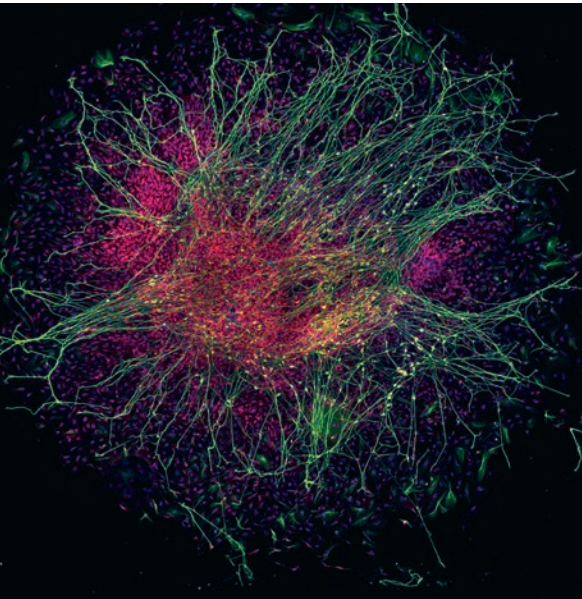


CHAPTER 25

Experience-Dependent Plasticity in the Developing Brain



Overview

ONCE THE BASIC FRAMEWORK of neuronal diversity, axon projections, dendritic arborization, and synapse formation is established in the nervous system, a final phase of developmental change begins. This phase of development—during late pre-natal and early post-natal life—relies on cellular changes driven by neural activity, most often elicited by environmental stimuli that reflect the newborn's experience of her environment. These limited times of postnatal developmental change are referred to as critical periods. As humans (and other mammals) mature, the cellular mechanisms that modify neural connectivity become less effective, and the dramatic changes in neural circuits and related behaviors seen during critical periods are no longer possible. Thus, critical periods are thought to optimize the brain of each individual so that circuitry is adapted to specific demands that confront that individual throughout the balance of life. There are, however, some parallels between cellular mechanisms that mediate activity-dependent developmental change and those that mediate synaptic modification that underlies learning and memory. Many of the effects of activity depend on secreted signals, including neurotrophins and neurotransmitters, transduced via second messengers and their effectors. These activity-elicited changes influence local gene expression, neurotrophic interactions leading to final adjustments of axon or dendrite growth, as well as synapse growth and stability. Much of our knowledge of the influence of activity on developing neural circuits comes from studies of the mammalian visual system, where differences in input from each eye influence patterns of connections in the visual cortex. Beyond the primary visual areas, changes in the structure and size of the human cerebral cortex from birth through late adolescence indicate that experience-dependent critical periods likely influence connectivity and complex behaviors. In humans, postnatal changes in cortical size may reflect the consequences of experience and activity for the differential growth of some cortical areas but not others. These mechanisms may be compromised in disorders that result in intellectual disability, developmental delay, autism, or psychiatric diseases such as schizophrenia.

Neural Activity and Brain Development

In 1949, the psychologist D. O. Hebb hypothesized that the coordinated electrical activity of a presynaptic terminal and a postsynaptic neuron strengthens the synaptic connection between them. **Hebb's postulate**, as it has come to be known, was originally formulated to explain the cellular basis of learning and memory, but the concept has been widely applied to situations involving long-term modifications in synaptic strength or distribution, including those that occur during development of neural circuits. In this context, Hebb's postulate implies that synaptic terminals strengthened by correlated activity during development will be retained or sprout new branches,

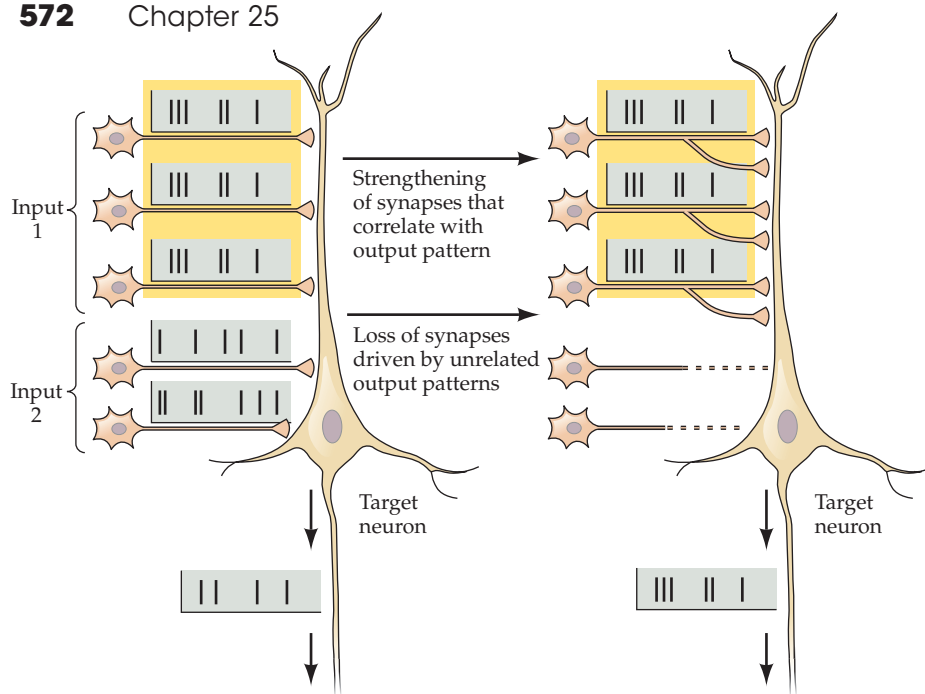


FIGURE 25.1 Hebb's postulate and the development of synaptic inputs. In this drawing, a postsynaptic neuron is shown with two sets of presynaptic inputs, each with a different pattern of electrical activity. Activity patterns, corresponding to action potential frequency, are represented by the short vertical bars. In the example here, the three correlated inputs at the top are better able to activate the postsynaptic cell. These inputs cause the postsynaptic cell to fire a pattern of action potentials that follows the pattern seen in the input. As a result, the activity of the presynaptic terminals and the postsynaptic neuron is highly correlated. According to Hebb's postulate, these synapses are therefore strengthened. The two additional inputs relay a different pattern of activity that is less well correlated with the majority of the activity elicited in the postsynaptic cell. These synapses gradually weaken and are eventually eliminated (right-hand side of figure), while the correlated inputs form additional synapses.

