CHAPTER 2

Brain Plasticity: The Impact of the Environment On the Brain As It Relates to Hearing and Deafness

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The brain is the organ of behavior. Perhaps the most important aspect of behavior is learning, where learning is defined as any change in behavior as a result of experience. Behavior is shaped by the interactions between the organism's genes and its environment, and the relative influence of nature and nurture vary in ways yet to be determined. The environment can modify even the most stereotyped behavior, and all behavior is bound by genetic factors. Different behaviors are dependent on separate classes of nerve cells that have specialized functions with highly organized interconnections between them. These connections define functional circuits, and it is the integration of neural activity across many circuits that presumably underlies our perception of the world.

Sound is created by vibrations in air. The brain forms the physical substrate for our ability to hear, which is involved in the acquisition of language and social communication, the localization of sounds in space, and the appreciation of music. Changes in brain function are thought to mediate changes in behavior, and vice versa. The malleability or "plasticity" of these mutually dependent functions represents the topic for the present chapter as we discuss some of those factors that underlie brain mechanisms of hearing.

We now know that the brain is constantly changing throughout our lives. The adult brain is composed of approximately 100 billion nerve cells, with characteristic gyri and sulci where certain functions can be attributed to certain locations. How do neural cells acquire their specific identities and how do they form their patterns of neural connections? This daunting question is frequently asked because mammals, with all their complexity, arise embryologically from the merging of two germ cells. The brain develops in an orderly progression of steps, with a precise temporal sequence that is characteristic for each neural entity and system. Moreover, individual neurons connect with only a selected subset of potential target neurons, and these connections are made only at specific regions along the surface of the target cell.

The total genetic information available to an animal, roughly 100,000 genes in mammals, is insufficient to specify on a one-to-one basis the total number of neural connections made in the brain, which is estimated at around 10^{15}. To accommodate this mismatch, the nervous system relies on environmental triggers to activate different subsets of genes at specific times during development. It is the orchestration of these environmental signals with the normal time course of brain development that controls neural differentiation. The external environment provides nutritive factors, sensory and social experiences, and learning. These internal and external signals impinge on the developing cell in the form of diffusible factors and surface molecules. In this way, a complex array of specific factors is timed so as to induce the proper differentiation of individual neurons.

It is thought that brain cells continue to be produced until shortly after birth. In humans, after 2–3 years of age, new neurons are no longer generated, and all of the basic neural connections are thought to be completed by the late teenage years. The consequence is that most of the changes in brain function occur through modification of the "wiring" at the level of cells and molecules. Thus, not only proper development but also proper maintenance of the brain depends on an interactive balance between the organism's genetic makeup and environmental influences.

CRITICAL PERIODS OF DEVELOPMENT

More than 100 years ago, it was reported that newly hatched chickens, as soon as they were able to walk, would follow any moving object.[1] This sight-guided behavior endowed the chick with no more predisposition to follow a hen than to follow a duck or a human. When hatchlings were "blinded" by placing an opaque hood over their heads, this indiscriminate following of the first object they saw endured for the first 3 to 3.5 days. At 4 days and later, however, the chicks exhibited the opposite response on unhooding and fled from the first object they

Figure 2-1 ■ Imprinting is a curious form of learning that is quick to develop and difficult to reverse. The best known and most illuminating example of imprinting comes from the pioneering experiment performed by ethologist Konrad Lorenz in Austria in 1935. He first divided a clutch of eggs laid by a single graylag goose into two groups. One group of hatched goslings was permitted to associate with their mother goose. A test group of goslings were hatched in an incubator and the first living creature they saw was Lorenz. In the first few days of their lives, they were allowed to follow Lorenz as if he were their parent. Later, the goslings were marked according to their early posthatching experience and placed together under a box. When released, the two groups separated from each other and sought their respective, adopted parent. (H. Karcher)

encountered. The normal attachment of newborn chicks to their parents was termed "imprinting."[2] The brief period of time during which imprinting could occur was called the "critical period" in the life of the organism (Fig. 2-1).[3]

The concept of critical period has been applied to explain other phenomena that occur or are affected most severely during relatively restricted time windows during development. These critical periods reinforce the notion that there are clearly defined times when the physiologic readiness of the organism must coincide with the occurrence of certain specific externally derived experiences. To understand the human brain, neuroscientists tend to study the brains of other mammals, such as rats or monkeys. With animal "models" it is possible to examine, experimentally, cellular mechanisms of sensory processing such as vision, touch, or hearing and motor processes such as spinal reflexes, paralysis, or recovery of function. Language, however, is a largely human characteristic and therefore the study of rats and monkeys provides little insight into its development or neural substrates. On the other hand, birds have a natural song, which although clearly different from human language is nevertheless a highly complex auditory-motor production and serves a communicative function. Investigations of bird song have provided highly instructive examples of how genetic factors interact with the environment.

The song of the white-crowned sparrow has a distinctive and elaborate acoustical pattern when learned in a natural environment. A male sparrow raised in social isolation develops an abnormal song. Birds deafened at birth produce an even more distorted song.[4] To mitigate the effects of social isolation on song development, the experimenter can play recorded songs to the isolated male. After 3 weeks of listening to 60 songs per day, the male will develop a normal song. This result suggests that an auditory template of the natural song resides in the brain against which the bird's song is compared, and that birds need to be able to hear themselves sing to perfect their song. A template must exist because, even when the bird is deafened, the resulting abnormal song is not random but has some crude resemblance to the normal song. Variations in the song that a young bird hears result in corresponding variations in the song produced. These variations are called dialects, such that groups of birds living only a few miles apart sing with distinctly different song patterns.[5] Heredity not only limits the effects that the environment can have but also facilitates the learning of certain things.

The importance of auditory experience is crucial for vocal learning in songbirds. Young songbirds innately recognize and prefer to learn the songs of their own species. In fledgling white-crowned sparrows lacking song experience, it was revealed that songs composed of parts of the total song or songs played in reverse elicited behavioral responses as strongly as did normal songs.[6] In all cases, these responses surpassed those of other species' songs. The discrimination by baby birds of songs of their species seems to parallel a process observed in human infants, who recognize individual vowels and consonants common to their language before they learn words, phrases, and sentences.[7,8] These kinds of studies lie at the heart of how the environment interacts with innate substrates and are providing insight into how language and the brain develop in humans.

Over the years there have been reports on the lack of language development in humans reared in apparent social isolation or under adverse conditions. Perhaps the most noteworthy example concerns *Le Sauvage de l'Aveyron*, a report of a boy, 12 or 13 years old, captured by hunters in

Figure 2-2 ■ Le Sauvage de l'Aveyron ("Savage of Aveyron"). This portrait shows the only surviving depiction of the "savage of Aveyron," a boy aged approximately 12–13 years old who was found living alone in the wilderness of southern France. Although his exact origins remained a mystery, the boy, later named Victor, was believed to have spent his entire young life in isolation from civilization. Victor was unable to acquire any language skills despite exhaustive attempts to teach him how to speak. (Courtesy of Bibliothèque Nationale.)

the southern part of France, in the middle part of the Pyrenees mountain range near Lourdes (Fig. 2-2).[9,10] This boy, later named Victor, seemed to be feral, living in the wild without clothes, social companions, or spoken language. He was initially thought to be deaf but was later shown to have highly developed sensory and motor skills, but no aptitude for spoken language (or other social skills).

Victor's story is important because his tutor for 5 years was Dr. J.M.G. Itard, who used his experience teaching Victor to develop entirely novel strategies for teaching language to deaf and retarded individuals and advocated the use of sign language. Despite the success and international acclaim that Itard enjoyed as an educator for the hearing and mentally impaired, he was unable to help Victor develop language. The general inference from this and other similar cases is that spoken language cannot develop in a vacuum, whether that vacuum is a result of social isolation or deafness. Instances of social isolation are understandably infrequent, and considerably more data are available addressing language development in the deaf population. The main conclusion is that congenitally deaf individuals rarely acquire normal spoken language, but those who retain a certain measure of hearing can eventually acquire spoken language. These findings are likewise applicable to those individuals who lose hearing shortly after birth but prior to the development of speech. Exposure to speech early in life, however brief, seems to be a necessary requirement for the acquisition of spoken language, and the longer the exposure, the better the outcome.[10]

BRAIN PLASTICITY UNDERLIES BEHAVIORAL PLASTICITY

These behaviors, whether they are imprinting or language development, obviously have their bases in brain function. The concept of the critical period also must reflect brain mechanisms and processes. As we consider features of auditory plasticity, we naturally must turn to the brain for answers. Indeed, much of what we understand about brain plasticity is derived from experiments in nonauditory systems—such as the visual and somatosensory systems. One example of the detrimental effects on the brain has been illustrated in the visual system, where uncorrected amblyopia, myopia, or cross-eyedness results in functional blindness in one eye.

