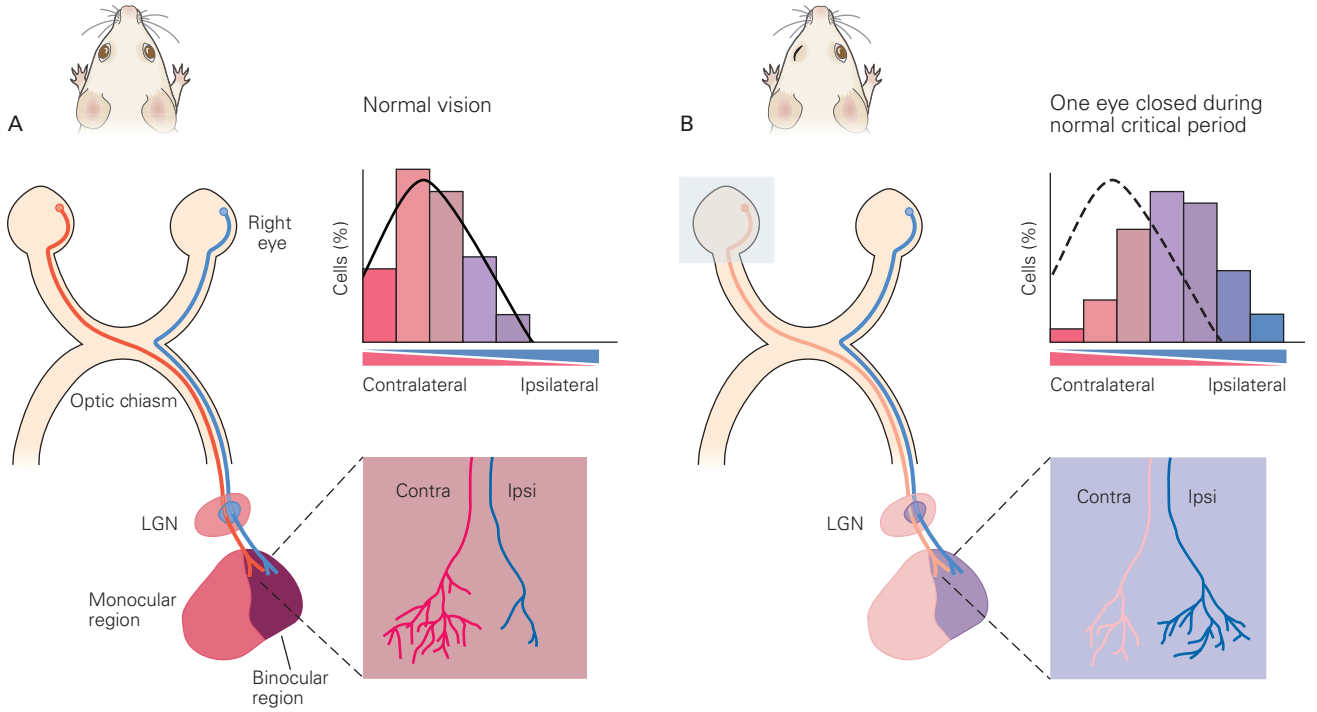


Figure 49–8 A critical period for ocular dominance plasticity is evident in mice. (Adapted, with permission, from Hensch 2005.)

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.

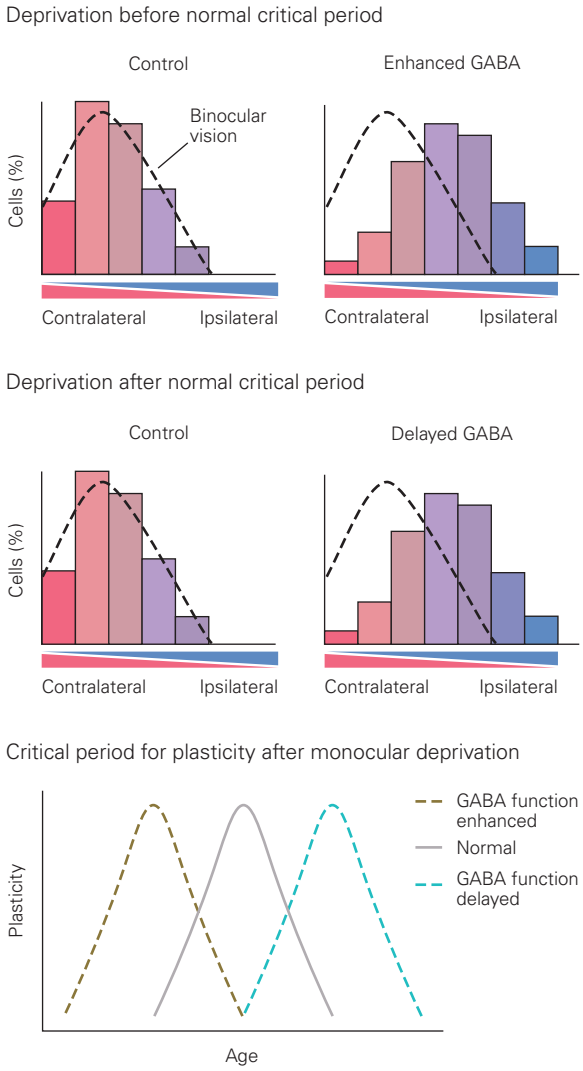


Figure 49–9 The timing of the critical period for ocular dominance plasticity in mice is sensitive to the level of GABAergic neurotransmission. Altering the status of γ-aminobutyric acid (GABA) synthesis and signaling shifts the period in which monocular deprivation can change the response properties of neurons in the visual cortex. Enhancing GABA signaling (through administration of benzodiazepines) shifts the critical period for monocular deprivation to an earlier developmental time. In contrast, delaying GABA signaling (by reducing GABA synthesis genetically and then administering benzodiazepines at a later time) shifts the critical period for monocular deprivation to a later developmental time. (Adapted from Hensch et al. 1998.)