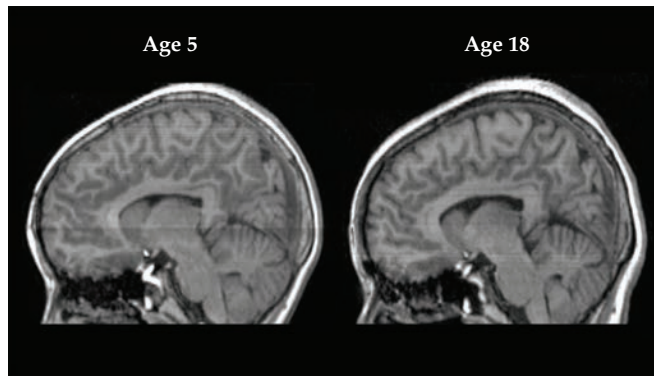
whereas those terminals that are persistently weakened by uncorrelated activity will eventually lose their hold on the postsynaptic cell, either leading to the death of the cell that gives rise to those synapses, or to the stabilization and growth of synapses from that cell on another target (Figure 25.1; see also Chapter 22).

This Hebbian formulation of the role of activity in influencing the ongoing organization of neural circuits provided an initial clue to understanding three obvious phenomena in brain development. First, behaviors not initially present in newborns emerge and are shaped by experience throughout early life; second, there is superior capacity for acquiring complex skills and cognitive abilities during early life; and third, the brain continues to grow after birth, roughly in parallel with the emergence and acquisition of increasingly complex behaviors and the addition of pre- and postsynaptic processes (dendritic and axonal branches). The parallel growth of dendritic and axonal branches and the addition of synaptic connections early in life must account for a significant portion of postnatal brain growth (Figure 25.2A,B) and perhaps provide a substrate for enhanced behavioral capacities. Not surprisingly—especially if Hebb's postulate is correct—there is a subsequent decline in synapse number during adolescence (Figure 25.2C). Accordingly, synaptic connections and related neuronal growth are the ultimate

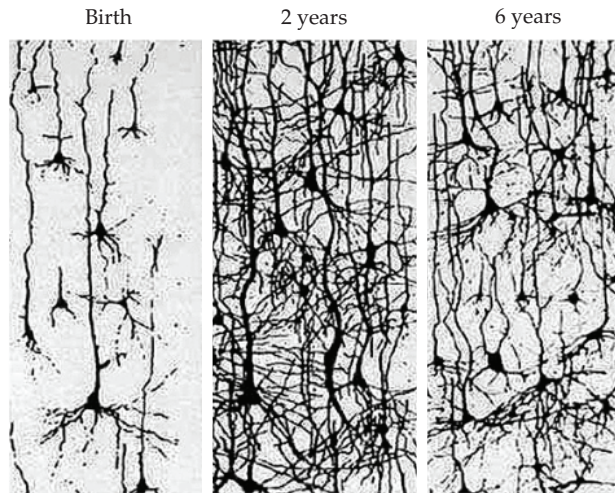
targets of activity-dependent change during early postnatal life—initially for progressive construction, and then selective elimination of connections. During the initial phases of progressive construction the brain gets larger because of post-natal growth of dendrites, axons and synapse—but not (with few exceptions) the addition of neurons. During the elimination phase, counter-intuitively, the brain continues to grow. This reflects the continued elaboration of the synapses that remain, and the neurons that are their targets. From birth through early adulthood, these events occur in synchrony with the acquisition of sensory and motor abilities, the capacity for social interaction, and increasingly sophisticated cognitive behaviors including spoken, signed, or written language in humans (see below and Chapter 33). These coincidences suggest that the combination of activity-dependent modification of connections initially suggested by Hebb and corresponding brain growth and behavioral changes during early life must underlie how each individual's brain ultimately develops to meet the challenges of adapting to a dynamic environment.

The electrical activity initiated by exposure to and interaction with the environment following birth is a key element in the construction of any individual's nervous system. Intrinsic mechanisms (including those that constrain axon growth, initiate the formation of topographic maps, and establish the first synapses; see Chapter 23) establish the general circuitry required for most behaviors. These cellular and molecular mechanisms, however, do not yield a final pattern of connectivity. "Typical" experiences evidently validate initial wiring and preserve, augment, or adjust the initial arrangement that is established by intrinsic developmental mechanisms. In the case of "diminished" experiences due to lack of sensory exposure or disrupted sensory transduction and relay, these adjustments do not occur appropriately and brain connectivity and behavioral capacity can be altered. These alterations can have some adaptive advantage—for example, in the context of compromised capacity of the individual to acquire information from the environment (e.g., sensory impairments such as blindness or deafness)—and sometimes to the detriment of optimal brain function as the individual matures (e.g., sensory deprivation or trauma due to life circumstances for an otherwise intact infant or child). The eventual decline of the capacity to remodel cortical (and subcortical) connections most likely explains changes in the capacity of the brain to acquire new information and direct

(A)



(B)



(C)

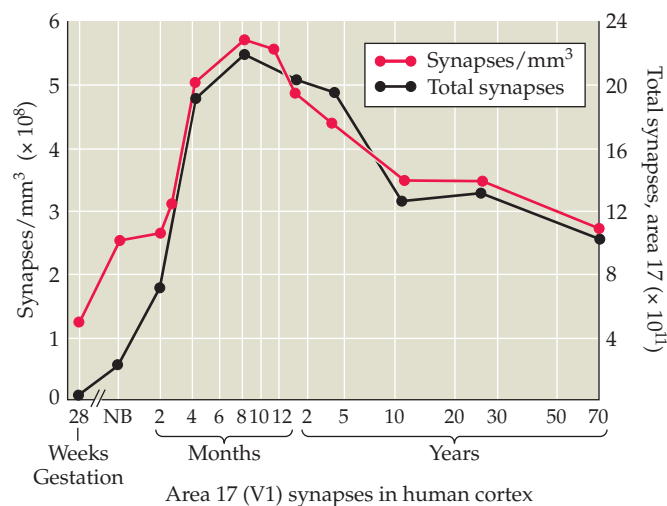


FIGURE 25.2 The human brain changes significantly during postnatal life. (A) MRI images of a brain from the same individual at 5 years and 18 years of age. The brain at 18 years is slightly larger, and the pattern of sulci and gyri in the cerebral cortex is more prominent. (B) Axons and dendrites in the human cerebral cortex at birth, 2 years, and 6 years of age. These drawings are based upon Golgi-stained neurons in the cerebral cortex from individual post-mortem samples of different ages. (C) Addition and then elimination of synapses in the human brain. This data is based upon electron microscopic analysis of synapse density in the human primary visual cortex. (A courtesy of Jay Giedd and P. Shaw; B from Conel, 1939–1967; C after Huttenlocher et al., 1982).

new behaviors over a lifetime—a concept with obvious educational, psychiatric, and social implications.

