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

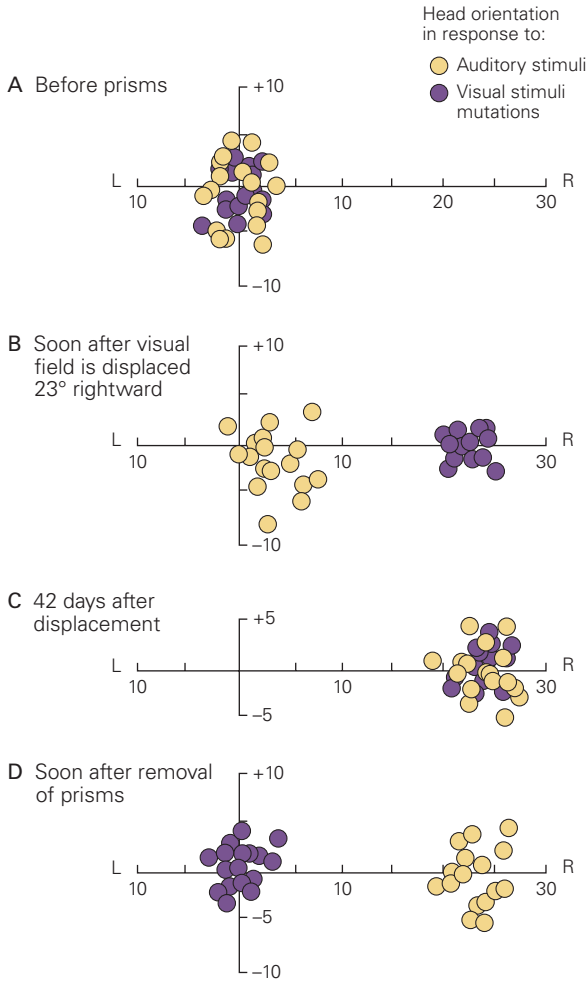

Figure 49–16 (Right) **Reorganization of sensory maps in the optic tectum of owls after systematic displacement of the retinal image.** The retinal image in adolescent owls can be displaced by prism goggles, which shift images from 5° to 30°. (Adapted, with permission, from Knudsen 2002. Copyright ©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