Synaptic Structures Are Altered During the Critical Period

Many studies have sought structural changes that correlate with the altered responsiveness of the visual cortex to input from the closed and open eyes. Particular attention has been paid to dendritic spines as potential sites of plasticity.

Spines are small protrusions from the dendrites of many cortical neurons on which excitatory synapses form. They are dynamic structures, and their appearance and loss are thought to reflect the formation and elimination of synapses. Spine motility is especially marked during early postnatal development, and increases in spine dynamics and number have been associated with changes in behavior.

Striking alterations in the motility and number of dendritic spines on neurons in the mouse visual cortex are observed following closure of one eye. Two days after eye closure in young mice, the motility and turnover of dendritic spines on neurons in the visual cortex increases, suggesting that synaptic connections are beginning to rearrange (Figure 49–10). A few days later, the number of spines begins to change; the number of spines on the apical dendrites of pyramidal neurons decreases initially, but after longer periods of deprivation increases again.

These alterations in spine motility and number can be correlated with three known features of the critical period. First, rather than occurring in layer IV, the changes occur primarily in superficial and deep layers of the cortex, where binocular cells lie. Second, they occur only in the portion of the visual cortex that normally receives binocular input. Third, they fail to occur following eye closure in adult mice (Figure 49–10).

Together, these results support a linkage of spine dynamics with critical period plasticity. According to one model, spine motility may result from the imbalance of inputs to binocular neurons from the open and closed eyes, and it may reflect the first stages in synaptic rearrangement. In turn, the loss of spines, and presumably of synapses, corresponds in time and space to the loss of input from the closed eye and may provide a structural basis for the permanence of this loss. The later growth of new spines occurs as or after responsiveness to the open eye increases and may underlie the adaptive rearrangement that permits the cortex to make the best use of the input available to it.

Thalamic Inputs Are Remodeled During the Critical Period

How are local changes in spines related to the large-scale structural changes in ocular dominance columns

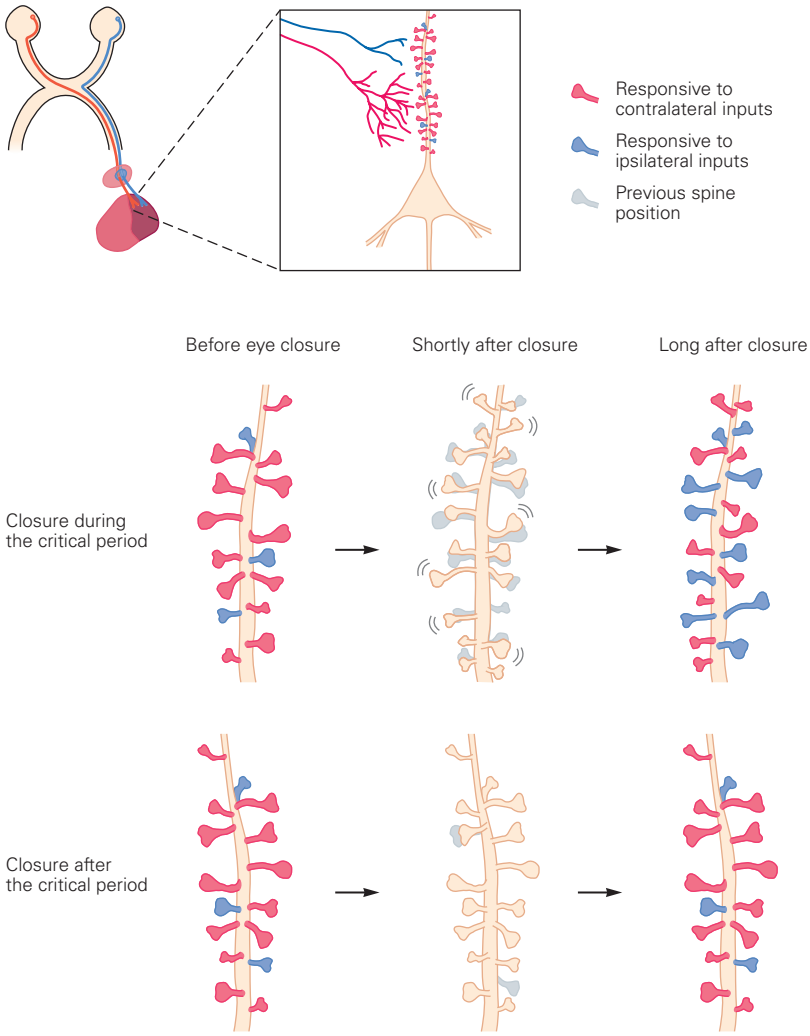


Figure 49–10 The motility of dendritic spines in the mouse visual cortex changes after one eye is closed. The dendrites of pyramidal neurons in the visual cortex have many spines, the density of which remains comparatively constant under normal conditions. Closure of one eye (contralateral in this example) during the critical period for binocular development enhances the motility of dendritic spines and, over time, results in an increase in the proportion of spines that receive synaptic input from the open eye. Similar changes in spine motility are not observed if the eye is closed after the critical period. (Adapted from Oray, Majewska, and Sur 2004.)