Critical Periods

For most animals, the behavioral repertoire for basic survival, including foraging, fighting, and mating strategies, largely relies on patterns of connectivity established by intrinsic developmental mechanisms. Indeed, embryonic mechanisms and their developmental consequences are sufficient to create some remarkably sophisticated innate or “instinctual” behaviors, including the complex repertoire for parental identification, feeding, and responding to predators seen in newborn birds and mammals (see Chapter 24). Nevertheless, the nervous systems of animals with increasingly complex repertoires of behaviors, including humans, clearly adapt to and are influenced by the particular circumstances of an individual’s environment beyond innate behavioral capacities. These environmental factors are especially influential in early life, during temporal windows called **critical periods**—the time when experience and the neural activity that reflects that experience have maximal effect on the acquisition or skilled execution of a particular behavior. Some behaviors, such as parental imprinting in hatchling birds (the event by which the hatchling recognizes its “parent” based on initial recognition after emerging from the egg), are expressed only if animals have certain specific experiences during a sharply restricted time (hours or days) in early postnatal (or post-hatching) development (Box 25A). By contrast, critical periods for sensorimotor skills and complex behaviors end far less abruptly and provide far more time for environmentally acquired experience. In some cases, such as the acquisition communication skills in songbirds (see Chapter 24), or language in humans, detailed instructive influences from the environment (i.e., exposure to complex calls in songbirds or words and sentences in humans) and opportunities for mimicry and repetition are required for an extended period to ensure normal development of the behavior. The availability of instructive experiences from the environment, as well as the neural capacity to respond to them, is key for successful completion of the critical period. These instructive influences are important for territorial and reproductive behaviors in a subset of non-human species. In some songbirds, both male and female birds acquire the capacity to produce species-specific song by mimicking tutor birds during a limited period of postnatal life (see Chapter 24). If this essential instruction is withheld or disrupted, the birds are not effective in using communication to define their territories and compete for mates.

Although they vary widely in both their duration and the behaviors affected, all critical periods share some basic properties. Each critical period encompasses the time during which a given behavior is especially susceptible to—indeed, requires—specific environmental influences

BOX 25A ■ Built-In Behaviors

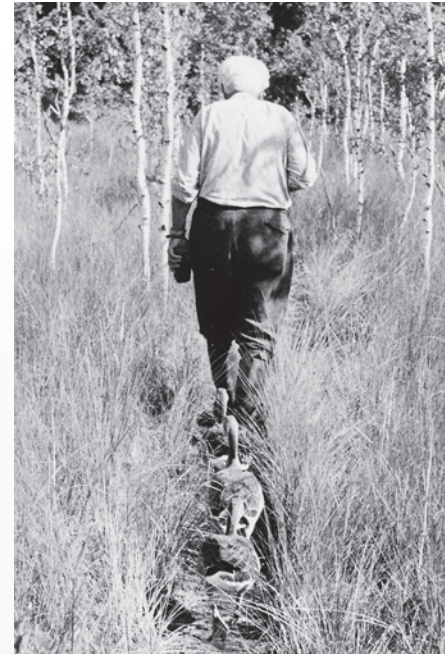
The idea that animals possess an innate set of behaviors appropriate for a world not yet experienced has always been difficult to accept. However, the preeminence of instinctual responses is obvious to any biologist who looks at what animals actually do. Perhaps the most thoroughly studied examples occur in young birds. Hatchlings emerge from the egg with an elaborate set of innate behaviors. First, of course, is the complex behavior that allows the chick to escape from the egg. Once the chick has emerged, a variety of additional abilities indicate how much early behavior is “pre-programmed.”

In a series of seminal observations based on his work with geese, Konrad Lorenz showed that goslings follow the first large, moving object they see and hear during their first day of life. Although this object is typically the mother goose, Lorenz found that goslings will imprint on a wide range of animate and inanimate objects presented during this period, including Lorenz himself. The window for imprinting in goslings is less than a day; if animals are not exposed to an appropriate stimulus during this time, they will never form the appropriate parental relationship. Once imprinting occurs, however, it is irreversible, and geese will continue to follow inappropriate objects (male conspecifics, people, or even inanimate objects).

In many mammals, auditory and visual systems are poorly developed at birth, and maternal imprinting relies on olfactory or gustatory cues. For example, during the first week of life (but not later), infant rats develop a lifelong preference for odors associated with their mother’s nipples. As in birds, this filial imprinting plays a role in the rats’ social development and later sexual preferences.

Imprinting is a two-way street, with parents (especially mothers) rapidly forming exclusive bonds with their offspring. This phenomenon is especially important in animals such as sheep that live in large groups or herds in which all the females produce offspring at about the same time of year. Ewes have a critical period 2 to 4 hours after giving birth during which they imprint on the scent of their own lamb. After about 4 hours, they rebuff approaches by other lambs.

Work by Harry Harlow and his colleagues at the University of Wisconsin in the 1950s underscored the relevance of these studies of avian imprinting to primates. Harlow isolated monkeys within a few hours of birth and raised them in the absence of either a natural mother or a human substitute. In the best known of these experiments, the baby monkeys had one of two maternal surrogates: a “mother” constructed of a wooden frame covered with wire mesh that supported a nursing bottle, or a similarly shaped object covered with soft terrycloth but without any source of nourishment for the young monkey. When presented with this choice, the baby monkeys preferred the terrycloth mother and spent much of their time clinging to it, even though the feeding bottle was with the wire mother. Harlow took this to mean that newborn monkeys have a built-in need for maternal care and have at least some innate idea of what a mother should feel like. Several other endogenous behaviors have been studied in infant monkeys, including a naïve monkey’s fear reaction to the presentation of certain objects (e.g., a snake) and the “looming” response (fear elicited by the rapid approach of any formidable object). Most of these built-in behaviors have analogs in human infants.



Konrad Lorenz followed by imprinted geese. (Photograph courtesy of H. Kacher.)

Taken together, these observations make plain that many complicated behaviors, emotional responses, and other predilections are well established in the nervous system prior to any significant experience, and that the need for certain kinds of early experience for normal development is predetermined. These built-in behaviors and their neural substrates have presumably evolved to give newborns a better chance of surviving in a reliably dangerous world.

in order to develop normally. Environmental influence elicits neural activity in the relevant sensory or motor pathway, and the nature of this activity—its frequency, amplitude, duration, and correlation—ultimately drives changes in synaptic connections. These experience or activity influences can be as subtle as the ongoing stimuli of light or sound encountered by an infant, or the precisely articulated instruction in one’s native (or a foreign) language required to achieve fluent speech and accurate comprehension. Once a critical period ends, the core features of the behavior are largely unaffected by subsequent experience.