In normal conditions, the two eyes function together so that the world appears as a single, unified whole even though it is seen with two separate eyes that project slightly different images on the two retinas. We perceive a single perspective because proper alignment of the eyes causes convergence of the separate images upon corresponding loci of the retinas. The result of this convergence is termed "fusion." Even with normal convergence, fusion is not perfect for images that lie outside the focal plane of fixation. This small amount of noncorrespondence is called binocular disparity and is used by the visual system to perceive depth. The projection of the visual pathway from each eye through the lateral geniculate nucleus and up to layer IVc of the visual cortex remains segregated and monocular. In the visual cortex, the projections are organized into distinct but parallel stripes, where alternating stripes represent the inputs from each eye.[11] These stripes are called ocular dominance columns (Fig. 2-3). Connections within and across these columns are thought to form the substrate for visual perception. Blocking input to the cortex from one eye during the first 6 months of age renders this deprived eye functionally blind. The result of the deprivation is that the projections from the deprived eye are atrophic (the ocular dominance stripes are abnormally thin) compared with the robust projections from the intact eye (their projections have characteristically expanded). The deprived eye loses its ability to activate cortical neurons, and thus visual perception from that eye is lost. This loss is permanent and irreversible if uncorrected early on.

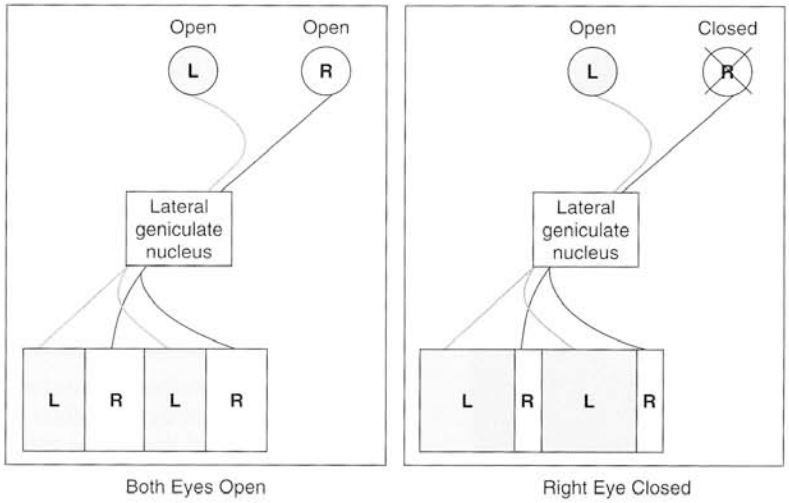

Figure 2-3 ■ Diagram of the effects of monocular deprivation on visual cortex development. **Left Panel:** Schematic representation of the visual pathway from the eye to the visual cortex. The diagram illustrates the normal development of ocular dominance columns, as occurs when both eyes are left open during development. The *gray circle* represents the left eye, and the *open circle* represents the right eye. The *gray and black lines* represent afferent nerve fibers from the eyes, passing through the lateral geniculate nucleus of the thalamus and traveling to the ocular dominance columns in the primary visual cortex. As diagrammed by the rectangles, the ocular dominance columns representing left and right eyes alternate with one another. Since both eyes are open in this case, the ocular dominance columns are equal in size. **Right Panel:** Schematic representation of the visual pathway in the case of a monkey raised under conditions of monocular deprivation. The *"X"* over the right eye represents forced eye closure during development. As a result of monocular deprivation, the ocular dominance columns from the closed eye fail to form properly, and they are abnormally thin. In contrast, the ocular dominance columns representing the left eye have expanded into the regions formerly activated by the right eye. These figures illustrate the importance of sensory input for proper development of the brain. *L,* left; *R,* right.

These experimental conditions in animal models resemble monocular amblyopia, cross-eyedness, or monocular myopia in newborn infants. In such cases it is hypothesized that the inability of the system to fuse the separate visual fields leads to a crisis in the cortex.[12] Both eyes are functioning, and both have robust projections into the cortex. Because the images are disparate, however, the brain selects the inputs from one eye and suppresses the inputs from the other so that a single image is achieved. Over time, the suppressed eye behaves as if it were blind. That is, visual stimuli to that eye can no longer activate cortical neurons (the eye loses its ocular dominance stripes) and no visual stimuli are perceived through that eye. Consistent with other developmental processes that involve a critical period, a similar visual deprivation in an adult has no effect on cortical responses to visual stimulation and no effect on visual perception.[13] These are the kinds of data that have guided the decision to correct surgically some forms of amblyopia almost as soon as they are detected.

The blindness produced in the deprived eye, then, is of central rather than peripheral origin. Consequently, even though the peripheral sensory structures were intact, normal vision is impossible. These findings emphasize the point that even a perfect sensory prosthesis will be inadequate if the central nervous system is not appropriately functional to receive and process information. Moreover, the results of these studies highlight the crucial importance of environmental stimuli during periods of development. Further experiments by Wiesel and Hubel showed that the monkey was most vulnerable to monocular deprivation during the first 6 weeks of life.[11] Because this early period represented the greatest susceptibility of the visual system to experimental manipulations, they applied the term critical period to describe this aspect of visual development. The effects of monocular deprivation were less severe if deprivation took place after the critical period, presumably because the brain and environment had already interacted sufficiently to establish the basic organization of the system.

Central changes produced by sensory deprivation are not limited to the visual system. Many mammals, including rodents, seals, cats, and foxes, display facial hairs called vibrissae through which a great deal of tactile information is received. Vibrissae differ from whiskers by virtue of the presence of striated muscle at the base of the vibrissa follicle that enables movement. In rodents, individual vibrissa acts as an independent sensory structure, and a spatial map of the vibrissa pad is topologically represented in the somatosensory cortex by distinct cytoarchitectonic units known as "barrels."[14] Barrels are comprised of organized accumulations of cells in layer IV that receive a correspondingly

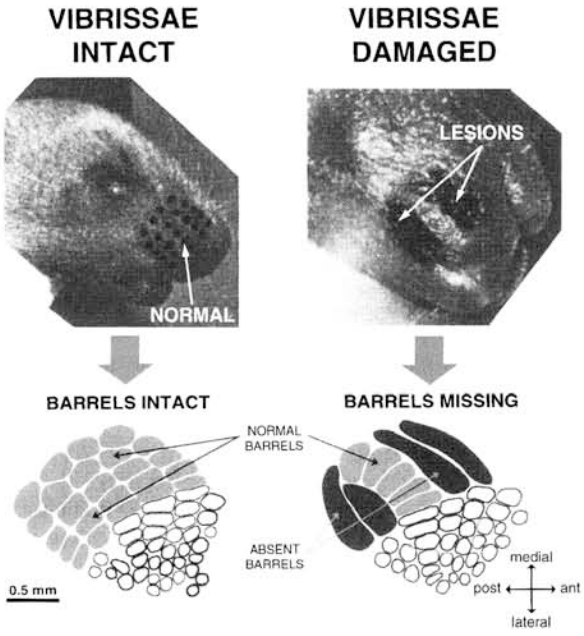

Figure 2-4 ■ The effects of vibrissae ("whiskers") damage on the development of barrels, the cortical structures that receive input from each individual vibrissa. **Left Panel:** The top photograph shows a normal mouse pup with ink placed on each vibrissa for ease of visualization. Below the photograph is a schematic diagram showing the somatosensory cortex with individual barrels corresponding to the main mystacial vibrissae (*gray ovals*) and other minor facial vibrissae (*open ovals*). There is a one-to-one relationship between vibrissae and barrels, and the cortical barrels are discrete and normally developed. **Right Panel:** The top photograph shows a closeup of a mouse pup with lesions made of selected vibrissae. The lesions are arranged in two parallel stripes, flanking a row of normal vibrissae. The cortical barrels corresponding to the damaged vibrissae failed to develop, and appear to have merged together. These data emphasize the importance of the intact peripheral sensory structure on the normal development of cortical organization. *post,* posterior; *ant,* anterior. (Adapted from van der Loos H, Woolsey TA. Somatosensory cortex: structural alterations following early injury to sense organs. Science 1973;179:395–398.)

organized projection from the thalamus.[15] The barrel region of the somatosensory cortex undergoes an age-related differentiation from birth to maturity under normal conditions.[16] If, however, an individual vibrissa is selectively injured at birth, the barrel, which corresponds to that damaged vibrissa, fails to develop (Fig. 2-4).[17] Furthermore, this effect has a relatively narrow time window such that by 5 days after birth, vibrissae damage does not disrupt cortical organization.[18] Thus, damage to vibrissae after the critical period produces no loss of cortical barrels. This disruption of cortical organization by vibrissae damage seems to be mediated at least in part by the thalamus because neonatal vibrissae removal results in a failure of thalamocortical barrel projections to form.[15]

As there are no identifiable barrels at birth in normal animals, these studies suggest that deprivation of vibrissae input at birth interrupts the process of morphogenesis. Resembling vision in monkeys, the developing cortical structures that process vibrissae input are dependent on proper functioning of the peripheral end organ during growth. If peripheral structures are damaged during the critical period, the brain fails to form normally, and subsequent modifications in peripheral structures will not ameliorate the changes in the central nervous system. In the case of barrel cortex, the organizational loss is clearly obvious and the impact on cortical processing is expected to be profound. The very matrix by which individual vibrissae maintain segregated information channels is lost.

