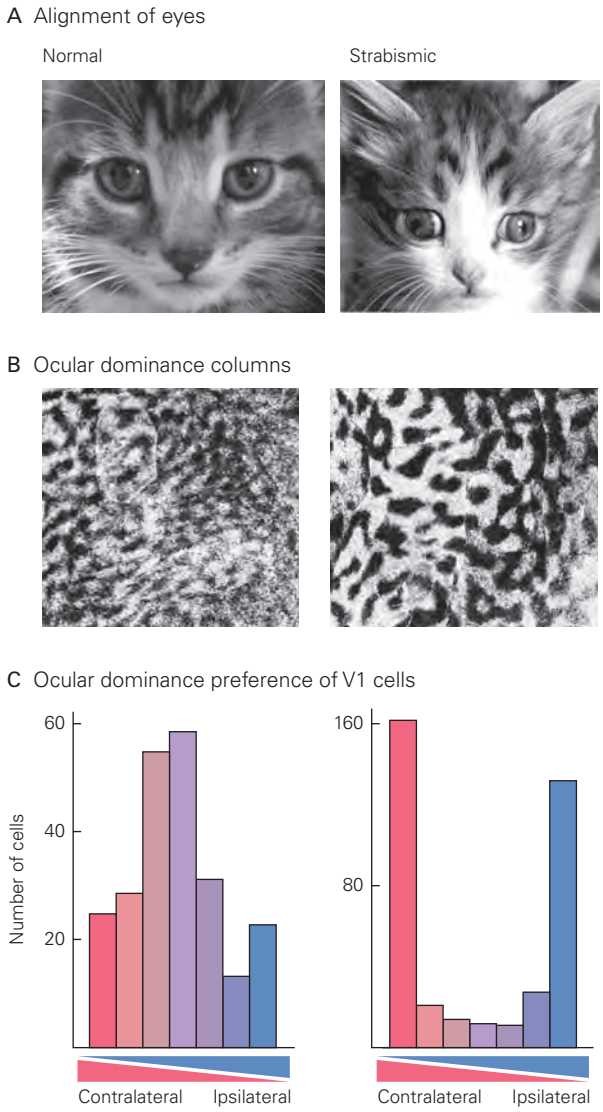

Figure 49–6 Inducing strabismus in kittens impairs the formation of binocular response regions in the primary visual cortex.

A. The eyes of strabismic cats are misaligned. (Photos [*left*] Steve Richardson/Alamy Stock Photo and [*right*] reproduced with permission from Van Sluyters and Levitt 1980.)

B. In strabismic animals, left and right eye domains are more sharply defined, an indication of the paucity of binocular regions. (Reproduced, with permission, from Löwel 1994. Copyright © 1994 Society for Neuroscience.)

C. Strabismic animals have fewer binocularly tuned neurons in the visual cortex. (Reproduced, with permission, from Hubel and Wiesel 1965.)