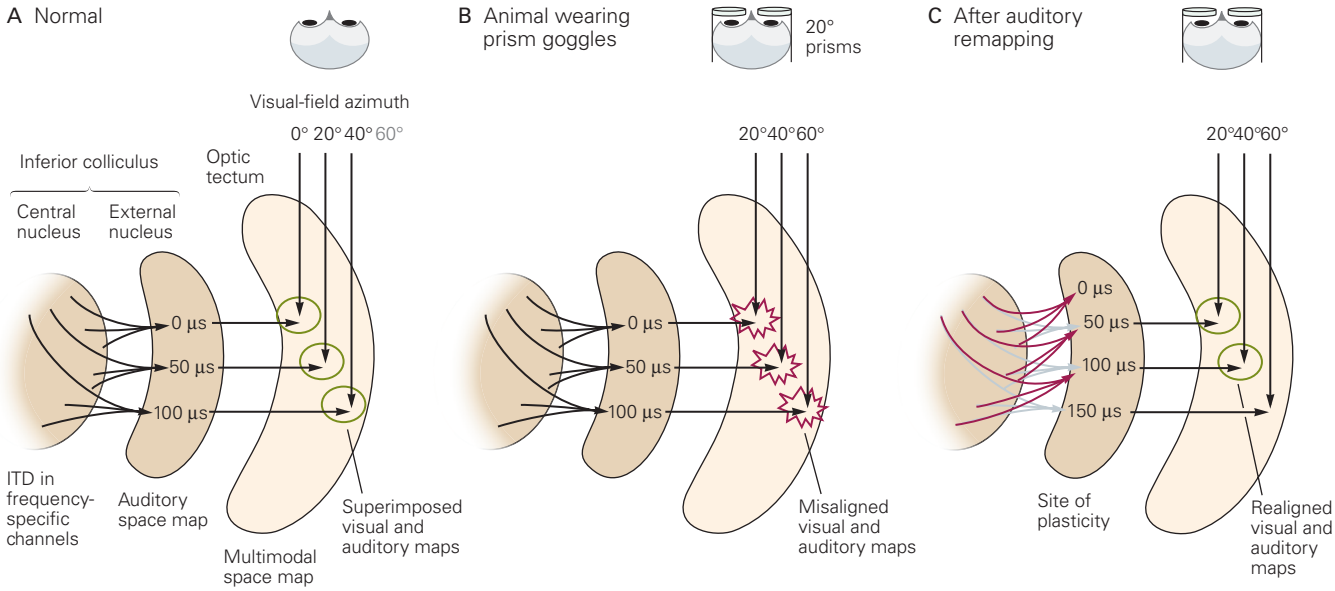

Figure 49–17 The effect of prism experience on information flow in the midbrain auditory localization pathway in the barn owl. (Adapted from Knudsen 2002.)

A. The auditory pathway in a normal owl. The interaural time difference (ITD) is measured and mapped in frequency-specific channels in the brain stem. This information ascends to the inferior colliculus, where a neural map of auditory space is created. The map is conveyed to the optic tectum where it merges with a map of visual space.

B. After an owl is fitted with prism goggles, the visual and auditory space maps in the optic tectum become misaligned.

C. After reorganization of auditory maps, the visual and auditory maps are once again in alignment.

and monkeys. As an example, the neural connections in layer IVC of the visual cortex of the monkey are not affected by monocular deprivation by the time the animal is 2 months old. In contrast, connections in the upper and lower layers continue to be influenced by sensory experience (or lack of it) for almost the entire first year after birth. Critical periods for other features of the visual system, such as orientation tuning, occur at different developmental stages (Figure 49–18A).

The timing of critical periods also varies between brain regions (Figure 49–18B). The adverse consequences of sensory deprivation for the primary sensory regions of the brain are generally fully realized early in postnatal development. In contrast, social experience can affect the intracortical connections over a much longer period. These differences may explain why certain types of learning are optimal at particular stages of development. For example, certain cognitive capacities—language, music, and mathematics—usually must be acquired well before puberty if they are to develop at all. In addition, insults to the brain at specific early stages of postnatal life may selectively affect the development of certain perceptual abilities and behavior.

Critical Periods Can Be Reopened in Adulthood

By definition, critical periods are limited in time. Nevertheless, they are less sharply defined than originally thought. Extending or reopening critical periods in adulthood could increase brain plasticity and make it possible to facilitate recovery from strokes and other insults that impair discrete regions of the nervous system.

Some of the first evidence for plasticity in the adult cortex came from studies by Merzenich and colleagues on the representation of the fingers of monkeys in the somatosensory cortex. Recordings of neuronal receptive fields in normal adult animals showed that each digit is mapped in an orderly way on the cortical surface, with abrupt discontinuities between areas responding to different digits (Figure 49–19A). Amputation of a digit left the cortical representation of that digit initially unresponsive, but after several months, areas serving the neighboring digits filled in the gap (Figure 49–19B). Much as happens in the visual cortex following monocular deprivation, the somatosensory map was readjusted so that the cortex could devote