COMPETITION AND THE PLURIPOTENT CORTEX

The studies described above were seminal and opened up entirely new lines of scientific investigation. The notion of neuronal competition was introduced and suggested that the function of a given region of the brain was not necessarily established at birth. Rather, neurons themselves were integral in determining what function they would eventually serve by virtue of the signals they carried. The idea of the pluripotent neuron, a cell whose function was unassigned and therefore plastic, raised fascinating possibilities regarding the brain.

Ocular dominance remained a model system to explore anatomic and physiologic mechanisms of plasticity. Using a monocular deprivation paradigm, the visual cortex of cats was studied by making injections of radioactive label into the eyes of visually deprived cats.[19] These researchers saw a decrease in the number of geniculocortical afferents from the deprived eye and an increase in the number of such afferents from the nondeprived eye.

In addition to anatomic changes in the afferents serving the eyes, single-unit microelectrode recordings from cortical neurons revealed that the nondeprived eye exclusively drove most of the cells in the primary visual cortex. This finding is consistent with their anatomic data, and together suggest that early monocular deprivation of vision produces a visual cortex in which very few neurons represent the visual field of the deprived eye. The authors[19] postulated a physical reorganization of thalamocortical neurons in order to account for their observations. These studies provided experimental data to support the notion that regions of the cortex that would normally serve a particular function (e.g., left eye vision) could be recruited for other uses if necessary. Furthermore, this work helped to refine the idea of neuronal pluripotential, by showing specific, quantifiable alterations in brain anatomy and physiology in response to environmental manipulation.

These studies of visual deprivation suggest that competition and pluripotency are closely related phenomena, but the full extent of the brain's malleability still remains to be determined. Deafferentation experiments helped to define exactly how cortical areas evolve to serve their designated functions.[20] In neonatal ferrets, the authors[20] ablated

the normal target of retinal neurons with lesions to the superior colliculus (with subsequent degeneration of the lateral geniculate nucleus), and blocked the normal input to primary auditory cortex by selective transections of ascending auditory fibers to the medial geniculate nucleus. These lesions removed auditory fibers as a source of competition for retinal fibers in the medial geniculate nucleus, while also eliminating the normal recipient of retinal information. The result of these lesions was that retinal axons successfully invaded the medial geniculate nucleus, and, in turn, the medial geniculate nucleus projected to the auditory cortex, representing a two-dimensional map of visual space, not an acoustic representation of frequency.[20]

This dramatic change in cortical topography, such that an auditory cortex begins to function as a visual cortex, reveals that a single, immature cortical area is capable of supporting different types of sensory maps. It seems that the final fate of any cortical region might be mediated in part by the type and nature of its inputs. Although the space map in the auditory cortex exhibited some variability in receptive field location, the two-dimensional visual map was fairly accurate, showing that the responsiveness of the auditory neurons to visual stimuli was not random or useless but instead produced a functional visual cortex. Hence, cortex might well be modular in design with its function dependent on the particular inputs it receives.

Genetic Factors: Preprogrammed Development

We have discussed that the interaction between genomic and environmental factors is responsible for normal development. The studies described have illustrated dramatic effects from selective loss of environmental stimuli. While the conditions under which an animal is raised have pervasive effects, these effects are constrained by genetic determinants. For example, a terrestrial mammal raised under avian conditions is unlikely to learn to fly as a result. In experiments of binocular deprivation, cats were raised under two contrasting conditions in which both eyes were either open or closed. The cortical maps for orientation and ocular dominance developed normally for the first 3 weeks of life regardless of the conditions.[21] In fact, early pattern vision had no effect on the formation of cortical maps during this time period, a finding that suggests the existence of a strong and definite program that dictates initial development. These experiments also showed that central changes from sensory deprivation took place only following this initial period of development. The critical period of ocular dominance development may therefore begin after a brief initial period of environmental insensitivity.

The Effects of Early Experiences On Adult Behavior and Adaptation

Although sensory deprivation is a useful paradigm for the study of plasticity, such conditions are somewhat extreme. A subtler but equally relevant issue focuses on the effects that juvenile experience has on mature behavior. Do different methods of upbringing affect the ability to adapt to new situations in adulthood? The barn owl provides an animal model in which sound localization ability is extraordinarily sophisticated. Barn owls can locate a mouse in complete darkness using sound cues alone. The remarkable localization ability of the barn owl has provided the basis for an interesting series of experiments.[22] Prisms were placed over the eyes of young barn owls, such that vision was offset by a fixed number of degrees in a given direction. As a consequence of prism placement, a discrepancy was created between the auditory and visual cues received by the owl. The prisms remained on the eyes of young owls until the animals had learned to adjust for the auditory-visual discrepancy. Following removal of the prisms, these owls were in time able to adjust appropriately, and could correctly localize sounds. If, however, prisms were placed over the eyes of adult owls, only those owls with juvenile prism experience were able to adapt. Owls without prior experience, in comparison, were unable to adjust their auditory map to the new changes in visual input and could not accurately localize sounds.

The obvious conclusion from these studies is that juvenile experience has a significant effect on adult plasticity and, furthermore, that the information learned as a young animal can be selectively applied as an adult when required. An adult that has had experiences while young appears to be able to utilize the early functional connections with relative ease. An adult without prior experience finds adaptation largely beyond the capacity of his or her brain.

PLASTICITY AND BINAURAL SYSTEMS

Binaural hearing refers to the auditory processing involved in the comparison of sounds received by one ear with the sounds received by the other ear. The interaction between these sounds provides important spatial cues for determining the direction and distance of sound sources. Interaural time differences and interaural intensity differences are the dominant cues for identifying the direction of a sound source along the horizontal plane. Distance cues include the overall level of the sound, the amount of reverberation relative to the original signal, and timbre. There are also spectral cues that are created by the interaction between sound, the head, and the pinnae. These spectral cues are used to resolve front–back confusions, determine sound elevation, and localize sound using one ear alone. Accurate sound localization therefore requires the brain to extract, process, and combine this information arising from both ears.

The relationship between cue values and sound location must be established from experience because of the individual differences and asymmetries in head shapes, external ear morphology, and cochleae. Moreover, as the organism grows and matures, cue values associated with particular locations in space will change. During development, the brain must constantly recalibrate its three-dimensional coordinate system to preserve correct localization.

Approximately half of head circumference growth occurs in the first three years of life and the rest occurs over the next 17 years. The implication is that binaural pathways undergo continual plastic adjustments in order to maintain normal function. The neural pathways that subserve binaural hearing are altered by abnormal experience. Similar to what has been demonstrated in the visual system (as discussed above), balanced and correlated input from both ears is necessary for the proper development of binaural systems. For example, in barn owls, early experience exerts a potent influence on the development of neural circuitry and behavior. Juvenile owls, when fit with prismatic spectacles that produce horizontal displacement of approximately 20 degrees of the visual field, can learn to "fuse" auditory and visual space over a period of weeks. This abnormal early experience generates novel projections that serve to realign abnormal visual space to normal auditory space by way of topographically appropriate axonal sprouting and synaptogenesis.[23–25] When the optical prisms are removed, the owls readapt and adjust to the normal conditions yet the abnormal projections persist. These persistent projections represent the physical basis for readaptation when the owls are fitted with prismatic spectacles again. In contrast, adult owls that are never exposed to this early abnormal visual experience are unable to adapt to prismatic spectacles.[26]

These results demonstrate that anatomic changes promote learned behavioral adaptations but are restricted to a defined developmental time period. Moreover, the novel axonal connections accompanying this behavior can lie dormant even after the behavior is no longer necessary but can be reactivated for behaviorally appropriate responses when required.

In mammals, the medial superior olive (MSO) is considered the first structure in the auditory pathway to receive binaural inputs.[27] It has been considered a "coincidence detector" wherein the amount of delay between the inputs from the ears indicates the position of the sound along the horizontal plane. Simultaneous arrival of signals indicates a midline location, and progressive delays between the time of arrival at the MSO indicate more lateralized origins depending on whether the right or left ear led.[28] The available evidence suggests that the projections of the cochlear nucleus to the MSO work as "delay lines" to distribute spikes within favorable and biologically relevant interaural time differences.[29,30] MSO neurons receive these inputs, act as coincidence detectors, and generate an acoustic space map in each frequency band along the dorsoventral axis of the nucleus.