This suggests that the cellular and molecular mechanisms that are influenced by experience via neural activity must also change. Failure to be exposed to appropriate stimuli during the critical period is difficult or impossible to remedy subsequently—likely because the biological mechanisms needed to change connections during the critical period are no longer available in an older individual (however, see Box 26B). In most mammals, including humans, critical periods seem to rely particularly on changes in organization and function of circuits in the cerebral cortex. Thus, much of our subsequent discussion of critical periods

will focus on the consequences of experience and activity for influencing cortical growth, connections, and function from birth through young adulthood.

The Role of Oscillations in Establishing Critical Periods

The evidence for critical periods initially relied on behavioral observations, then on electrophysiological data that measured action potential activity elicited by relevant stimuli—especially visual stimuli—coupled with anatomical assessment of changes in patterns of connections. These approaches provided definitive proof of the critical period for the visual system. It is beyond doubt that “elicited” sensory experience—that driven by external stimuli resulting in action potential activity—is key. Nevertheless, there are additional forms of subthreshold as well as action potential-mediated physiological activity that occur prior to experience-driven activity. These forms of electrical activity establish a framework within which sensory experience can further influence patterns and function of connectivity. Local **oscillations**, or “waves,” of electrical activity that are initially beneath the threshold for action potential generation are now known to be essential for shaping circuit networks so they are prepared for optimal experience-driven activity.

Most of the insights into the developmental importance of neuronal oscillations have come from analyses of the mammalian visual system (see Chapter 11). The initial evidence for oscillatory activity came from analysis of activity in the retina that begins long before birth in most mammalian species and is referred to as **retinal waves** (Figure 25.3A,B). It had long been known, based on anatomical tracing (see below), that a scaffold of segregated inputs from the lateral geniculate nucleus (LGN), driven in turn by segregated afferents from retinal ganglion cells in the left versus right eye, is present in many animals, including rhesus monkeys, cats, and ferrets either slightly before or after birth. It was unclear, however, how this segregation, prior to experience-driven competition

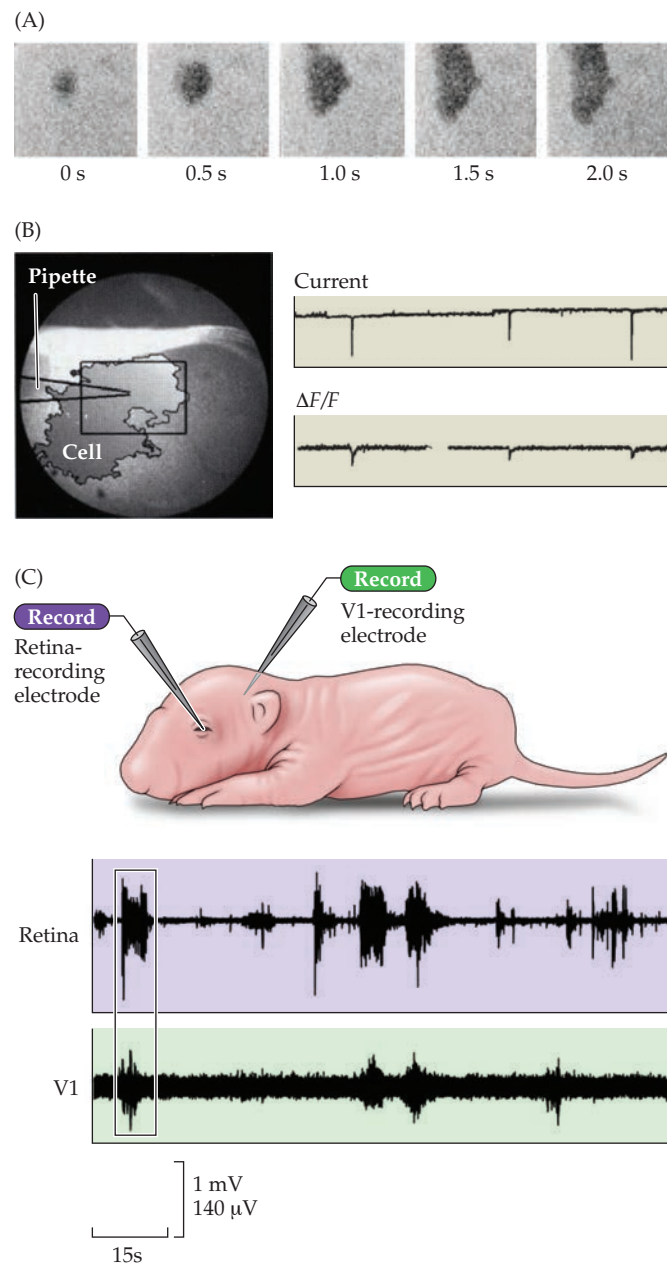


FIGURE 25.3 Spontaneous activity establishes rudimentary patterns of connectivity in the retinogeniculocortical pathway. (A) Retinal waves, measured here by imaging calcium transients (proportional to action potential activity) in a flattened retina *in vitro*. The activity that defines a single wave, depicted using a grey scale that maps the local change of Ca^{2+} influx over time, measured by the change in fluorescence intensity ($\Delta F/F$) spreads across the retinal surface. The small gray spot in the upper left quadrant of the far left panel indicates the initiation of the wave at time 0 (0s). The subsequent images, taken every 0.5 second, show the spreading excitation across a sub-region of the retinal surface that defines the wave (which is ultimately relayed to the thalamus via action potential activity in retinal ganglion cells) until the wave abates (not shown). (B) The relationship between single cell excitation measured intracellularly (the downward deflections in the top trace indicate

excitatory postsynaptic potentials) and calcium transients that define each retinal wave. Within the wave region outlined at left, the firing of a cell recorded at the position (shown by the pipette cartoon and box is synchronized to the maximal depolarization events that define the wave, shown as the downward traces in the fluorescence intensity record (bottom trace). (C) Simultaneous extracellular recordings are made in the retina and primary visual cortex of an early postnatal rat pup, prior to eye opening and the capacity of the retina to relay light information from rods and cones to the ganglion cells. The spontaneous activity that defines retinal waves is shown as bursts of action potential activity. These bursts in the retina are highly correlated with bursts of action potential activity recorded in primary visual cortex in the same pup. (A,B from Feller et al., 1996, images courtesy of C. Shatz; C from Hanganu et al., 2006.)