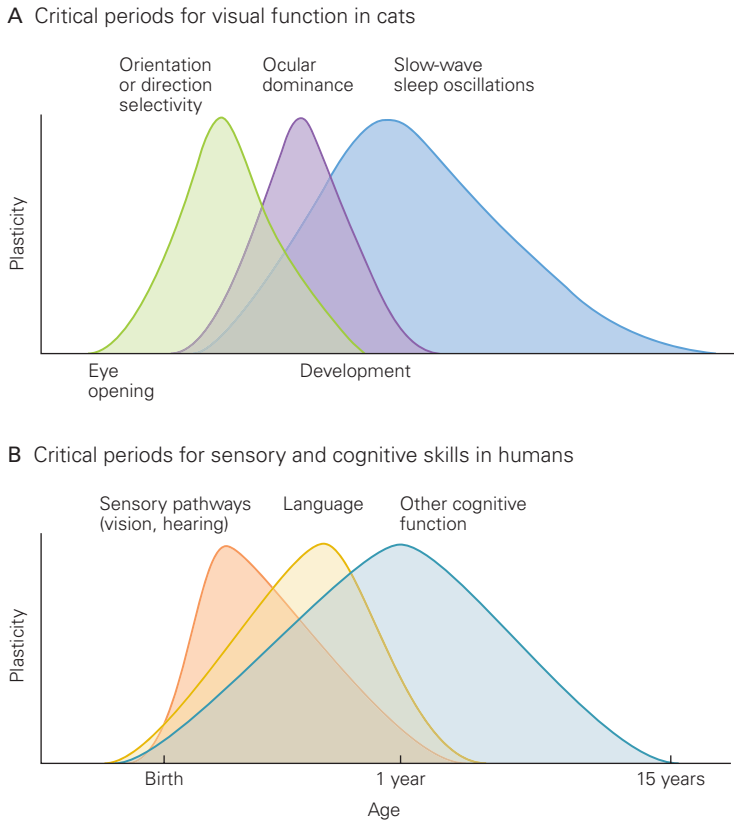

Figure 49–18 The timing of critical periods varies with brain function. (Reproduced, with permission, from Hensch 2005. Copyright © 2005 Springer Nature.)

A. In cats, the critical periods for development of orientation or direction selectivity in visual neurons occur earlier than those for establishment of ocular dominance and slow-wave sleep oscillation.

B. In humans, the timing of periods for development of sensory processing, language, and cognitive functions varies.

most of its resources to useful inputs. Conversely, when two fingers were sutured together so they received coincident input, a swath of cortex on both sides of the border between the two digit areas eventually became responsive to both areas (Figure 49–19C). This result suggests that, as in the visual system, borders may result from competition and can be blurred when competition declines. What was most surprising was that these effects occurred in adulthood, long after all known critical periods had closed.

In the years since Merzenich's studies, evidence has accumulated that critical periods can be reopened in many systems. We illustrate this principle by returning to two areas in which critical periods have been well mapped, the optic tectum in the owl and the visual cortex in the mouse.

Visual and Auditory Maps Can Be Aligned in Adults

In initial studies of the matching of auditory and visual maps in owls, realignment following displacement of the visual field with prism goggles was largely restricted to an early sensitive period (Figures 49–16 and 49–17). However, three strategies dramatically enhance binaural tuning plasticity in adult owls.

First, when adult owls that had worn goggles as adolescents are refitted with the goggles, the auditory map again shifts to align with the new visual map (Figure 49–20A). In contrast, in adult owls that had not worn the goggles as adolescents, the use of goggles has little effect on the organization of the auditory map. Thus, the events of map rearrangement during the normal critical period must leave a neural trace that permits rearrangement later in life. In fact, in the owls that wore prisms in early life, axons to auditory nuclei that were normally pruned were maintained, providing a structural basis for the reorganization in adulthood.

A second method for inducing late plasticity is to displace the retinal image in small steps by having the owl wear a series of prism spectacles of progressively increasing strength. Under these conditions, adjustment of the auditory map is typically three- to fourfold greater than the response to a single large displacement of the retinal image (Figure 49–20B).

The third technique is to allow owls to hunt live prey. In earlier experiments, animals were housed and fed under standard laboratory conditions. However, when adult prism-wearing owls are allowed to capture live mice under low light conditions for 10 weeks, they exhibit far greater plasticity of binaural tuning

than owls fed dead mice (Figure 49–19C), albeit less than that exhibited by juvenile owls that did not hunt. The finding that hunting increases the plasticity of binaural tuning in adult owls dramatically demonstrates that behavioral context affects the ability of the nervous system to reorganize. Whether this effect results from increased sensory information, attention, arousal, motivation, or reward needs to be resolved.