shown in Figure 49–4? When developing axons from the lateral geniculate nucleus first reach the cortex, the terminal endings of several neurons overlap extensively. Each fiber extends a few branches over an area of the visual cortex that spans several future ocular dominance columns. As the cortex matures, axons retract some branches, expand others, and even form new branches (Figure 49–11A).

With time, each geniculate neuron becomes connected almost exclusively to a group of neighboring cortical neurons within a single column. The arbors become segregated into columns through the pruning or retraction of certain axons and the sprouting of others. This dual process of axon retraction and sprouting occurs widely throughout the nervous system during development.

What happens after one eye is closed? Axons from a closed eye are at a disadvantage, and a greater than normal proportion retract. At the same time, axons from the open eye sprout new terminals at sites vacated by fibers that would otherwise convey input from the closed eye (Figure 49–11B). If an animal is deprived of the use of one eye early during the critical period of axonal segregation, the normal processes of axon retraction and outgrowth are perturbed. In contrast, if an animal is deprived of the use of one eye after the ocular dominance columns are almost fully segregated, axons conveying input from the open eye actually sprout collaterals in regions of the cortex that they had vacated earlier (see Figure 49–5).

Initially, it was believed that rearrangements of thalamocortical axons in monocularly deprived animals caused the changes in cortical responsiveness to the open and closed eyes. We now know, through electrophysiological recording and imaging of spines, that physiological changes and synaptic alterations

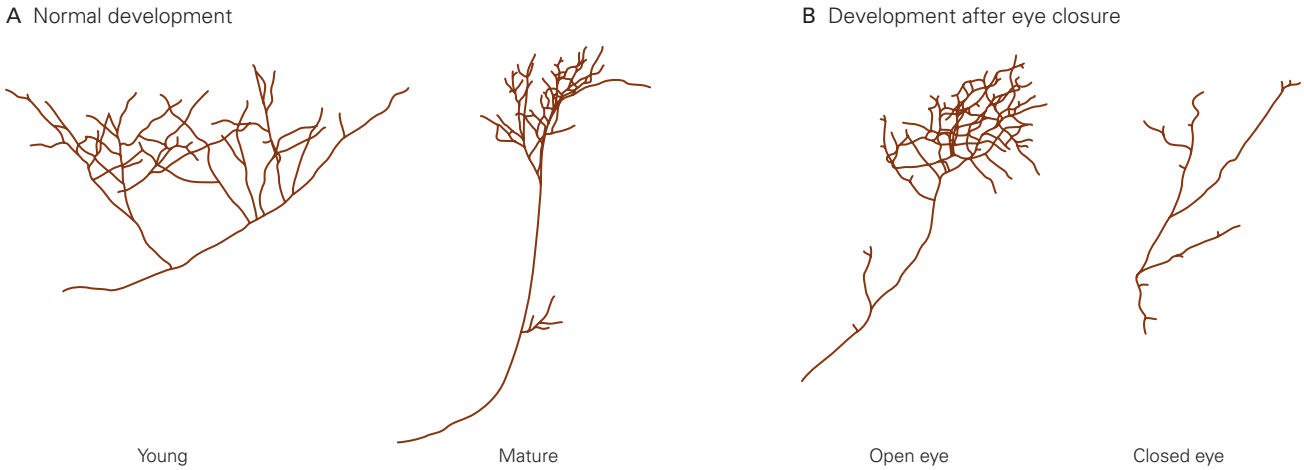


Figure 49–11 The branching of thalamocortical fibers in the visual cortex of kittens changes after the closure of an eye. (Adapted, with permission, from Antonini and Stryker 1993. Copyright © 1993 AAAS.)

A. During normal postnatal development, the axons of lateral geniculate nucleus cells branch widely in the visual cortex. The branching eventually becomes confined to a small region.

B. After one eye is closed, the terminal arbors of neurons in the pathway from that eye are dramatically smaller compared to those of the open eye.

precede the large-scale axonal rearrangements. So rather than causing the physiological changes, axonal remodeling may contribute to making these changes enduring and irreversible. The question then becomes: How do alterations in synaptic structure and function within the cortex lead to alterations in the input?