between the two eyes, was put into place. There are some molecular affinities reflecting the origin of ipsilateral projecting versus contralateral projecting retinal ganglion cells in the nasal versus temporal retina (see Box 23A) that biases them toward distinct target regions in the LGN. Nevertheless, these affinities alone are not sufficient to explain the initial pre- or perinatal segregation of the inputs from the two eyes. A substantial amount of this initial segregation is due to organized electrical activity in the retinas of individual animals before they are born or their eyes have opened. Each retina in an individual fetus or newborn (prior to eye opening) independently generates a pattern of waves of electrical activity (usually measured as Ca^{2+} influx) that moves across large populations of retinal cells in an orderly fashion. The waves are initiated in local retinal cells (amacrine cells), and this subthreshold activity leads to action potential firing by ganglion cells that is then relayed to the lateral geniculate nucleus (LGN). These waves, though coherent in each eye, are asynchronous between the two eyes. The lack of correlated activity establishes a modest competitive interaction—leading to Hebbian synaptic reinforcement—between the two eyes for target space in the LGN and via the LGN to the primary visual cortex. Thus, afferents driven by one eye are likely to segregate, at least partially, from those of the other eye. Retinal waves can be abolished via pharmacological blockers of various neurotransmitters, or in mice in which a variety of receptors or neurotransmitter transporters have been inactivated by mutation. These experiments suggest that a nascent circuit that includes acetylcholinergic, GABAergic, and glycinergic synaptic transmission from retinal amacrine cells combined with glutamatergic release from bipolar cells onto retinal ganglion cells (see Chapter 6) is responsible for the generation of retinal waves. In the absence of such synaptic signaling and the waves of electrical activity that result, segregation in the LGN by left eye versus right eye is substantially diminished or eliminated.

The excitatory drive established by retinal waves via the synaptic signals delivered to ganglion cells and transmitted through LGN relay neurons that project to the primary visual cortex, establishes related oscillatory activity in the visual cortex. These oscillations can be recognized with multi-unit recordings from the neonatal primary visual cortex in animals. Such activity in developing cortical networks reflects voltage changes—synaptic as well as action potential activity—in large numbers of neurons can be recorded using extracellular electrodes placed in the cortex or thalamus in early postnatal animals such as a rat or mouse, or can be detected using electroencephalography (EEG) in pre-term as well as full-term human infants (Figure 25.3C; also see Chapter 1). In early postnatal rat visual cortex, bursts of action potential activity in the cortex are highly correlated with the wave-induced bursts of action potential activity from the retina. The absence of this cortical activity delays or abolishes appropriate maturation of visually evoked responses in the cortex. In humans, similar activity, detected as bursts of population

electrical activity (generally called spindles) via EEG recordings, indicates that even before extensive visual experience, there is subthreshold oscillatory activity as well as bursts of action potential signaling that influence synapse and circuit maturation in the cortex. This activity is thought to be essential to prepare the cortex for visual-experience-dependent critical period plasticity.

Critical Periods in Visual System Development

Fundamental understanding of how changes in activity and connectivity might contribute to critical periods and behavioral capacity has come from studies of the developing visual system in animals with highly developed visual abilities, particularly cats and monkeys. The visual system is extremely amenable to the sorts of experimental manipulations necessary to test the relationship between experience, activity, and circuitry. It is relatively easy to either deprive or augment visual experience in an experimental animal; eyes can be sutured shut, or animals can be reared in illumination conditions ranging from total darkness to maximal light and pattern. Such control of sensory experience is almost impossible in any other modality—it is much harder to deprive an animal of auditory, somatosensory, olfactory, or taste stimuli. Moreover, the organization of the visual pathways provides ideal opportunities to evaluate how experience influences ongoing function and connections.

Information from the two eyes is first integrated in the primary visual (striate) cortex (see Chapters 11 and 12), where most afferents from the LGN of the thalamus terminate. In some mammals—carnivores, anthropoid primates, and humans—the afferent terminals form an alternating series of eye-specific domains in cortical layer 4 called **ocular dominance columns** (Figure 25.4). Ocular dominance columns can be visualized by injecting tracers such as radioactive amino acids into one eye; the tracer is then transported along the visual pathway to specifically label the geniculocortical terminals (i.e., synaptic terminals in the visual cortex) corresponding to that eye. In the adult macaque, the domains representing the LGN input from the two eyes are stripes of about equal width (0.5 mm) that occupy roughly equal areas of layer 4 of the primary visual cortex. Electrical recordings confirm that the cells in layer 4 of macaques respond strongly or exclusively to stimulation of either the left or the right eye, while neurons in layers above and below layer 4 integrate inputs from both the left and right eyes and respond to visual stimuli seen by both eyes. Complete ocular dominance is thus seen in the domains (stripes) in cortical layer 4, where all neurons are driven exclusively by one eye or the other reflecting convergent information from LGN axons driven by one or the other eye. Ocular dominance can be seen beyond layer 4. It is measured based upon the extent to which one or both eyes activate individual cortical neurons (i.e., in layers 2 to