Binocular Circuits Can Be Remodeled in Adults

As the body of observations on monocular deprivation grew, it became apparent that some plasticity persisted beyond the classical critical period in cats, rats, and mice. In mice, for example, modest shifts in ocular dominance occur even when one eye is deprived of vision at 2 or 3 months of age. By 4 months of age, however, monocular deprivation has no detectable effect.

Over the past decade, several interventions have been discovered that enhance the extent of ocular dominance plasticity in young adults and even enable substantial plasticity in older animals. Some are noninvasive: Environmental enrichment, social interaction (via group housing), visual stimulation, and exercise all increase the magnitude and speed of changes that occur following monocular deprivation in adults. A second group of interventions targets mechanisms that appear to affect the timing of the normal critical period. As noted above, treating the cortex with chondroitinase to disrupt perineuronal nets or interference with the inhibitory effects of myelin on axonal growth can both extend and reopen the critical period. Remarkably, transplantation of immature inhibitory interneurons into the visual cortex also reopens the critical period even in 6-month-old mice.

How can we reconcile the strong evidence for critical periods with the newer evidence for reorganization

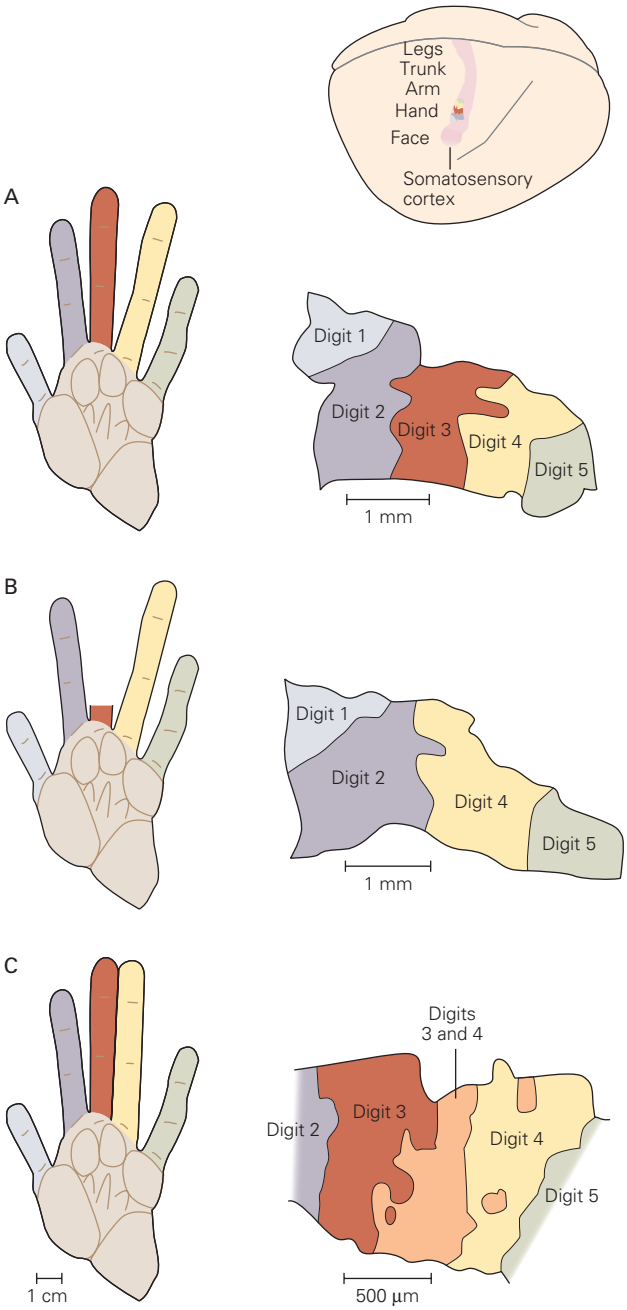

Figure 49–19 (Left) Representation of digits in somatosensory cortex can be remapped in adult monkeys. (Adapted, with permission, from Merzenich et al. 1984 and Allard et al. 1991.)