The MSO is especially important for processing interaural time differences in signals containing low frequencies. The main input to this structure is from both cochlear nuclei (Fig. 2-5). The neurons of this structure are bipolar and extend dendrites toward the left and the right.[27,31] Normally, the left cochlear nucleus sends projections that terminate on dendrites facing left, whereas the right cochlear nucleus sends projections that terminate on dendrites facing right.[32,33] These inputs are excitatory. A lesion on the right side depletes essentially all of the inputs to that side. This result has been essentially confirmed in birds[34] and gerbils.[35]

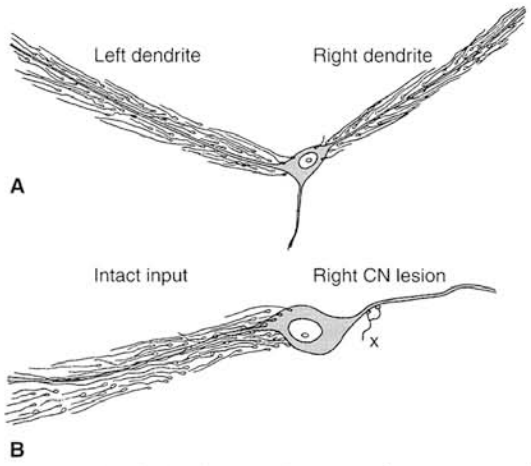

Figure 2-5 ■ Line drawings based on photographs of MSO neurons before **(A)** and after **(B)** a lesion of the right cochlear nucleus. The MSO is a columnar structure whose neuronal cell bodies form a sheet and with dendrites extending to the left and to the right. The right dendrites receive inputs from the right cochlear nucleus; the left dendrites receive inputs from the left cochlear nucleus. Following ablation of the right cochlear nucleus, there is a dramatic loss of terminals on the right dendrites.

Reports are scant on the effect of deafness on MSO neurons. In congenitally deaf white cats, it is clear that bilateral deafness results in severe shrinkage of MSO cell bodies, but analyses of dendrites and afferent terminals have not been done.[36,37] The effect of unilateral deafness on MSO organization is unknown. Collectively, these data demonstrate that the integrity of MSO dendritic domains depends on input from each cochlear nucleus. Moreover, the inputs are sufficiently specific that one set of dendrites can serve as a control (facing the intact side) and the other can serve as the experiment (facing the deaf or stimulated side).

Localization of sounds in auditory space is an important attribute not only for self-defense and survival but also for providing cues that humans use to segregate sound streams.[38] The discrimination of signals in noisy backgrounds uses localization cues, an ability that is notably lost by users of hearing aids and cochlear implants. This topic will be addressed later in the section discussing bilateral cochlear implants.

ANIMAL MODELS OF DEAFNESS

We have learned from animal studies of the visual system that peripheral lesions produce central nervous system changes. Similar changes occur in the central auditory system under conditions of deafness. Several animal models have been examined in studies aimed at characterizing the anatomic changes found in deafness and the

molecular mechanisms that underlie these changes. There are many studies of peripheral deafening induced by experimental manipulation, including cochlear ablation, acoustic trauma, and application of ototoxic agents. Other studies of deafness have examined naturally occurring models of deafness, such as the congenitally deaf white cat and various strains of mice that are deaf.

The cochlea contains the sensory epithelium, which transduces acoustic information and sends it to the brain in the form of electrical signals via the auditory nerve. Studies have shown a close relationship between peripheral sensory structures and the central nervous structures that receive inputs from them. The cochlear nucleus provides the first interface between the peripheral and central auditory systems and is the initial site of central processing of auditory signals within the brain. As one might expect, deafferentation of the auditory system produces significant changes in the structure and function of the central auditory pathways. Following unilateral cochlear aspiration in 6-day-old mice, 39 days later there was a 46% overall reduction in size of the cochlear nucleus, as well as a 34% decrease in overall number of neurons.[39] Cochlear ablation in gerbils also shows an age-dependent response, emphasizing a vulnerability to peripheral cochlear ablation (measured by changes in neuron number and size in the anteroventral cochlear nucleus). The effect on the cochlear nucleus was most pronounced in the first week of life, even before the onset of hearing or cochlear functionality.[40] Ablations in older animals resulted in less drastic effects.[41]

Similar kinds of results were obtained when ablating the basilar papilla of newborn chickens, illustrating the much more severe effects of neonatal manipulations compared with those in adults.[42] Deafferentation prior to 6 weeks of age caused a 25–30% decrease in neuron number and a 10–20% decrease in ipsilateral cell size. However, deafferentation at 66 weeks of age produced a less than 10% decrease in neuron number, and no change in cell size. These studies addressed the idea of a critical period in the auditory system and suggested that early sensory ablation produced marked central changes in the auditory brainstem, which were minimized if ablation occurred at a later age.

Anatomic changes alone are less significant if functionality remains intact. However, cochlear removal has age-dependent functional consequences.[43] The authors studied the response of neurons in the inferior colliculus and superior colliculus of the ferret to unilateral cochlear removal. They showed that the age at which cochlear ablation occurred (postnatal day 5 versus postnatal day 40) affected the responses seen, with earlier deafferentation producing lower thresholds and broader dynamic responsivity. Superior colliculus neurons showed a volume-dependent response to acoustic stimuli presented to the intact ear, with high-level sounds producing broader spatial tuning in animals subjected to early deafferentation. These results support the notion that physiologic properties of auditory neurons in the brainstem are also susceptible to cochlear ablation, in an age-graded fashion that implicates a critical period of heightened vulnerability.

The above-mentioned studies employed cochlear ablation as the method of inducing sensory deprivation, but the results must be interpreted with caution. Cochlear ablation produces other changes in the developing organism, including disruption of the blood supply, direct damage to spiral ganglion neurons, and traction on auditory nerve axons. It is therefore difficult to isolate the specific cause for the changes observed in the cochlear nucleus. One study addressed the issue of whether activity in particular was responsible for the central changes seen in cochlear ablation.[44] These researchers applied tetrodotoxin, a sodium channel blocker, to the perilymph of developing gerbils and compared their findings with that of cochlear ablation. Analysis of protein synthesis (measured by change in incorporation of tritiated leucine) and cell size revealed that similar transneuronal changes occurred in both experimental groups, although the time course of the changes differed somewhat. These data suggest that the blockade of activity alone is sufficient to produce the central changes seen in cochlear ablation and support the idea that neural activity is a crucial variable for proper development of the auditory system.

Animal models of congenital deafness provide an alternative means of addressing issues pertaining to the effects of deafness on development. An advantage of studying animals with congenital cochlear defects is that cochlear ablation or traumatic insults are not necessary to produce deafness. Thus, it may be concluded that the pathologic changes seen in the central nervous system are produced by the peripheral deafness. The deaf white cat represents a congenital model of deafness and mimics the Scheibe deformity seen in humans.[45,46] Studies of this cat revealed a 50% reduction of cochlear nuclei volume compared with that of normal cats, and a 30–40% decrease in cochlear nucleus cell size.[36,47] Although these studies do not directly address critical periods, they are relevant to development because the changes seen are the result of lifelong acoustic deprivation. Other studies of the deaf white cat have focused on endbulb synapses[48] and their correlation to single-unit activity in the auditory nerve and cochlear structure.[49] The endbulb of Held is a large, axosomatic synapse located in the anteroventral cochlear nucleus and has a distinctive, calyceal shape with multiple branches that clasp the postsynaptic cell body (Fig. 2-6). This ending is thought to be involved in the preservation of timing information, an important cue for the comprehension of speech and localization of sound. The endbulbs of deaf white cats were atrophic, with decreased branching in comparison with normal-hearing cats. Ultrastructural examinations in 6–8 year old cats using electron microscopy confirm the degenerate nature of endbulbs in deafness, showing near depletion of synaptic vesicles together with a hypertrophy of the neurotransmitter receptor sites.

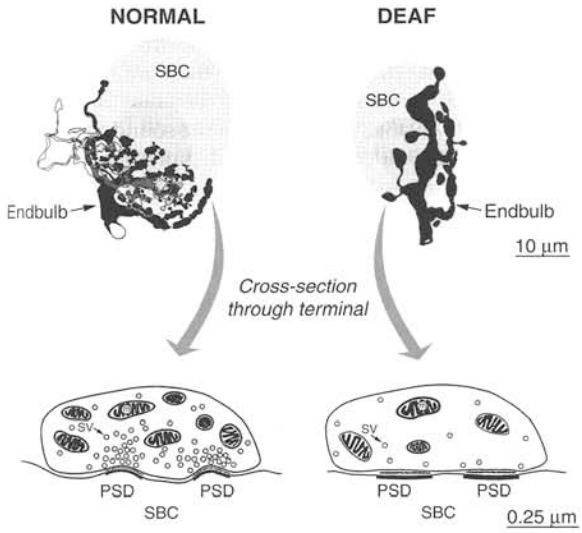

Figure 2-6 ■ Endbulb synapses from middle-aged normal and deaf cats, with a schematic diagram of the fine structure of each ending. **Left Panel:** A drawing of a typical, normal endbulb terminal (*black*) is shown as it synapses onto a spherical bushy cell (*silhouette in gray*). The *slightly darker circle* within the cell represents the cell nucleus. The endbulb terminal is a highly arborized and complex structure, with numerous branches and points of apposition between it and the recipient cell. A cross section through the terminal (*shown below*) depicts the normal ultrastructure of the ending. Synaptic vesicles are clustered around the postsynaptic density, indicating the site of neurotransmitter release and reception. The postsynaptic densities are characteristically curved toward the presynaptic ending. **Right Panel:** This endbulb (*black*) is typical in a congenitally deaf white cat. The postsynaptic bushy cell body (*gray*) is characteristically smaller than normal. The appearance of the endbulb is atrophied, with a loss of complexity and tertiary branching. The number of appositional points between the ending and the postsynaptic cell is decreased. Ultrastructural analysis reveals deafness-induced changes, including the relative absence of synaptic vesicles and hypertrophied postsynaptic densities. *SBC,* spherical bushy cell; *PSD,* postsynaptic density; *sv,* synaptic vesicles; *m,* mitochondria.