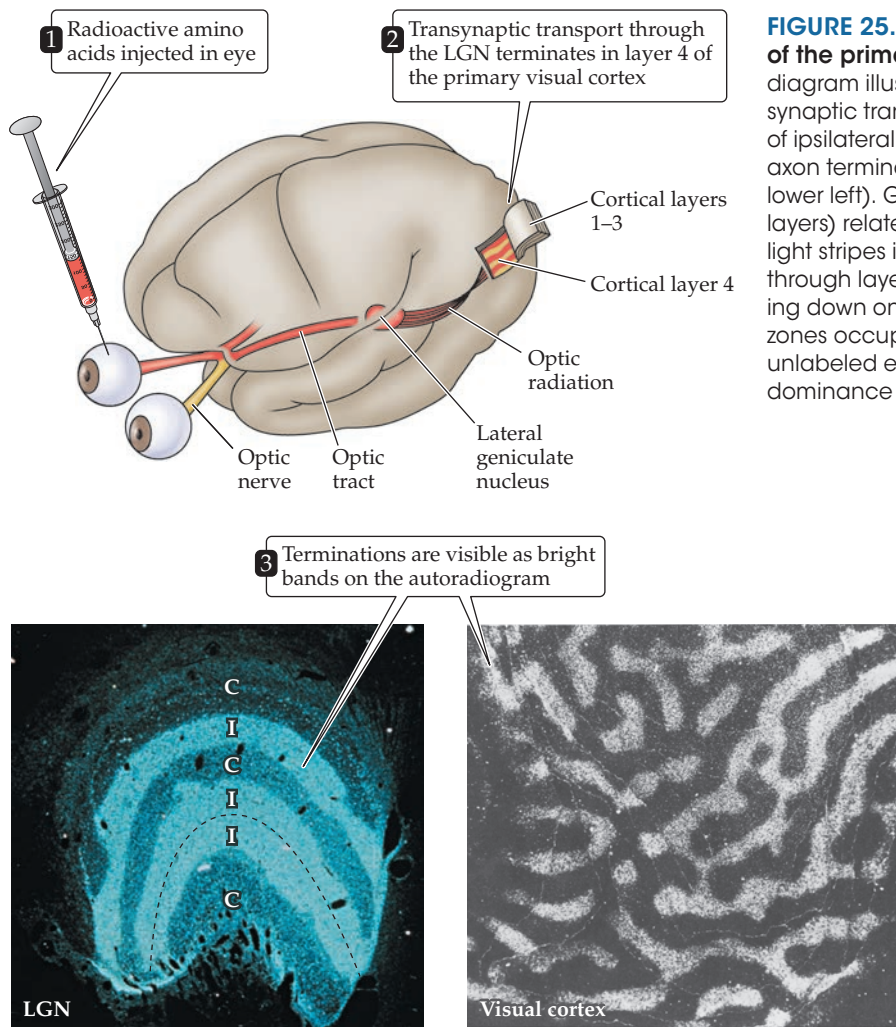


FIGURE 25.4 Ocular dominance columns in layer 4 of the primary visual cortex of an adult macaque. The diagram illustrates the labeling procedure. Following transsynaptic transport of the radioactive label, the distribution of ipsilateral (I) versus contralateral (C) retinal ganglion cell axon terminals is seen in the lateral geniculate nucleus (LGN; lower left). Geniculocortical terminals (from the labeled LGN layers) related to the injected eye are visible as a pattern of light stripes in an autoradiogram (lower right) of a section through layer 4 in the plane of the cortex (that is, as if looking down on the cortical surface). The dark areas are the zones occupied by geniculocortical terminals related to the unlabeled eye. (LGN micrograph courtesy of P. Rakic; ocular dominance columns from LeVay, et al., 1980.)

3 and 5 to 6). The clarity of these patterns of anatomical and functional connectivity, and the precision by which experience via the two eyes can be manipulated led to a series of experiments that defined the relationship between activity, experience and circuitry. These experiments greatly clarified the neurobiological processes underlying critical periods. It was clear that the critical period for vision relied upon correlated activity due to visually evoked stimuli delivered to each eye, changes in functional innervation, that underlie changes in patterns of connectivity measured both physiologically and anatomically.

Effects of Visual Deprivation on Ocular Dominance

The clear distinction between activation of visual cortical neurons by one or the other eye via the retinogeniculocortical pathways was the primary measure of how peripheral experience influences visual development. As described in Chapter 12, if an electrode is passed at a shallow angle through the cortex while the responses of individual neurons to light stimulation of one or the other eye are being

recorded, detailed assessment of ocular dominance can be made at the level of individual cells that share, more or less, the same laminar location (see Figure 12.11). The original studies of visual cortical plasticity and critical periods were performed using a similar physiological approach. Accordingly, visual cortical neurons within individual cortical layers were divided into seven “ocular dominance” groups based on their degree of response to either the contralateral or ipsilateral eye (Figure 25.5). Group 1 cells are driven only by stimulation of the contralateral eye; group 7 cells are driven entirely by the ipsilateral eye; and neurons driven equally well by either eye are assigned to group 4. Based on this measurement scheme, ocular dominance distribution in all layers but layer 4 in primary visual cortex is roughly Gaussian in a normal adult (cats were used in these experiments). Most cells were activated to some degree by both eyes (distributed around a mean defined by “group 4” cells), and a substantial minority was more activated by either the contralateral or ipsilateral eye (see Figure 25.5A).

This normal distribution of ocular dominance at the level of single cortical neurons can be altered by visual