One idea is that synaptic activity regulates the secretion of neurotrophic factors by cortical neurons. Such factors may then regulate survival of some neurons at the expense of others (Chapter 46) or promote the expansion of some axonal arbors at the expense of others. One such factor, brain-derived neurotrophic factor (BDNF) is synthesized and secreted by cortical neurons, and administering excess BDNF or interfering with its receptor trkB modifies the formation of ocular dominance columns. Nevertheless, interpreting the actions of BDNF is not straightforward. BDNF and trkB signaling affect the cortex in many ways, including enhancing the growth of thalamocortical axons. BDNF can also speed the maturation of inhibitory circuits, which, as noted above, can influence plasticity. It remains unclear whether BDNF is a specific catalyst of the competition that preferentially promotes expansion of some arbors.

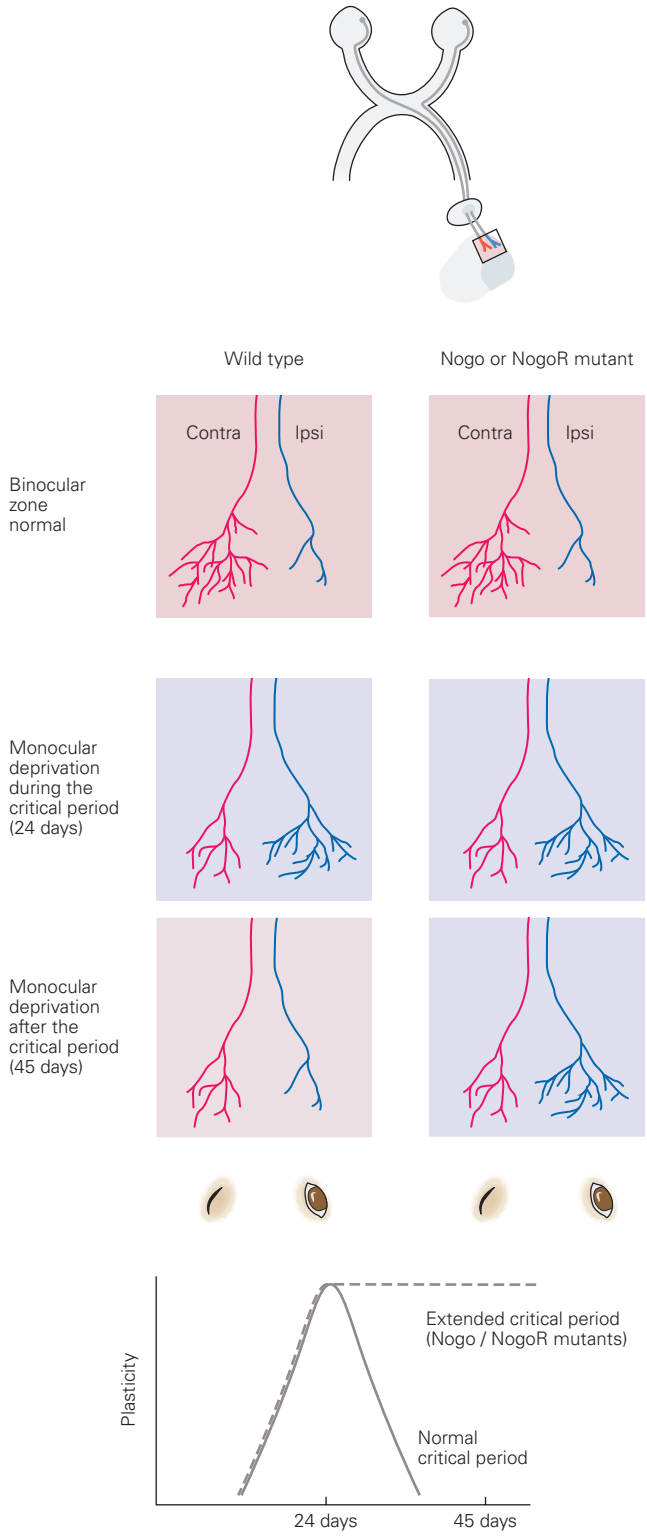
Synaptic Stabilization Contributes to Closing the Critical Period

A hallmark of critical periods is that the interval in which experience affects the development of neural circuits is limited. What brings this period of heightened plasticity to a close?

Since synapses and circuits are labile during critical periods, investigators have sought developmental changes in cortex that could lead to stabilization. One parameter is the state of myelination of axons, which occurs around the time the critical period closes. Formation of myelin creates physical barriers to sprouting and axonal growth. Moreover, as discussed in detail in Chapter 50, myelin contains factors such as Nogo and myelin-associated glycoprotein that actively inhibit growth of axons. In mutant mice lacking Nogo or one of its receptors, NogoR, the critical period remains open into adulthood, suggesting that the appearance of these receptors normally contributes to closing the critical period (Figure 49–12).

Another possible agent of closure is the perineuronal net, a web of glycosaminoglycans that wraps certain classes of inhibitory neurons. These nets form around the time that the critical period closes. Infusion of the enzyme chondroitinase, which digests perineuronal nets, maintains plasticity. Thus, critical periods may close once molecular barriers to synaptic growth and rearrangement come into play.

Additional agents of closure may be intrinsic to the neurons. In Chapter 50, we will see that neuronal growth programs decrease with age, and in Chapter 51, we will describe epigenetic mechanisms that "lock in" experience-dependent patterns of gene expression established in early postnatal life.