These structural changes suggest that the endbulbs of Held might not faithfully transmit afferent activity. A fundamental question regarding natural animal models of deafness pertains to causality: Does the state of deafness induce changes seen, or is deafness the result of underlying pathology? This question can best be addressed by the study of naturally deaf animal models throughout development. The endbulbs of Held of a deaf young cat (6 months old) have been found to exhibit morphologic abnormalities resembling those of a 6-year-old deaf adult cat.[48] This observation suggests that synaptic abnormalities are fully developed by 6 months of age and that there is no progressive deterioration with age. The implication is that there is a critical period for the developing auditory system, during which time a lack of organized neural activity causes synaptic remodeling in the form of hypertrophy and eventual loss of synaptic vesicles in the cochlear nucleus. We need to know if these changes interfere with synaptic transmission and whether they are permanent. Would a cochlear implant serve to prevent the remodeling? Such experiments were conducted in which miniaturized cochlear implants were surgically inserted into the inner ear of 3-month-old congenitally deaf cats. Cats were stimulated 7 hours a day, 5 days a week for 3 months using the same programming strategy applied to children. In addition to an enriched acoustic environment provided by the implant, these cats were trained to come to a computer-generated stimulus that signaled a special food reward. In this way, we could be confident that biologically significant sounds were being processed at the highest levels of the nervous system. When the brains were harvested at the end of the stimulation period, the auditory nerve synapses were preserved (Fig. 2-7).[50] Thus, it was shown that the restoration of activity in the auditory nerve by way of cochlear implants preserves synaptic morphology in congenitally deaf white cats. The implication is that maintenance of endbulb synapses enables the rest of the central pathways to

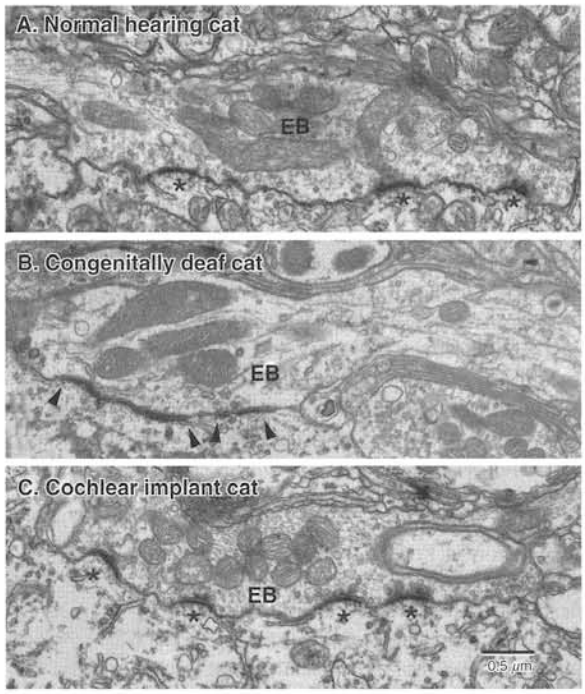

Figure 2-7 ■ Electron micrographs of endbulbs (*EB*) and their synapses from **(A)** a normal-hearing cat; **(B)** a congenitally deaf cat that was untreated; and **(C)** a congenitally deaf cat that received 3 months of stimulation from a cochlear implant. The cochlear implant cats were trained to come to a food award when they heard a specific auditory stimulus, demonstrating that biologically significant signals were processed and translated into appropriate behavior. All micrographs were collected from cats that were 6 months of age. Note that endbulbs from the hearing and stimulated cats exhibit synapses that are punctate, dome-shaped, and accompanied by nearby synaptic vesicles (*asterisks*). In contrast, the synapses from untreated deaf cats were large and flattened (*arrowheads*). The interpretation of these data is that activity in the auditory nerve fibers generated by the cochlear implant restored synaptic structure and function. Scale bar equals 0.5 µm. (From Ryugo DK, Krezmer EA, Niparko JK. Restoration of auditory nerve synapses by cochlear implants. Science 2005;310:1490–1492, with permission.)

process time-varying acoustic features from the cochlear implant with temporal precision.

The higher order processing of implant information, while mediated through "rescued" synapses in the cochlear nucleus, most likely occurs in the auditory cortex. Congenitally deaf white cats that were implanted as kittens and stimulated for 2–5 months exhibited striking expansion of active cortical areas to electrical stimulation with a cochlear implant. In fact, with increasing stimulation durations, there was a corresponding increase in active cortical areas.[51,52] The white cat data collectively reveal the importance of developmentally sensitive periods in auditory plasticity and underlie how human cochlear implant users make sense of their auditory world.

NEURAL COMPENSATION: A FORM OF PLASTICITY IN HUMANS

It is natural to question the applicability of so much animal research to human pathology. Data regarding auditory critical periods of development in humans are less readily available than they are for animal models. However, cross-modal plasticity clearly appears to take place in developing humans with sensory deprivation. Functional imaging studies with blind humans reveal striking differences in cortical activation between those blinded at an early age and normal-sighted individuals.[53] Subjects who were blind from an early age were found to use their visual cortex when reading Braille, a task normally requiring primarily somatosensory activity. In contrast, sighted individuals do not exhibit visual cortical activity when presented with somatosensory stimulation. Disruption of the visual cortex using transcranial magnetic stimulation did not interfere with tactile discrimination in normal subjects but did distort tactile perceptions of blind subjects. Transient stimulation of the visual cortex had no effect on tactile performance in normal-sighted subjects, although similar stimulation is known to disrupt their visual performance. The results demonstrate that the visual cortex is recruited during early blindness to have a role in somatosensory processing, but the exact significance of this cross-modal plasticity is unclear. It appears that the developing brain, if deprived of a specific input, will not permit that deprived region to go unused.

Anecdotal notions of human sensory deprivation hold that individuals with certain deficits compensate by having extraordinary refinements of their other senses. For example, blind subjects are often considered to have hearing that is better than normal. In a study of human subjects, people with and without vision were tested for their ability to identify sound sources in space.[54] The authors found that early-blind people were better at monaurally localization of sound sources than were normal-sighted subjects. The ability to localize sounds in space with one ear relies on spectral cues created by interference patterns created by the canal and the folds of the external ear. One must learn to use these pinna spectral cues to locate sounds with one ear. When binaural timing cues are not available, such as when the sound originates directly overhead or behind the head, pinna spectral cues are also useful for localization.

A more recent study of enhanced auditory abilities in blind subjects showed that subjects with early blindness, but not late-onset blindness, were much better at detecting the direction of pitch changes than were control subjects. Moreover, within the early-blind group, these effects were more pronounced the younger the age of blindness onset.[55] The enhanced performance by blind subjects is consistent with the idea that selective sensory deprivation applies pressure on the remaining sensory systems to "sharpen up" as a form of compensation.

ADULT PLASTICITY

Thus far we have discussed plasticity as it relates to the immature, developing brain, but what about plasticity in the adult brain? We know that adult animals and humans are able to learn new skills and change their behaviors, albeit not as easily as the young for some tasks. Is learning always associated with structural evidence underlying plasticity? Over the last 20 years, researchers have made significance progress in defining and characterizing the nature of adult plasticity. One might consider the phenomenon of plasticity in terms of ultimately manipulating these changes to improve brain function. One goal for auditory scientists and neuro-otologists is that we may be able to facilitate functional recovery in patients who suffer from hearing loss, regardless of the cause or age of onset. Experience with implants thus far has shown that the most opportune time to place a cochlear implant in children is at a very young age and that implanting prelingually deafened adults does not have satisfactory outcomes. But how does this notion apply to adults who have lost their hearing postlingually, after acquiring language? At the present time, cochlear implants have varying degrees of success in this population—Can we exploit the phenomenon of plasticity in adults in order to increase the benefits of a cochlear implant?

To answer some of these questions, we must first start by defining the nature of adult plasticity and discover and describe its role in the brain. Fortunately, many of the principles that apply to one area of the brain, such as the somatosensory or visual cortex, often apply to other areas, such as the auditory cortex. This generality of observations may be very helpful to auditory researchers, especially given that some techniques required to study the auditory system, such as cochlear ablation, have significant limitations. A common feature of areas of sensory cortex is their topographic representation of peripheral receptor inputs.

For instance, adjacent regions of skin will send input of sensation back to adjacent areas of the somatosensory cortex. Likewise, the auditory cortex is laid out with a tonotopic map that mimics the frequency organization of the cochlea, and the visual cortex is organized with a spatial map of the visual field known as a retinotopic map.