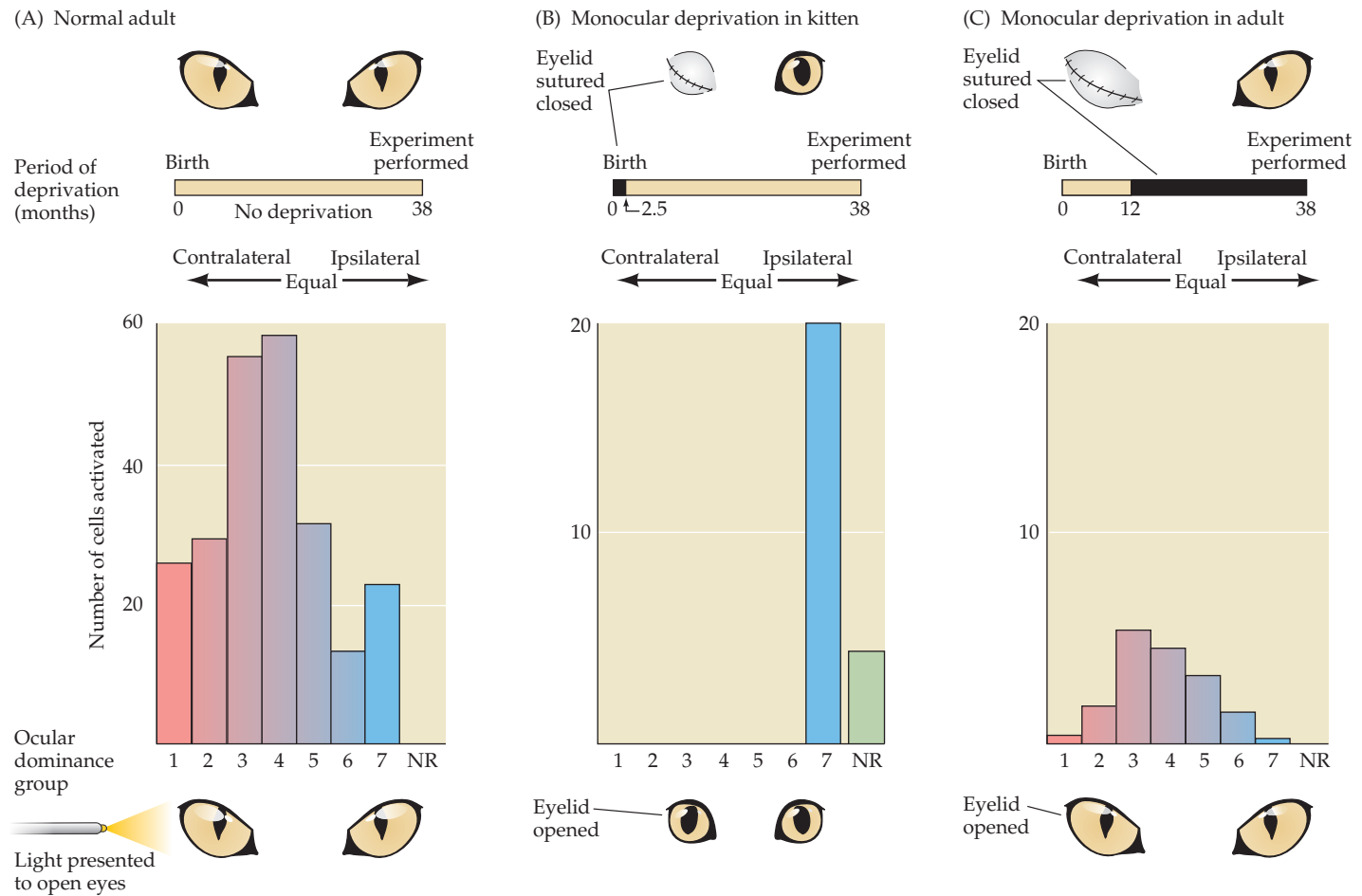


FIGURE 25.5 Effect of early eyelid closure of one eye on the distribution of cortical neurons driven by stimulation of both eyes. Histograms plot the number of cells that fall into one of the seven ocular dominance categories, defined based on the frequency of action potential activity elicited from visual cortical neurons following illumination in the relevant eye. In all three cases, the experimental readings were performed on cats 38 months after birth, at which time a penlight was shined into both wide-open eyes to elicit responses in the visual cortex. (A) Ocular dominance distribution of single-unit recordings from a large number of neurons in the primary visual cortex of normal adult cats. Cells in group 1 were activated exclusively by the contralateral eye, cells in group 7 by the ipsilateral eye. There were no cells that were not responsive (NR) to light stimulation in the retina. (B) One eye of a newborn kitten was closed from

1 week after birth until 2.5 months of age. After 2.5 months, the eye was opened and the kitten matured normally to 38 months. Note that the deprivation was relatively brief—the sutured eye had been open for 35.5 months of the cat’s life. Even so, light presented to the open but transiently deprived eye elicited no electrical responses in visual cortical neurons. The only visually responsive cells responded to the ipsilateral (non-deprived) eye. (C) A much longer period of monocular deprivation in an adult cat showed little effect on ocular dominance, although overall cortical activity was diminished. Most of the responsive cells were driven by both eyes. In addition, some cells (groups 1 and 2) were uniquely or mostly responsive to the deprived eye. (A after Hubel and Wiesel, 1962; B after Wiesel and Hubel, 1963; C after Hubel and Wiesel, 1970.)

experience. When one eye of a kitten was sutured closed early in life and the animal then matured to adulthood (which takes about 6 months), a remarkable change was observed. Once the eyelid was opened, electrophysiological recordings showed that very few cortical cells could be driven from the deprived (previously sutured) eye. Recordings from the retina and LGN layers in response to direct electrical stimulation in the deprived eye (as opposed

to light-elicited electrical responses) indicated that these more peripheral stations in the visual pathway worked quite normally. Nevertheless, the ocular dominance distribution in the visual cortex had shifted; the eye that remained open was uniquely able to drive most cortical cells (see Figure 25.5B). Thus, the absence of cortical cells that responded to stimulation of the closed eye was not a result of retinal degeneration or a loss of retinal connections to

the thalamus. Rather, the deprived eye had been functionally disconnected from the visual cortex. Consequently, such animals are behaviorally blind in the deprived eye. This “cortical blindness,” or *amblyopia*, is permanent (see below). Even if the formerly deprived eye remains open, little or no recovery occurs.

Remarkably, the same manipulation—closing one eye—performed in adulthood has no effect on the responses of

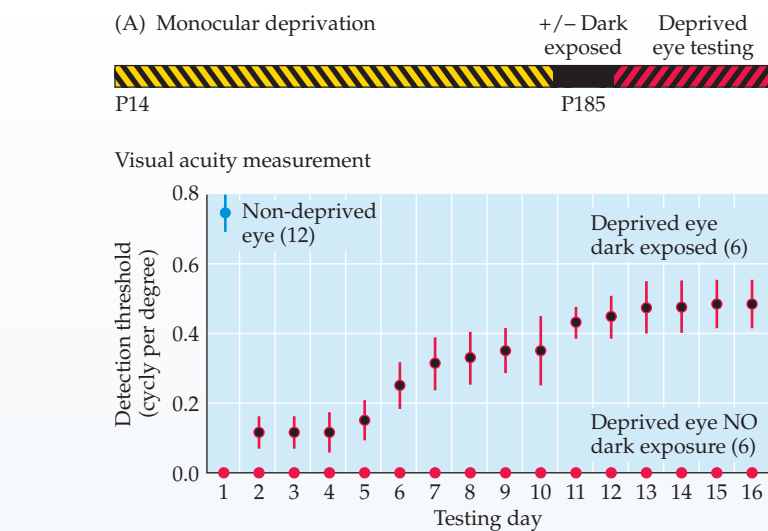
cells in the mature visual cortex (see Figure 25.5C; Clinical Applications). If one eye of an adult cat was closed for a year or more, both the ocular dominance distribution measured across all cortical layers and the animal’s visual behavior were indistinguishable from normal when tested through the reopened eye. Thus, sometime between when a kitten’s eyes open (about a week after birth) and 1 year of age, visual experience determines how the visual cortex

CLINICAL APPLICATIONS

Dancing in the Dark

Nearly 60 years ago, David Hubel and Torsten Wiesel demonstrated the fundamental properties of experience-guided, activity-dependent critical period plasticity in the visual cortex. Within the next decade, the implications of these foundational observations for diagnosis and early treatment of amblyopia were understood. Early intervention was possible only if early diagnosis was made. Unfortunately, then as now, early diagnoses were not always available before the critical period had closed for children with monocular eye alignment or eye occlusion anomalies. The challenge that remains, despite the capacity of pediatricians and ophthalmologists to detect and treat amblyopia before the close of the critical period, is whether binocular visual acuity and depth perception can be restored in individuals for whom uncorrected abnormal ocular competition early in life results in permanent visual impairment thereafter.