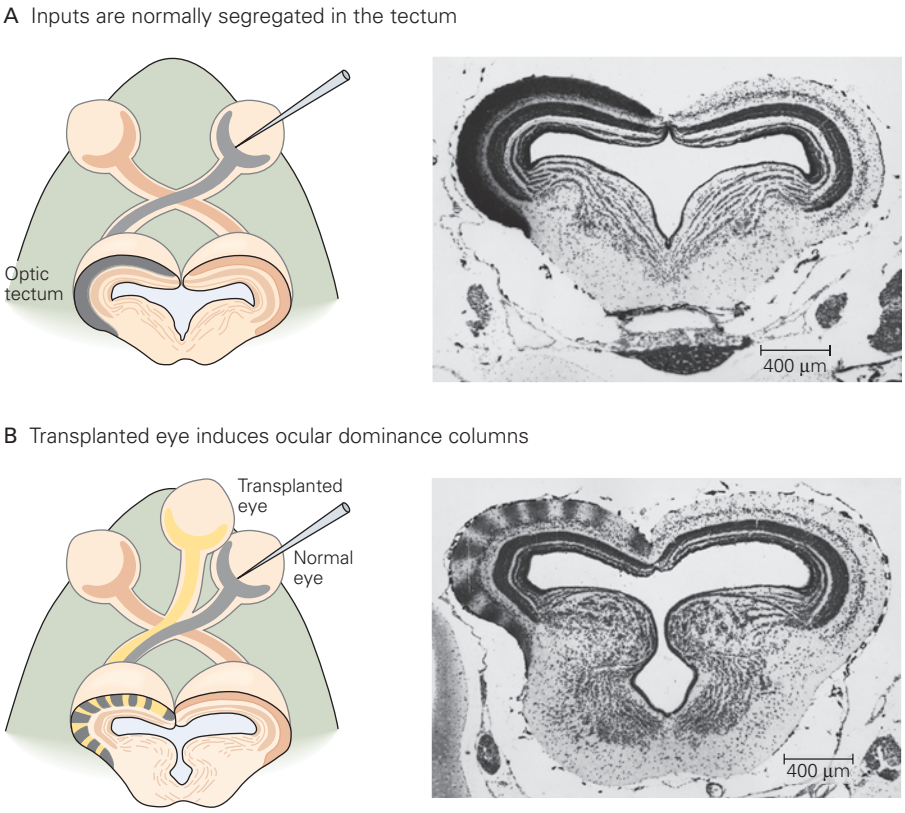

Figure 49–7 Ocular dominance columns can be experimentally induced in a frog by transplantation of a third eye. (Adapted, with permission, from Constantine-Paton and Law 1978. Copyright © 1978 AAAS.)

A. Three days before the transplant, the right eye was injected with a radiolabeled amino acid. The autoradiograph in a coronal section of the hindbrain shows the entire superficial neuropil of the left optic lobe filled with silver grains, indicating the region occupied by synaptic terminals from the labeled (contralateral) eye.

B. Some time after a third eye was transplanted near the normal right eye, the right eye was injected with a radiolabeled amino acid. The autoradiograph shows that the left optic lobe receives inputs from both the labeled eye and the transplanted eye. The normally continuous synaptic zone of the contralateral eye has become divided into alternating dark and light zones that indicate the sites of inputs from each eye.

Reorganization of Visual Circuits During a Critical Period Involves Alterations in Synaptic Connections

The pioneering work of Hubel, Wiesel, and their colleagues showed that early experience is required for the emergence of normal structure and function in the visual cortex. However, the cellular and molecular mechanisms that underlie the critical period remained mysterious. In recent years, many investigators have begun addressing these issues. Much of their work has involved the use of mice, because mice are more amenable to mechanistic analysis than the cats and monkeys studied by Hubel, Wiesel, and their disciples.

Cortical Reorganization Depends on Changes in Both Excitation and Inhibition

Unlike cats and monkeys, most of the mouse visual cortex receives only contralateral input and its binocular region is not divided into ocular dominance columns. Nonetheless, the small binocular region contains a mixture of monocularly and binocularly driven neurons, and closure of the contralateral eye during the critical period for ocular dominance markedly shifts the preference of binocular neurons to inputs from the ipsilateral eye (Figure 49–8).

What converts this early loss of input into a permanent alteration of functional capability? One idea is that thalamic axons carrying information from the deprived eye lose their ability to activate cortical neurons. However, although a decrease in efficacy of the thalamocortical synapse may contribute to this effect, this is not the whole story. Each thalamic axon carries input from only one eye (Figure 49–2). Because loss of responsiveness to the deprived eye occurs only if the other eye remains active, one might imagine that the earliest changes would occur at the first site where inputs from the two eyes have the opportunity to interact. Consistent with this idea, the first physiological changes are not observed in layer IV neurons, each of which receives input from only one eye. Rather, they occur in the binocular neurons of layers II/III and V, which receive convergent input from both right eye– and left eye– driven monocular layer IV neurons. This implies that the loss of cortical responsiveness to the deprived eye results from a circuit alteration rather than from a simple loss of input.

Several possible cellular mechanisms have been proposed to account for these changes in circuitry.