Recent evidence suggests that the adult sensory cortex is not necessarily static. Under experimental conditions, the range of sensory exposure can be limited or the sensory end organ can be deprived of its normal input. In response, the topographic representations will undergo organizational changes, even in an adult brain, such that the sensory maps become distorted to reflect the conditions of the periphery. Lesion studies in many different animals have demonstrated that the somatosensory, visual, and auditory cortex of adult brains all have some degree of plasticity. It is not clear what the purpose of this plasticity is or if it even confers an adaptive advantage to the animal. Nevertheless, it is still pertinent that plasticity exists in the adult brain, and that a similar pattern of reorganization occurs in the cortex of each of these sensory systems.

Plasticity in the adult somatosensory cortex has been well documented in numerous experiments. In one particular series of experiments in monkeys, the cortical representations of the hand were examined before and after the amputation of one or two digits.[56] Two to eight months after amputation, the sensory region that had responded to the skin of the amputated digits reorganized to respond to tactile stimulation from adjacent digits or the subjacent palm. There was, however, no significant increase in the representation of nonadjacent digits. Other, similar examples of reorganization in the adult somatosensory cortex have been reported in response to denervation or amputation in many different mammals, including the cat,[57] the raccoon,[58] the rat,[59] and the flying fox.[60] Several studies in humans have also indicated large-scale remodeling in the somatosensory and motor cortical areas in the weeks and months following limb amputation.[61–64]

Deprivation studies of the visual system in the adult demonstrate robust cortical plasticity. Removal of normal retinal input to part of the adult primary visual cortex (V1) results in map reorganization. It is necessary to lesion both retinas to deprive the cortex of input because most neurons of the primary visual cortex, V1, exhibit binocular receptive fields. In one study, a 5–10-degree area of one retina was lesioned and the other retina was removed entirely. Weeks later, the cortical field previously responsive to the area of the lesioned retina acquired new receptive fields corresponding to areas surrounding the retinal lesion.[65] Further studies showed that focal lesions in one eye will produce an altered retinotopic map in response to the lesioned eye while simultaneously retaining a normal retinotopic map for the normal eye.[66] In short, the denervated region of the cortex adopts the properties of neurons contained in the adjacent, intact cortical region.

Of special interest to auditory scientists and neurotologists, the auditory cortex has shown similar capacities for reorganization. Unilateral lesions to the cochlea of adult guinea pigs produced a reorganization of the tonotopic map of the ipsilateral cortex.[67] The part of cortex that normally responded to frequencies represented by the damaged cochlea was silent (Fig. 2-8). One month after lesioning, however, neurons in the deprived cortex were responding to tone frequencies that corresponded to normal regions of the cochlea adjacent to the lesion site. In addition, the intensity thresholds of recorded responses in the reorganized zone were similar to those recorded in normal cortex.[67] Similar patterns of reorganization have been reported in cats[68] and in monkeys.[69]

The previously discussed studies have mostly focused on remodeling at the cortical level. While such

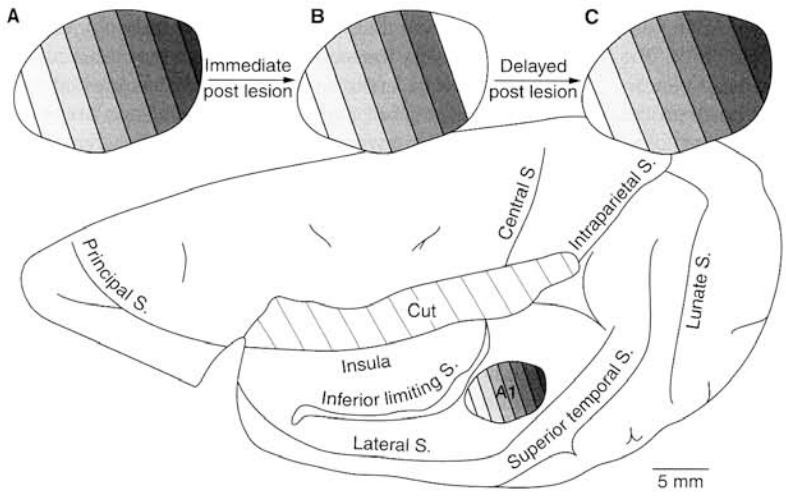

Figure 2-8 ■ Graphic presentation of the A1 region of the auditory cortex, illustrating its frequency reorganization after high-frequency cochlear damage. The superior temporal gyrus of a monkey brain is viewed from a dorsolateral perspective following removal of the overlying parietal cortex (*cross hatching*). The *blue areas* are shaded from light to dark, representing the tonotopic progression of low to high frequencies. The normal A1 region **(A)** before and immediately after cochlear ablation **(B)** shows loss of high frequency responsiveness (*white area*). Some time later, the intact, adjacent frequencies take over the denervated cortical region **(C).** (Adapted from Schwaber MK, Garrachty PE, Kaas JH. Neuroplasticity of the adult primate auditory cortex following cochlear hearing loss. Am J Otol 1993;14: 252–258.)

studies are important and revealing, they do not necessarily describe what happens at lower levels of the central nervous system. In what other areas of the brain might plasticity occur? If plastic changes occur at lower levels, the changes might simply be passively expressed at the cortical level. It remains important to determine the nature as well as the site of plasticity.

Two studies reveal different mechanisms that may underlie new representations in the deprived area of the sensory cortex. Both studies involved limb amputation and both resulted in cortical remodeling that produced expansion of adjacent areas into areas of the sensory-deprived cortex. These studies, however, differed in the location of their limb lesions and revealed different thalamic and brainstem contributions to plasticity. One study investigated the distribution of thalamic and cortical connections in macaque monkeys with long-standing, accidental trauma to their peripheral forelimb. Injections of dyes into the neocortex revealed a normal thalamocortical projection but significant sprouting of horizontal cortical connections by the normal areas into adjacent deprived areas.[70] A parallel study used macaque monkeys that had long-term denervation of an upper limb caused by severing the sensory nerve root as it entered the spinal cord. This manipulation caused the primary sensory neurons to degenerate, causing degeneration of axons in the dorsal columns and producing transneuronal degeneration of topographically appropriate sectors of the brainstem and thalamic nuclei. The thalamic nuclei were reorganized with the representation of the face directly adjacent to the body trunk, and this reorganization was mirrored by a new pattern of thalamocortical projections. The cortex exhibited a remodeled somatosensory map.[71]

The most interesting result to emerge from these studies is that cortical mapping using electrophysiologic methods produced maps where responses of the normal, adjacent regions emerged in the deprived regions. The mechanism providing this remodeling, however, was quite different. In the case where there was no primary neuron degeneration,[70] cortical sprouting of new horizontal connections from the adjacent, intact areas provided the remodeling. In the case where there was primary neuron degeneration, remodeling occurred around transneuronal degeneration, and the new cortical map was produced by remodeled thalamocortical projections.[71] These studies indicate the many "faces" of plasticity and that the nature of the lesion can determine the mechanism of remodeling. In the case of cochlear implants, one of the key issues for candidate selection is the degree of auditory nerve survival. It seems that sensorineural hearing loss has direct implications for not only whether an implant can effectively activate sufficient numbers of auditory nerve fibers but also where and what form of plasticity has been unleashed.

These examples of cortical reorganization have all been produced by lesions to limited areas of the peripheral receptors and depriving the cortex of normal sensory input. This situation has direct relevance to individuals who have suffered a loss of function as a result of trauma or disease. But perhaps the most common form of plasticity has an ordinary and frequent occurrence, that is, in the learning and development of specific tasks and abilities. Acquisition of new skills is termed a "training effect," and it is of particular interest to auditory scientists and neuro-otologists who hope to discover how to help adult patients using cochlear implants to re-establish hearing and language skills.

Training-dependent changes in the auditory cortical map have been noted after training monkeys on a frequency discrimination task. After several weeks of behavioral training, the monkeys' ability to discriminate different frequencies significantly improved, and detailed mapping of the tonotopic representation of the primary auditory cortex (A1) revealed that the representation of the conditioned frequency band was several times larger in trained monkeys than in controls. There was also significant correlation between the successful behavioral performance of the monkeys and the size of the cortical areas representing the trained frequencies.[72] Studies in humans also revealed a strong training effect for auditory tasks, such as sound localization and discrimination of differential time intervals between pairs of sounds.[73,74]

Classic conditioning involves the systematic pairing of a neutral signal (e.g., the sound of a bell) to a reward (e.g., food) or punishment (e.g., shock), thereby giving significance to a previously neutral signal.[75] Frequency-specific receptive field plasticity has been demonstrated using a classic conditioning protocol.[76] The researchers paired a tone of a given frequency with an aversive electrical shock. Tuning curves recorded from the auditory cortex before and after conditioning revealed a shift in the best frequencies in the direction toward the frequency of the conditioned stimulus (Fig. 2-9). This result means that training caused the recruitment of extra neurons to be sensitive to the "important" stimulus. Paradoxically, it seems that conditioning should also teach the animal about the "safe" frequencies (all those that were not paired to a shock), so it is a mystery as to why the recruitment was only in the direction of the conditioned stimulus. With all that is learned on a regular basis coupled with the changes in brain maps and brain activity, it is a wonder that we wake up each morning as the same person who went to sleep, with a constant view of the world.