Within the last decade, several observations, primarily in animal models, have provided hope that a combination of noninvasive interventions in adults who experienced some form of monocular deprivation early in life (e.g., amblyopia, lens or cornea occlusion) can restore a great deal of lost visual capacity. In the key experiment, adult rats experienced monocular deprivation starting at the onset of the critical period (after eye opening, approximately 14 days of age) through adulthood (185 days, or approximately 6 months, of age). Half the rats were then placed in a completely light-free environment (“dark exposure”; see Figure A) for 10 days while the other half was maintained in standard illumination conditions. Thereafter, all the rats were tested on a task that evaluated their vi-



(A) Top panel: Experimental strategy for monocular deprivation of a rat pup at P14, the onset of the visual-experience-dependent critical period, through adulthood at P185, approximately 6 months of age. The rat pup can then be subjected to “dark exposure” (DE) for 10 days, or not. Subsequently, visual acuity can be tested to evaluate the function of the deprived eye, with and without DE. Bottom panel: Visual acuity measurement (based on the frequency of a line grating that can be resolved; i.e., cycles per degree) of the deprived eye with and without DE (6 animals measured in each treatment). Acuity in a deprived eye with no DE is 0 at the outset of the 16-day testing period. Acuity in a deprived eye with DE begins modestly higher than that without DE, and increases substantially over the subsequent days of testing. While this restoration of acuity is significant, it does not reach acuity levels measured in the non-deprived eye (12 animals measured). (After Eaton et al., 2016.)

sual acuity (the capacity to resolve linear patterns of increasing frequency). Rats that had 10 days of dark exposure following the monocular deprivation had modest acuity at the outset of testing, and showed substantial improvement in acuity over the course of the 16-day testing period. In contrast, rats that had been monocularly deprived without dark exposure (standard luminance) following the end of the deprivation period had no measurable visual

acuity in the deprived eye after 16 days of repetitive testing. Although the acuity values in the deprived eye of dark-exposed rats did not reach those of the non-deprived eye, there was nevertheless a substantial increase in visual resolution capacity associated with dark exposure following the chronic disruption of binocular competition (Figure A).

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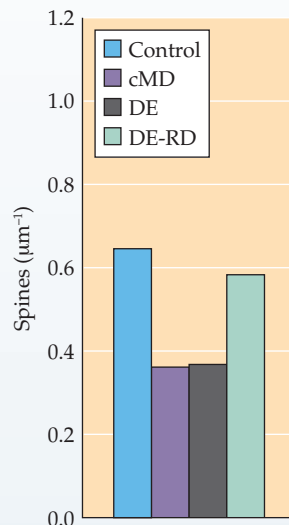
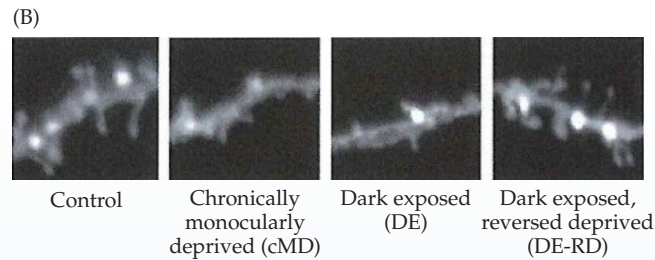
CLINICAL APPLICATIONS (continued)

The mechanisms by which dark exposure reactivates cortical synaptic plasticity and permits successful, repetition-mediated reacquisition of visual capacity remain uncertain. Earlier work indicated that dark exposure beginning in the critical period can prolong the critical period. These changes were accompanied by the upregulation of expression for genes that encode proteins essential for synaptic transmission and excitability or electrical activity in neurons. In addition, much of the retention of plasticity was thought to reflect delayed maturation of GABAergic inhibitory interneurons and their influence on distinct forms of synaptic plasticity. Cellular analysis in adult animals monocularly deprived from the critical period onward, and then visually “rescued” via dark exposure as adults as described above, shows that dark exposure increases the density of spines on visual cortical neuron dendrites toward levels that approximate those in non-deprived animals. In contrast, monocular deprivation over the same period without dark exposure results in substantial reduction in the density of visual cortical dendritic spines (Figure B).

Together, these results indicate that the adult visual cortex, after prolonged changes in binocular competition and subsequent binocular activity, retains measurable capacity for plasticity that can improve visual function, if certain conditions are put in place. Those conditions include dark exposure, which apparently restores cell biological and

molecular mechanisms that can accommodate plasticity and functional recovery, and repeated training to elicit maximal reacquisition of function. Thus, there is a new reason, hardly romantic

but far more beneficial, for “Dancing in the Dark.” With apologies to Fred Astaire, no more will one just “face the music,” but can hope to “see the light.”



(B) The images at top (from left to right) show dendritic spines on a visual cortical neuron from a normal, non-deprived rat (control), a chronically monocularly deprived rat without dark exposure (cMD), a dark-exposed rat (DE), and a monocularly deprived then dark-exposed rat in which the previously deprived eye is given a competitive advantage by occluding the previously non-deprived eye (DE-RD). Reverse deprivation renders the chronically deprived eye maximally active. This activity, and advantage of correlated synaptic drive it gives to neurons in the visual cortex driven by that eye, causes dendritic spines and presumably functional synapses to be added. Such changes may correct the cellular consequences of either cMD or DE. The graph below shows that the combination of DE plus RD increases spines on visual cortical neurons to control levels. DE or cMD alone diminishes spine numbers to a similar extent. (From Montey and Quinlan, 2011.)

is wired with respect to eye dominance. At the height of this critical period (about 4 weeks of age in a cat), as little as 3 or 4 days of eye closure profoundly alters the ocular dominance profile of the striate cortex (Figure 25.6). After this time, deprivation or manipulation has little or no permanent, detectable effect. In fact, eye closure is effective only if the deprivation occurs during the first 3 months of a kitten's life. In keeping with the ethological observations described earlier in the chapter, David Hubel and Torsten Wiesel called this period of susceptibility to visual deprivation the critical period for ocular dominance development. Similar experiments in monkeys have shown that the same phenomenon occurs in primates, although the critical period is longer (up to about 6 months of age).

Visual deprivation during the critical period must result in some sort of cortical connectivity changes that influence the functional response properties of individual

neurons—especially since neither retinal nor retinogeniculate activity is altered. Indeed, the segregation of afferents by eye of origin in the LGN, and the separation of the single eye recipient LGN layers is present at birth, and does not change in deprivation experiments. Subsequent anatomical studies established that physiological changes were due to changes in patterns of connections in the visual cortex, especially those made by geniculocortical axons. In monkeys, the striplike pattern of geniculocortical axon terminals in layer 4 that defines ocular dominance columns is already present at birth, and this pattern reflects the functional segregation of inputs from the two eyes (Figure 25.7A; also see Figure 25.4). Indeed, the early formation of this pattern in layer 4 reflects a significant amount of segregation of the LGN axons that relay information from one eye or the other, and this early segregation occurs even in the absence of meaningful visual