A. Lightly touching specific spots on the digits (*left*) elicits responses from neurons in somatosensory cortex (*right*), revealing orderly topographic maps of each digit on the cortical surface. Abrupt discontinuities distinguish regions serving adjacent digits.

B. Following amputation of a digit, the cortical region it previously supplied is left unresponsive. Several months later, axons from the adjacent digits (2 and 4) have formed synaptic connections in the unresponsive area.

C. After digits 3 and 4 have been sutured together, they received simultaneous sensory stimulation, and cortical regions at the border between areas representing the digits become responsive to both.

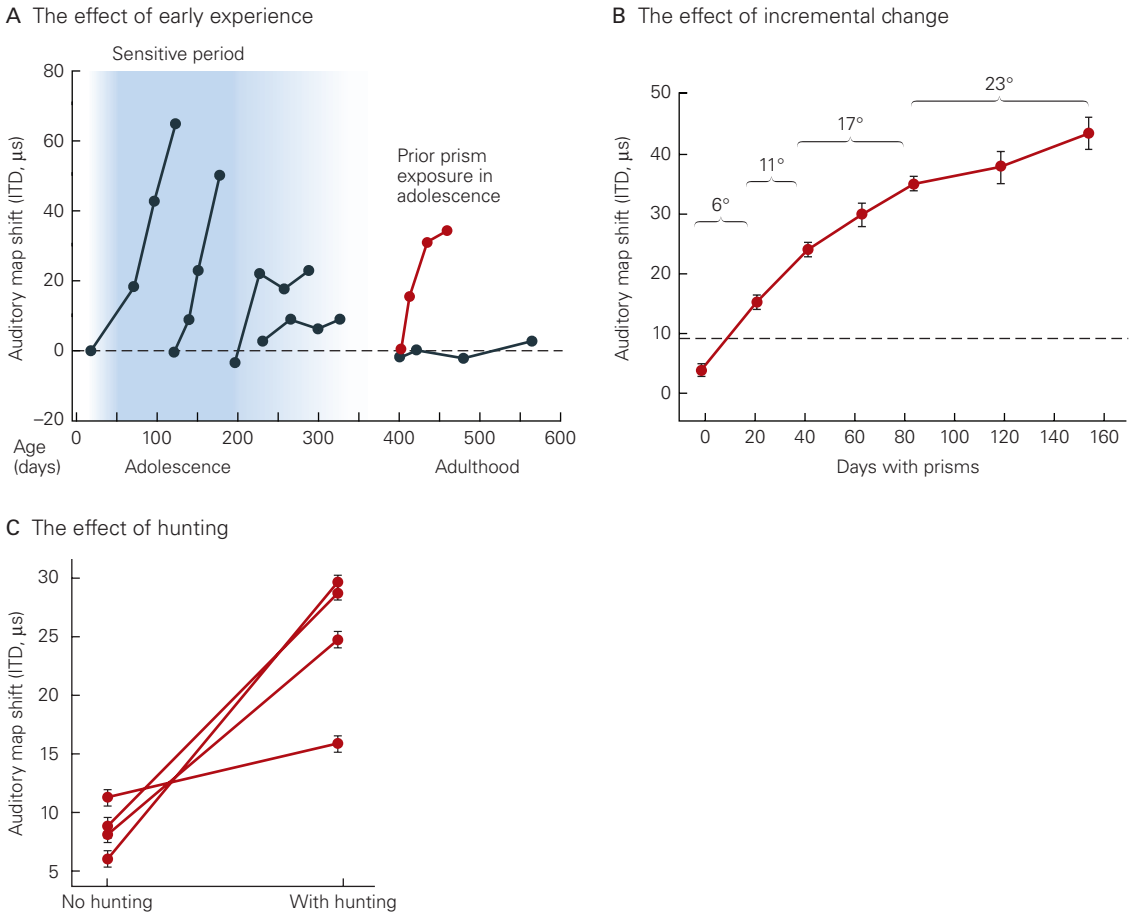

Figure 49–20 Different behavioral conditions have different effects on the realignment of visual and auditory neural maps in the mature barn owl.

A. The remodeling of the auditory maps that results from wearing prism goggles for a brief period during adolescence leaves a neural trace that can be reactivated in the adult. When these birds are fitted with the goggles as adults, the auditory map is still able to realign with the visual map. (Abbreviation: ITD, interaural time difference.) (Reproduced, with permission, from Knudsen 2002. Copyright © 2002 Springer Nature.)

B. When an animal is fitted with a series of prisms, each of which produces a small displacement in the visual image, the auditory map is successfully brought into alignment. The dotted line shows the extent of realignment if the animal is fitted with a 23° prism on day 0. (Reproduced, with permission, from Linkenhoker and Knudsen 2002. Copyright © 2002 Springer Nature.)