Although these studies support the existence of plasticity in the adult brain, the effects are still quite muted when compared with those seen in young brains. It is almost as if the mechanisms of plasticity, present at birth, are restrained in the adult. Will we be able to discover these underlying mechanisms in the immature brain and use them to increase plasticity in adults? Given the above evidence for adult plasticity, the question of an age-related effect still remains: Why should a younger brain have greater plasticity than an older brain?

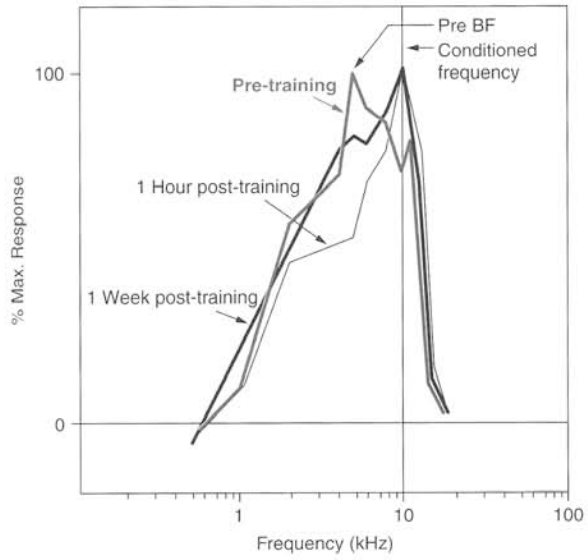

Figure 2-9 ■ Graph illustrating short-term (1 hour) and long-term (1 week) changes in neuronal "tuning" after training. These plots show that a neuron originally tuned to a best frequency (*BF*) of 5 kHz changes its optimal responsiveness after training to a 10-kHz conditioned stimulus. The *light blue line* indicates the pretraining best frequency (5 kHz). (Adapted from Weinberger NM, Javid R, Lepan B. Long-term retention of learning-induced receptive field plasticity in the auditory cortex. Proc Natl Acad Sci USA 1993;90:2394–2398.)

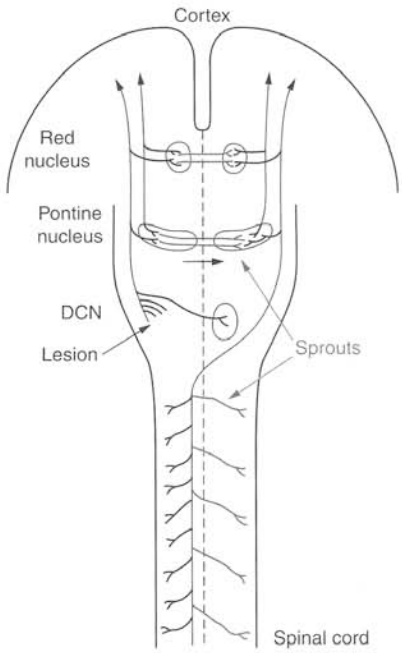

Figure 2-10 ■ Diagrammatic representation of the brain with the corticospinal tract. A lesion of the corticospinal tract on the left side (*arrow*) denervates the right side of the spinal cord. After treatment with IN-1, newly sprouted fibers cross the midline of the spinal cord to innervate the denervated hemicord. Sprouts also crossed into the contralateral red nucleus, pontine nuclei, and dorsal column nucleus (*DCN*). (Adapted from Schwab ME, Thallmair M, Metz GAS, et al. Neurite growth inhibitors restrict plasticity and functional recovery following corticospinal tract lesions. Nature Neurosci 1998;1:124–131.)

Examination of some of the components of brain tissue suggests possible mechanisms that underlie plasticity.

Myelin is a cellular substance that surrounds the axons of neurons throughout the nervous system. Myelin is essential for the timely propagation of electrical signals along the course of an axon. Recent evidence supports the notion that myelination, a process that takes place throughout early life, may be partially responsible for the gradual restriction of plasticity over time. Myelin-associated neurite growth-inhibitory proteins (MNGIP) are known to prevent regeneration of nerve fibers. Although such proteins may seem maladaptive, closer consideration reveals that there must be stable components of the brain whose neural connections, once formed, remain permanent. One group of researchers used a monoclonal antibody to neutralize the MNGIP in adult rats in conjunction with a unilateral lesion of the corticospinal tract. This lesion caused a motor paralysis of the right forelimb. Rats treated with antibody-secreting cells at the site of damage produced new "sprouts," or collateral fibers, in the damaged area from the remaining intact fibers (Fig. 2-10). Rats without antibody treatment showed no such collateral growth.[77]

The most intriguing aspect of this study is the effect of antibody treatment on the animal's motor skills, even in the presence of a lesion in the corticospinal tract. On various tests designed to isolate right forelimb motor skills, rats treated with antibodies to MNGIP showed performance that was equal to that of normal, unlesioned rats. In other words, the inhibition of MNGIP in adult rats produced a state of heightened plasticity within the damaged spinal cord, the result of which was the full recovery of gross motor abilities.[77]

PLASTICITY AND THE TREATMENT OF HEARING DISORDERS

Remedies for the treatment of hearing loss have evolved from the early use of the ear trumpet, a funnel placed in the external auditory canal, to the modern multichannel cochlear implant. While skeptics might question the crudity of such a device for a process as complex as audition, it is now widely accepted that properly selected recipients of cochlear implants can benefit tremendously from this intervention.

Why should a cochlear implant work at all? It seems that the tight temporal coupling of environmental sounds to neural events represents a key element for the proper development of auditory function and validation of the auditory pathways. We speculate that the cognitive appreciation of this timing is learned, that it begins early in postnatal life, and that congenital deafness impairs auditory

system development by removing these timing cues. During development, as we have described, the plasticity of the brain is at its maximum. The brain is primed to receive input. In a sense, the brain acts as a sponge during early life, and absorbs any useful information it receives from the environment. Therefore, it is likely that the most important factor for proper development of the brain, and the auditory system in particular, is stimulation. For the auditory system, stimulation normally occurs in the form of sounds. However, as we have reported, the malleability of the brain at a young age is extraordinary, and the brain can utilize areas of cortex deprived of input for other purposes. The brain is remarkably capable of extracting useful information from seemingly sparse input. It follows, then, that the stimulation received by the auditory system need not be acoustic in nature. Electrical stimulation, as provided by cochlear implants, is triggered by external cues. As such, this stimulation has both a firm basis in and a relationship to the real world, and a developing child can learn to associate visual, somatosensory, and other environmental cues with the incoming electrical signals provided by a cochlear implant. Cochlear implants, therefore, prevent a state of sensory deprivation, even though they do not replace the normal mechanism of the ear. We have discussed the importance of environmental input for proper brain development. Cochlear implants can provide this crucial information. Whereas the exact requirements for proper development of the auditory system have not been defined, evidence suggests that the single most important variable may be simply the presence or absence of activity, rather than its type, nature, or cause.

IMPLANT PERFORMANCE AND PLASTICITY

What accounts for the success of a cochlear implant in some individuals and not in others? These findings are far from arbitrary. The success of auditory rehabilitation methods such as the cochlear implant lies in its ability to present sound as a physiologically useful code to the auditory pathway. The ability to comprehend speech with a cochlear implant requires that the central auditory pathways encode, process, and organize the patterns of electrical stimulation into an auditory percept. Moreover, this processing must occur effectively in both quiet and noisy conditions. Results of cochlear implantation in children[78,79] as well as in adults[80–82] suggest young children represent the best candidates for a cochlear implant. Delayed implantation after the early onset of deafness predicts lower levels of speech reception. The available evidence further suggests that children with even minimal hearing abilities tend to perform better than congenitally deaf children.[83–85]

This effect of timing of cochlear implantation is even more striking in cases of long-term deprivation. Clinical trials have confirmed that profoundly deaf adult recipients who have benefited most from the implants are those who developed linguistic skills prior to becoming deaf.[86,87] The 1995 NIH Consensus Development Conferences on Cochlear Implants[88] recognized that congenitally deaf adult recipients often demonstrate few, if any, objective gains in speech recognition from preoperative to postoperative conditions. Although speech-reading assessments reveal a trend toward improved lip reading in this population, there is little indication that pure auditory speech discrimination is achieved. However, recent improvements in technology have had a positive effect on these trends, and it is certainly likely that non–speech-based tests will continue to reveal greater differences between preoperative and postoperative auditory function in this population. In certain cases, prelingually deafened adults have demonstrated striking auditory abilities postimplant, including the ability to use telephones and to play musical instruments.