Why should there be an end to critical periods? Would it not be advantageous for the brain to maintain its ability to remodel into adulthood? Perhaps not—the ability of our brain to adapt to variations in sensory input, to gradual physical growth (eg, increases in the distance between the eyes affecting binocular correspondence), and to various congenital disorders is a valuable asset. At an extreme, if one eye is lost, it is advantageous to devote all available cortical real estate to the remaining eye. However, one would not want wholesale reorganization, possibly accompanied by loss of skills and memories, if vision through one eye were lost temporarily in adulthood due to disease or injury. So, enhancing plasticity during a critical period may represent an adaptive compromise between flexibility and stability.

Experience-Independent Spontaneous Neural Activity Leads to Early Circuit Refinement

As noted above, the segregation of visual cortex into ocular dominance columns in cats and monkeys begins before the onset of visual experience. What drives this early phase of segregation? One possibility is that axons from the ipsilateral and contralateral eyes bear different molecular labels that lead to their association. A similar mechanism occurs in the formation of the olfactory projection (Chapter 48). However, no such molecule or mechanism has yet been discovered in the visual projection. Instead segregation appears to rely on spontaneous activity, which not only occurs prior to sensory input but also exhibits striking patterning. This mechanism was initially discovered in studies of the lateral geniculate nucleus, whose neurons provide visual input to the visual cortex.

The arbors of retinal ganglion cells from the two eyes are segregated into alternating layers in the lateral geniculate nucleus, much as the projections from this nucleus are segregated in alternating ocular dominance

Figure 49–12 (Left) The critical period for monocular deprivation is extended in mice lacking Nogo signaling. The drawings show arborization patterns of thalamocortical axons carrying signals from contralateral and ipsilateral eyes to the binocular zone in visual cortex. Monocular deprivation during the critical period results in a shift in ocular preference in neurons in the binocular zone in both wild-type mice and mice mutant for Nogo or the Nogo receptor (**NogoR**). After the normal critical period (at 45 days), the shift in ocular preference continues in mice with mutant Nogo-A or the Nogo receptor but not in wild-type mice. The plot shows that elimination of Nogo signaling prevents closure of the critical period. (Adapted from McGee et al. 2005.)

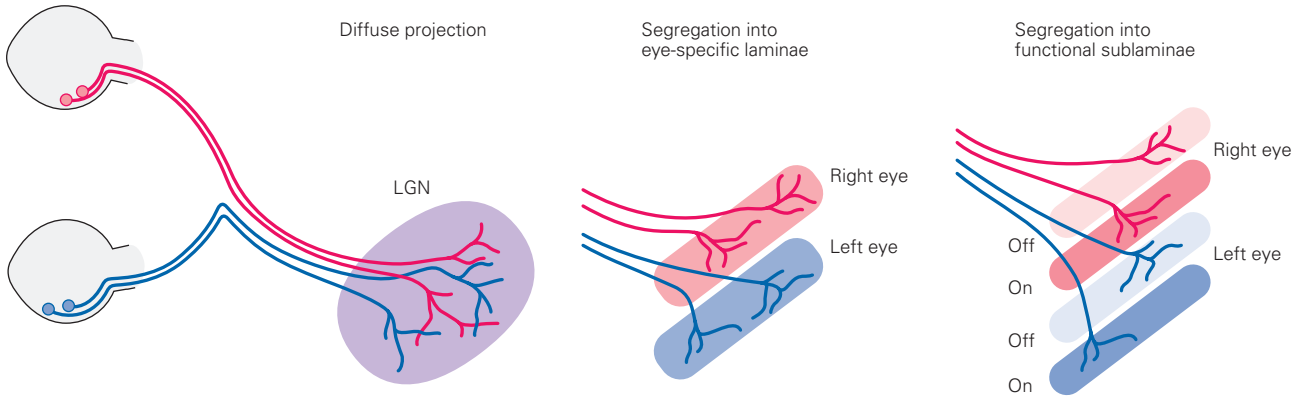


Figure 49–13 The terminals of retinal ganglion cells in the lateral geniculate nucleus (LGN) become segregated during normal development. At early stages of development, the terminals of axons from each eye intermingle, but at later stages, they segregate into separate layers of the nucleus. In some species, axons from one eye even segregate into functionally specialized sublayers (on and off layers in ferrets). (Adapted, with permission, from Sanes and Yamagata 1999.)

columns in the visual cortex (Figure 49–13). In both structures, individual axons at first form terminals in multiple domains (layers in the geniculate nucleus, columns in the cortex). Later, the terminals become segregated by a process of refinement. The refinement involves both growth of terminal arbors in the "appropriate" layer and elimination of terminals from the inappropriate layer (Chapter 48).

As in the cortex, application of tetrodotoxin to the optic nerves disrupts the segregation of the inputs from each eye, indicating that activity is essential for segregation. In contrast to cortex, however, segregation of inputs is complete before the onset of visual experience—prior to birth in monkeys and postnatally but prior to eye opening in mice. Thus, vision cannot drive the neural activity essential for segregation.

It turns out that the axons of retinal ganglion neurons are spontaneously active in utero, well before the eyes open. Neighboring ganglion cells fire in synchronous bursts that last a few seconds, followed by silent periods that may last for minutes. Sampling the activity of retinal ganglion neurons across the entire retina revealed that these bursts propagate across much of the retina in a wave-like manner (Figure 49–14). This pattern of ganglion cell activity appears to be coordinated by excitatory inputs from amacrine cells in the overlying layer of the retina (Chapter 22).