C. If an adult owl has the opportunity to hunt live prey while wearing prism goggles, auditory remapping occurs, perhaps because of enhanced motivation to sharpen perception. (Reproduced, with permission, from Bergan et al. 2005. Copyright © 2005 Society for Neuroscience.)

of circuitry in adults? The plasticity observed in adults is modest and slow compared to that seen during the critical period, and its mechanisms differ in some respects from those for earlier deprivation. These differences result from two factors. First, from early postnatal life into adolescence, the molecular environment in the brain is conducive to axonal growth, and cellular mechanisms are optimal for promoting the formation, strengthening, weakening, and elimination of synapses. Under these conditions, circuits can readily change in response to experience. Conversely, in mature circuits, molecular and structural elements promote stability and impede plasticity. Second, in a developing circuit, no particular pattern of connectivity is firmly entrenched, so there is less to overcome. The connections specified by genetic determinants are less precise, and the connections themselves are relatively weak. The patterns of neural activity that result from experience sharpen and even realign these patterns of connectivity.

In sum, experience during critical periods has a potent effect on circuits because the cellular and molecular conditions are optimal for plasticity and because the instructed pattern of connectivity does not have

to compete with a long-existing pattern. These differences help explain the special behavioral, pharmacological, or genetic interventions needed to stimulate plasticity in adults.