These findings suggest that stimulus coding in this subpopulation of subjects often fails to provide adequate combinations of temporal and spectral cues to support comprehension. Can we exploit our understanding of critical periods and the phenomenon of plasticity in adults to increase the benefits of cochlear implants? Efforts to treat congenital deafness need to address deafness onset as well as the progressive degeneration that appears along the auditory pathway. Animal and human data suggest that cognitive and perceptual disorders may be based on an inability to perform temporal segmentation and spectral (frequency) discrimination despite normal auditory thresholds. One of the fundamental tasks in designing strategies for hearing rehabilitation is to understand how to compensate for the reduced temporal precision and frequency specificity of deafness. Frequency discrimination is critical for the proper perception of vowel sounds. Cortical plasticity in response to partial damage to the cochlea might impair frequency specificity because adjacent "intact" areas spread into the deprived areas. Such reactive plasticity might serve to diminish frequency separation. The faithful representation of timing information conveyed in speech is also essential to language understanding, and high-fidelity timing cues may be lost by plastic remodeling of synapses in the cochlear nucleus in cases of untreated deafness.

It has also been observed that auditory reception in children with impaired language-learning capabilities manifests a regular occurrence of certain perceptual effects. Among the more consistent patterns are limitations in identifying phonetic elements that are relatively brief in their presentation. Performance is often poor in sequencing short-duration acoustic signals presented with short interstimulus intervals.[89,90] By comparison, language-learning impaired children show improvements in identifying and distinguishing brief phonetic elements and in properly sequencing stimuli when stimulus presentation occurs at a slower speed. Intensive

practice with stimuli presented at progressively shorter intervals appears to result in significant improvements in temporal processing. This result indicates that the recognition of rapid speech elements can be improved with properly configured, incremental training paradigms.

The ability to treat hearing loss is often thwarted by an inability to restore speech comprehension—a sensory task that requires effective transfer of encoded speech information from the auditory nerve throughout the appropriate central pathways. Although total deafness does not appear to alter the basic tonotopicity of the auditory system, chronic electrical stimulation in deafened cats does produce profound alterations of spatial frequency representation in the auditory midbrain.[91,92] In addition, there may be other complications in temporal and spectral processing induced by reactive changes in primary synapses as a consequence of ear dysfunction.[48,49,93–95]

Observations from the studies discussed in this chapter may have direct relevance to neural mechanisms that underlie limitations in speech processing capabilities upon sensory restoration. Difficulties in pitch perception and frequency discrimination among implanted patients have been well documented in psychophysical studies.[96–100] These studies emphasize the fact that frequency encoding involves both place and temporal information.[101–103] Both basic science and clinical studies suggest some degree of variability in the precision with which temporal cues are encoded by electrical stimulation,[104–106] yet temporal discrimination capabilities are important in predicting speech comprehension in implant users.[107] The synaptic interface between endbulbs of Held and spherical bushy cells is one key site where temporal cues introduced in the periphery are relayed to ascending auditory pathways.[108] Pathologic atrophy at this site, as shown in the studies of deaf white cats described earlier,[48] would likely compromise the ability of synapses to transmit information accurately, thereby reducing the temporal fidelity with which auditory cues are processed.

Synaptic changes in deafness may thus represent a fundamental obstacle to sensorineural rehabilitation. It has been tempting to presume that restored input by itself is capable of reconstituting auditory connections, but the task remains a complicated problem of knowing both the processing capabilities of the neural network and the optimal time and form of prosthetic intervention. Much research has tried to define structural correlates of abolished activity of the auditory receptors and primary afferent fibers. Such studies provide insight into fundamental mechanisms by which activity influences neuronal form and lead us to consider exactly how and when intervention might ameliorate or reverse central auditory pathway degeneration induced by the loss of peripheral auditory activity.

Adult cochlear implant users provide clinical examples of the decline of neural plasticity with age. Prelingually deafened adults have passed their period of maximum plasticity by the time they reach adulthood. Furthermore, they have been unable to form the necessary neural structures required to process language. For these reasons, truly satisfying results in prelingually deafened adults have not been achieved with the current technology. Successful implantation of this group in the future, however, may depend wholly on our ability to manipulate the plasticity of the brain. Although the reasons why plasticity is greatest at early ages remain unclear, there must surely be an underlying principle that is responsible for such features of the brain. The example of MNGIP neutralization with resultant sprouting of neurons is one example that suggests that recovery of plasticity in the adult human may eventually become possible. With further research, the mature brain may some day be sufficiently understood such that language skills can be acquired by prelingually deafened adults as easily as they are by normal children.

BILATERAL COCHLEAR IMPLANTS

Bilateral implantation has been offered to increasing numbers of patients in an effort to expand the benefits obtained with unilateral cochlear implantation. Implantation of the second ear some time after implantation of the first ear and bilateral, simultaneous implantations have been described.[109] The potential benefit of bilateral implantation relies on the capacity for bilateral electrical stimulation to integrate within the central auditory system. Laboratory trials have focused on an examination of whether the various advantages of binaural hearing extend to those with bilateral implants. Binaural advantages include: (*a*) increased auditory sensitivity (i.e., improved pure-tone thresholds) as a result of summation effects; (*b*) improved sound source localization; and (*c*) improved speech recognition in noise. One advantage can occur through acoustic effects when the second ear is away from the noise. The "head shadow" establishes a favorable signal-to-noise ratio for the ear farthest from the noise. The other advantage occurs by neurologic effects when the second ear is closer to the noise source. In this instance, neural integration of bilateral inputs results in "binaural squelch" whereby suppression of the noise enhances speech perception.[110]

Although numerous issues regarding cochlear implant utility remain to be established, the clinical use of bilateral implantation has been increasing across implant centers. Preliminary results show promise in enabling the use of the head shadow, an expanded sound field, and some sound localization ability in the majority of bilateral implant recipients.[110–115] These findings have demonstrated that the brain can integrate electrical stimulation from the two ears. In children, bilateral cochlear implants seem to preserve the integrity of the central auditory pathways as represented by the magnitude and latency of the P1 evoked response. This middle latency auditory evoked potential is generated by thalamic and cortical sources and

its shape changes with age.[116] Thus, it has been used as an indicator for the maturational status of the auditory pathways.[117] It should be stressed, however, that our understanding of the implications of bilateral implantation is in its relative infancy and that the overall number of observations is still small. It is also unknown whether such effects can be enhanced with advanced systems of bilateral sound field processing (e.g., those that integrate the information between both implants rather than having each implant function independently) or the extent to which the neural substrate that supports binaural processing is subject to critical period effects. Finally, neurobiologic aspects of unilateral versus bilateral cochlear implantation are similarly unexplored and not all patients benefit from summation and squelch effects, thereby limiting the gains experienced by these patients on a practical level. At the present time, the auditory gains achieved from preimplantation to postunilateral implantation far outweigh those from unilateral implantation to bilateral implantation.

THE PARADOX OF PLASTICITY

The process of learning is inherently dependent on brain plasticity. The more pliable our brains are, the better they are at absorbing new information, forming neural connections, and modifying neuronal response properties as a result of this information. We have described the extraordinary degree of plasticity present in the developing organism, a feature of life that appears present in some form throughout all species and that seems to be an integral component of early development. Indeed, we have shown that this plasticity is required for normal development to occur and that the period of greatest plasticity, the critical period, is primarily responsible for the proper formation of those brain regions needed for sensory processing. We have also discussed evidence to support the notion that even adult brains exhibit plasticity. That is, although all critical periods of development have passed, the adult brain still maintains a large degree of plasticity that enables adaptation to new experiences. It may be argued that the decreased plasticity of adulthood is evolutionarily advantageous—for one, it allows organisms to eschew critical periods. On a more theoretical level, can you imagine a brain that is entirely plastic—that is, one in which all connections are malleable and none are permanent? Such an animal could never learn from prior experiences. Although such a brain might be able to handle new information easily, it could not place the separate pieces of information into an overall context, a general concept of the external world, because there would be no permanence. Memory stabilizes the world by providing permanence. These issues, perhaps absurd, point us to other relevant questions: How much plasticity is too much? If our brains are plastic, how do our external and internal worlds stay largely constant in the mind's eye?

Although the answers to these questions may never be answered and could lead us to a metaphysical conundrum, the data we need to address such questions are being collected at a rapid pace. Cochlear implantation and the response of patients to neural prostheses provide a major opportunity for us to help the deaf and also learn how the plasticity of the human brain actually works. Cochlear implants provide an artificial representation about the external acoustic environment. Although far from perfect in resolution, even the limited information provided by cochlear implants allows our brains to develop with some version of sound cues. The empirical fact that children receiving cochlear implants are able to develop sophisticated language skills, or that an adult can successfully process speech with only a small portion of auditory nerve fibers, implies that the brain possesses the means to function in abundance.

To what extent electrical stimulation of the auditory nerve prevents brainstem or cortical degeneration has not been established, nor is it known what particular components of the auditory pathway are most negatively affected by deafness or positively affected by cochlear implants. At present, the outcome of cochlear implantation is largely dependent on the natural course of plasticity that exists in the brain. As our understanding of plasticity evolves, our ability to provide useful hearing through implant technology should evolve in kind.

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