The spontaneous, synchronous firing of a select group of ganglion neurons excites a local group of neurons in the lateral geniculate nucleus. Such synchronized activity appears to strengthen these synapses at the expense of other nearby synapses, perhaps by a Hebbian mechanism similar to that posited for experience-dependent refinement. This does not mean that visually evoked activity has no role in sculpting the retinogeniculate pathway. At a later stage, other aspects of refinement, such as spatial rearrangement of synapses along the axon, are regulated by visual experience.

The discovery that spontaneous activity can lead to circuit refinement provides a likely explanation for the initial segregation of inputs to the visual cortex. More generally, the parsing of activity-dependent circuit refinement into two phases, the first dependent on spontaneous activity and the second on sensory input, now appears to be a general theme in the development of brain circuits that begin refinement before they have the chance to respond to environmental stimulation.

Activity-Dependent Refinement of Connections Is a General Feature of Brain Circuitry

We have seen that neural activity is critical for segregating axons from the two retinas into distinct layers in the lateral geniculate nucleus and then into distinct columns in the visual cortex. Is this developmental role of activity a special case, or does activity also affect maturation elsewhere in the visual system, and even in other parts of the brain? Studies of many systems show that activity-dependent control of refinement is a general property of neural circuits in the mammalian brain.

Many Aspects of Visual System Development Are Activity-Dependent

One well-studied example of activity-dependent development in the visual system is the sharpening

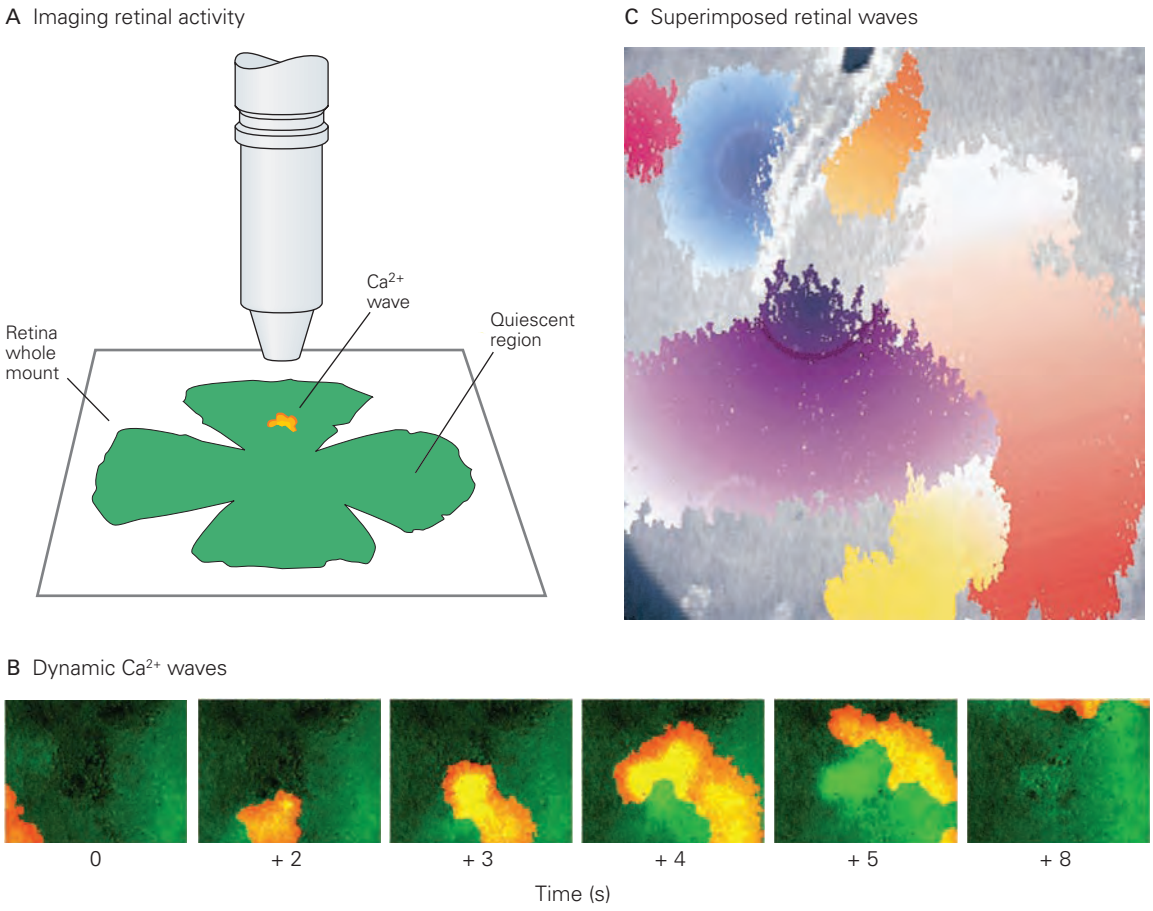


Figure 49–14 Correlated waves of neural activity in the developing retina.