Highlights

1. Although the nervous system is malleable throughout life, plasticity is particularly great during restricted intervals in early postnatal life called critical periods. Alterations that occur during these periods are nearly irreversible.
2. Critical periods vary in time among brain areas and tasks. For example, children with strabismus (crossed eyes) will never have good stereoscopic vision unless their eyes are brought into alignment during the first few postnatal years, and people cannot learn a new language without an accent after their early teens.
3. The richest understanding of critical periods comes from studies initiated by Hubel and Wiesel on how input from the two eyes is integrated in the cortex. They deprived one eye of vision for varying periods in young cats or monkeys. In normal animals, most neurons in visual cortex are binocularly responsive, but following monocular deprivation for a brief period in early postnatal life, most cortical cells permanently lost responsiveness to input from the once-closed eye. Responses in the eye itself and the lateral geniculate nucleus were nearly normal, pinpointing the cortex as the site of change. Much longer deprivation in adulthood had little effect.
4. A structural basis for the loss of binocularity was seen in the alternating pattern of ocular dominance columns, within which neurons are dominated by input from one eye or the other. Following monocular deprivation during the critical period, columns representing the open eye expanded at the expense of those representing the closed eye. This form of plasticity may be designed to optimize the use of cortical space for each individual at each time period—for example, subtly shifting binocular interactions as the head grows and the eyes become further apart.
5. The binocular interaction reflects competition between the two sets of inputs, since vision and symmetrical columns are retained following binocular deprivation. Many lines of evidence indicate that the competition depends on patterns of activity arising in the two eyes, with inputs from each eye being more synchronous with each other than with inputs from the other eye. Postnatally, synchrony is driven by visual experience. Prenatally or prior to eye opening, patterned spontaneous activity in the two eyes accounts for the synchrony.
6. Cellular mechanisms underlying the effects of monocular deprivation have been studied in greatest detail in mice. Following monocular deprivation, input from the closed eye is weakened rapidly by a process akin to long-term depression (LTD). Shortly thereafter, input from the other eye is strengthened, partly by a compensatory mechanism called homeostatic plasticity. Structural remodeling of thalamic axons and cortical dendrites occurs later.
7. Maturation of inhibitory interneurons is a main determinant of when the critical period opens. The end of the critical period is marked by the formation of myelin and proteoglycan-rich perineuronal structures that hamper structural remodeling.
8. Although plasticity of binocular interactions was initially believed to be confined to early postnatal life, it is now apparent that critical periods can be "reopened" to some extent in adults. In some cases, this can be done by altering the animal's environment or the way in which the altered experience is delivered. Critical periods can also be reopened by manipulating some of the factors that normally close them in adolescence.
9. Plasticity in adulthood is modest in magnitude and difficult to trigger compared to early postnatal critical periods. Nonetheless, reopening of critical periods could, if properly controlled, enable reorganization to compensate for losses incurred from injuries, disease, and early maladaptive experience.
10. Critical periods occur during development of numerous systems, such as formation of orderly maps of auditory, somatosensory, and visual input onto relevant sensory cortices. Many of the principles and mechanisms that characterize the plasticity of binocular interactions also regulate these critical periods, including roles of spontaneous and experience-dependent activity, competition, alterations in excitatory and inhibitory synapses, and selective growth and pruning of inputs to achieve appropriate patterns of adult connectivity.
11. The existence of critical periods demonstrates that the brain's ability to remodel declines precipitously in adulthood. This seems disadvantageous but may represent a useful adaptation, allowing each brain to adapt to its environment

as it develops, but then buffering it against excessive change later, perhaps even enabling skills and memories to persist. If this is the case, therapies based on reopening critical periods in adults may come at a cost.

Joshua R. Sanes

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Repairing the Damaged Brain

For much of its history, neurology has been a discipline of outstanding diagnostic rigor but little therapeutic efficacy. Simply put, neurologists have been renowned for their ability to localize lesions with great precision but until recently have had little to offer in terms of treatment. This situation is now changing.

Advances in our understanding of the structure, function, and chemistry of the brain's neurons, glial cells, and synapses have led to new ideas for treatment. Many of these are now in clinical trials, and some are already available to patients. Developmental neuroscience is emerging as a major contributor to this sea change for three main reasons. First, efforts to preserve or replace neurons lost to damage or disease rely on recent advances in our understanding of the mechanisms that control the generation and death of nerve cells in embryos (Chapters 45 and 46). Second, efforts to improve the regeneration of neural pathways following injury draw heavily on what we have learned about the growth of axons and the formation of synapses (Chapters 47 and 48). Third, there is increasing evidence that some devastating brain disorders, such as autism and schizophrenia, are the result of disturbances in the formation of neural circuits in embryonic or early postnatal life. Accordingly, studies of normal development provide an essential foundation for discovering precisely what has gone wrong in disease.

In this chapter, we focus on the first two of these issues: how neuroscientists hope to augment the limited ability of neurons to recover normal function. We shall begin by describing how axons degenerate following the separation of the axon and its terminals from the cell body. The regeneration of severed axons is robust in the peripheral nervous system of mammals and in the central nervous system of lower vertebrates, but very poor in the central nervous system of