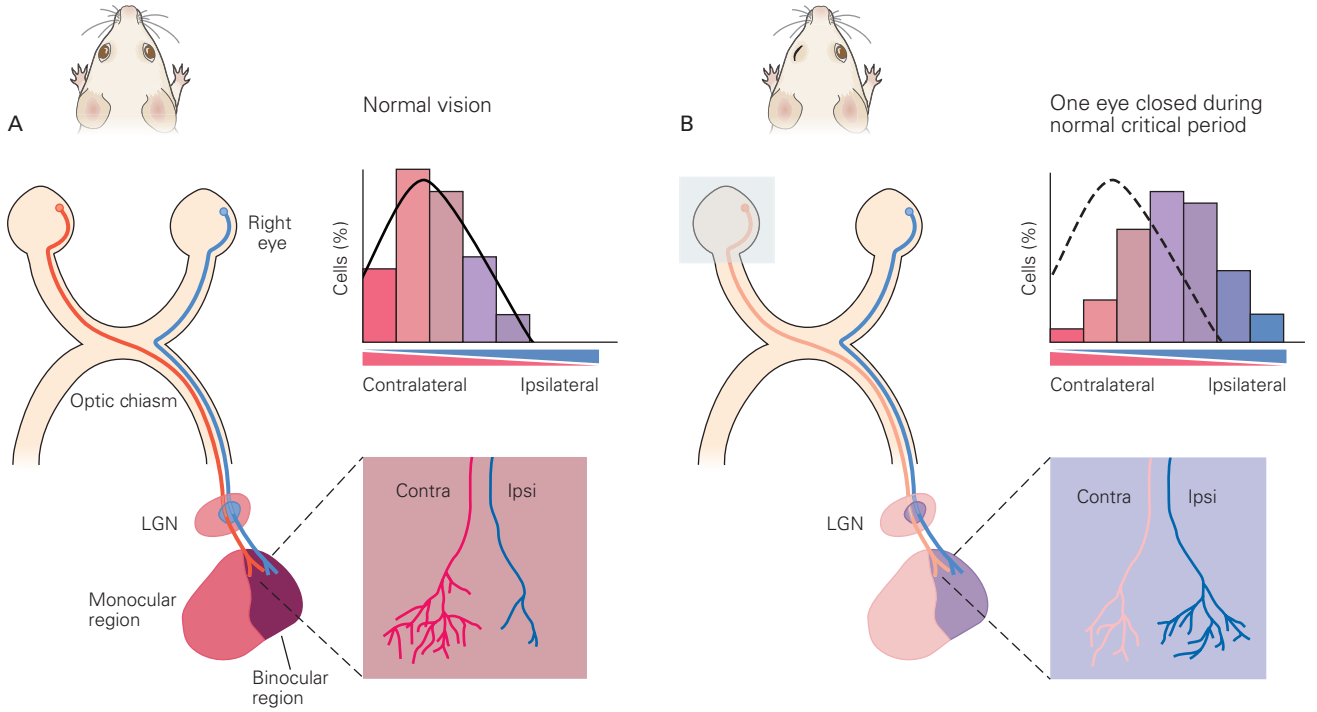

Figure 49–8 A critical period for ocular dominance plasticity is evident in mice. (Adapted, with permission, from Hensch 2005.)

A. The visual cortex in mice contains a small region that receives thalamic (lateral geniculate nucleus [**LGN**]) inputs from both eyes. In this binocular region, most neurons are predominantly responsive to contralateral eye input, fewer respond to binocular inputs, and very few respond to ipsilateral eye input only.

B. When the contralateral eye has been closed during the normal critical period and then reopened, inputs from that eye are underrepresented, and many more neurons respond to binocular or ipsilateral eye input. Eye closure before or after the time of the normal critical period does not elicit the same shift in responsiveness.

First, excitatory synapses within the primary visual cortex may weaken because of the decreased input from the closed eye, perhaps through long-term depression (LTD) (Chapter 53). Second, excitatory synapses carrying input from the open eye may become stronger. Third, the strength of inhibitory synapses may be altered, leading to a net decrease in the level of excitation of cortical neurons by inputs from the closed eye or a net increase in excitation from the open eye. Fourth, neuromodulation within the cortex may tune the circuit in more subtle ways, altering the balance between excitation and inhibition.

Careful analysis of neurons in mouse cortex has provided insight into roles played by some of these mechanisms. During the first few days after closing one eye, responses to input from the closed eye are greatly weakened, with no major effect on inputs from the open eye. The weakening results from a process like LTD or a closely related phenomenon called spike timing–dependent plasticity (STDP). Then, over the following few days, responses to inputs from the open eye become stronger. The increase results from a combination of synaptic changes called long-term potentiation and homeostatic plasticity. Homeostatic plasticity is a circuit mechanism that endeavors to maintain a steady level of input to neurons. In this case, loss of excitatory drive from the closed eye leads to a compensatory increase in excitatory drive from the open eye.

Further studies demonstrated that inhibitory interneurons have an important role in the timing of the critical period. Maturation of inhibitory input onto visual cortical neurons coincides with the beginning of the critical period. Moreover, manipulations that lead to earlier development of γ-aminobutyric acid (GABA) signaling result in advancing the critical period (Figure 49–9). Conversely, delaying GABA signaling delays the period in which monocular deprivation enhances the preference for ipsilateral eye input (Figure 49–9). Together these results and others suggest that a sufficient level of inhibitory input plays a critical role in "gating" the opening of the critical period, whereas excitatory mechanisms may play a more prominent role in enacting the alterations that occur during the critical period.