A. Microscopic visualization of the activity of retinal ganglion neurons in a flat-mounted preparation of mammalian retina. Spontaneous waves of neural activity are visualized by monitoring Ca^{2+} transients (**yellow domain**) after loading of cells with dyes that change their fluorescent emission spectrum in response to changes in intracellular Ca^{2+} concentration.

B. These still images from a movie sequence show the propagation of one Ca^{2+} activity focus (**yellow domain**) across the retina. Images were taken 1 second apart. Many cells within the activity focus are activated synchronously. (Reproduced, with permission, from Blankenship et al. 2009. Copyright © 2009 Elsevier Inc.)

C. Retinal activity waves recorded over time are superimposed in this image. Discrete waves are indicated in different colors; the origin of a wave is indicated by a darker hue. These waves originate in different retinal foci and spread in distinct, unpredictable directions. (Reproduced, with permission, from Meister et al. 1991. Copyright © 1991 AAAS.)

of the topographic distribution of retinal ganglion cell axons onto their central targets, a topic we introduced in Chapter 47. In vertebrates, molecular cues such as ephrins guide axons from the retina to appropriate sites in the optic tectum (called the superior colliculus in mammals—see Figure 47–11), but they are not sufficient to form the refined visual map.

Histological and physiological studies have found that the map formed initially in the superior colliculus/optic tectum is coarse and that individual retinal ganglion cell axons have large, overlapping arbors. These axonal arbors are later pruned to their mature size, resulting in a more restricted and precise field of termination. If retinal activity is inhibited, only the initial coarse map forms.

Is it the pattern of activity or activity itself that is important in visual map formation? Put another way, is activity simply a precondition for refinement, or does it have an organizing role, determining exactly which axons win or lose the competition? Many experiments show that the latter idea is closer to the truth.

In one study, the accuracy of the retinotectal map was assessed in fish raised in a tank illuminated only by brief flashes from a strobe light. A control group was raised in a normal laboratory environment. The total light intensity presented to the fish was similar

under both conditions, but the resulting pattern was very different. In control fish, the images fell haphazardly on various parts of the retina as the fish swam around their tanks. This input produces local synchronous activity of the sort generated by the waves of spontaneous activity described above—neighboring ganglion cells tend to fire together, but there is little correlation with the firing patterns of distant ganglion cells. In these fish, the map becomes precise. In contrast, stroboscopic illumination synchronously activates nearly all of the ganglion cells, and in these fish, the retinotectal map remains coarse.

Presumably, the tectum determines which retinal axons are near neighbors by judging which ones fire in synchrony, much as activity patterns in the lateral geniculate nucleus or visual cortex determine which axons carry signals from the same eye. This information is then used to refine the topographic map, through mechanisms similar to those in the cortex. When all of the axons fire in synchrony, the tectum cannot determine which axons are neighbors; refinement fails, and the map remains coarse.

Sensory Modalities Are Coordinated During a Critical Period

Our experience of the world is shaped by synthesizing sensory input from multiple modalities. For example, our mental image of where an object is with respect to our body is the same whether we localize it by touch, sound, or sight. For each modality, information is mapped in an orderly way within relevant brain areas, much like the retinotopic maps in the optic tectum and visual cortex. Multimodal localization requires that these maps, which are formed independently during development, be brought into register. This aspect of refinement occurs during critical periods.

Studies on barn owls have provided insight into how auditory and visual maps are coordinated during a critical period. During the day, owls use vision to localize their prey—mice or other small rodents—but at night, they rely on auditory cues, and at dusk, both sensory channels are used. The localization of sound must be precise if owls are to succeed in finding prey, and it is intuitively obvious that the visual and auditory cues for the same location need to be consistent.

Auditory localization in owls, as in people, results from the presence of neurons that vary in their sensitivity to sounds sensed by the two ears. For example, sounds arising from a source to the left arrive slightly sooner at the left ear than at the right ear and are slightly louder in the left ear. These discrepancies help us determine the point in horizontal space from which a sound arises (Chapter 28). Computation of the temporal difference in the arrival of sounds at the two ears is particularly crucial. The difference is only a few tens of microseconds, as expected from calculations based upon the speed of sound and the width of the head. Remarkably, the auditory system is sensitive to these extremely short interaural time differences (ITDs) and can calculate prey position from them (Figure 49–15). Moreover, many auditory neurons in the optic tectum

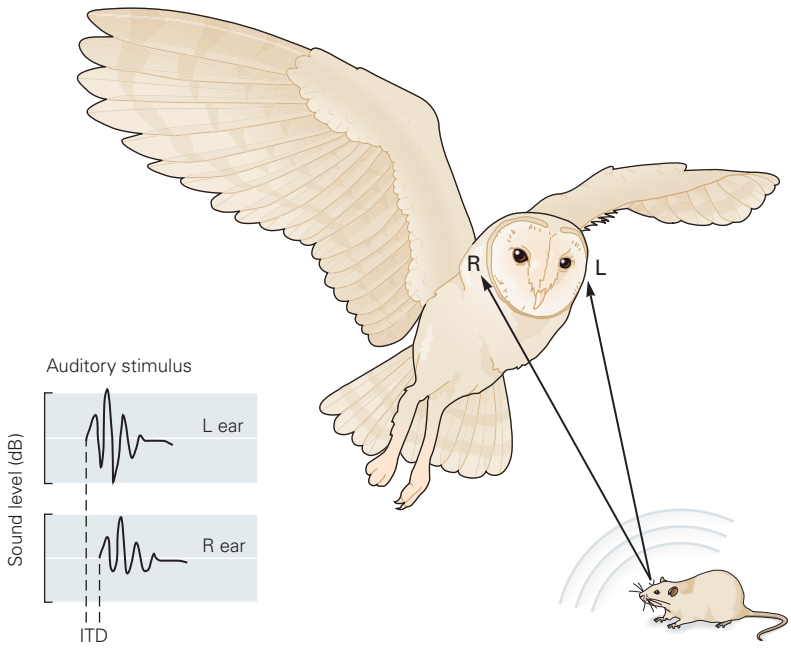


Figure 49–15 The barn owl uses interaural time differences to localize its prey. Sound waves generated by movements of a mouse are received by the owl's left and right ears. As the prey emits noise, the difference in the time of arrival of auditory stimuli at the two ears—the interaural time difference (ITD)—is used to calculate the precise position of the prey target. (Reproduced, with permission, from Knudsen 2002. Copyright © 2002 Springer Nature.)

with receptive fields centered on a particular location are also tuned to ITDs that correspond to sounds emitted from that same point in space. The registration is imprecise at early stages but becomes progressively more precise during early adolescence as a consequence of the animal's experience.

Crucial insight into how this registration occurs came from experiments in which prisms were mounted over the eyes of young owls. The prisms shifted the retinal image horizontally so that the visual map in the tectum reflected a world systematically displaced from its "actual" orientation. This change abruptly disrupted the correspondence between visual and auditory receptive fields. Over the next several weeks, however, the ITD to which tectal neurons responded optimally, ie, their auditory receptive field, changed until the visual and auditory maps came back into register (Figure 49–16). Thus, the visual map instructs the auditory map.

Further experiments showed that this reorganization resulted from rewiring of connections between two deeper auditory nuclei (Figure 49–17). When prism goggles were placed on young owls, changes in ITD tuning were fully adaptive in that the animals compensated completely for the effects of the prisms. In contrast, goggles placed on mature owls (older than 7 months of age) had little effect. Thus, reorganization of this auditory projection occurs optimally during a critical juvenile period.

Different Functions and Brain Regions Have Different Critical Periods of Development

Not all brain circuits are stabilized at the same time. Even within the visual cortex, the critical periods for organization of inputs differ among layers in both mice

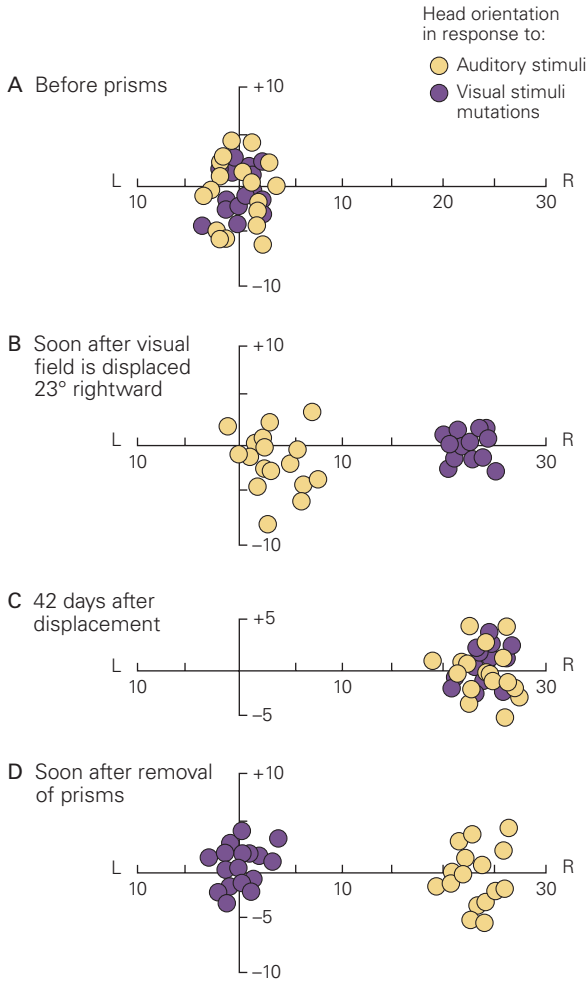


Figure 49–16 (Right) **Reorganization of sensory maps in the optic tectum of owls after systematic displacement of the retinal image.** The retinal image in adolescent owls can be displaced by prism goggles, which shift images from 5° to 30°. (Adapted, with permission, from Knudsen 2002. Copyright © 2002 Springer Nature.)

A. Before application of the prisms, the visual and auditory neural maps coincide.

B. The prism goggles displace the retinal image by 23°. Consequently, the neural and auditory maps are out of alignment.

C. The two brain maps are once again congruent 42 days after prism application because the auditory map has shifted to realign with the visual map.

D. Soon after the prisms are removed, the visual map reverts to its original position, but the auditory map remains in its shifted position.