

Neurophysiologic Aspects of Some Auditory Disorders

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Progress in several areas of the hearing sciences has caused an increased interest in the function of the cochlea and the auditory nervous system, and it is now important for the practicing otologist to be familiar with aspects of auditory neurophysiology that earlier only had academic and research-related importance. Cochlear implants are perhaps the most obvious application of auditory neurophysiology in clinical otologic practice. The function of cochlear implants is closely related to the physiology of the auditory system; therefore, patient selection criteria and applications of cochlear implants rely on knowledge of auditory neurophysiology.

Furthermore, it has gradually become evident that the symptoms and signs of some disorders of hearing arise from functional changes in the auditory nervous system caused by the expression of neural plasticity (ie, changes with no detectable morphologic correlates). Neural plasticity is important in the adaptation of the nervous system to changes caused by injury and disease, such as stroke, but it can also have negative effects and cause symptoms and signs of disease. Pain and muscle spasm are widely recognized as symptoms based in the expression of neural plasticity. In the auditory system, tinnitus is the best known symptom related to neural plasticity, but even age-related hearing loss and noise-induced hearing loss have components that are manifestations of auditory nervous system plasticity.

HEARING WITHOUT THE COCHLEA: COCHLEAR AND BRAINSTEM IMPLANTS

There was no remedy for total loss of function of cochlear hair cells before cochlear implants were introduced in

the late 1960s.¹ Development of cochlear implants was pioneered by Michelson and House and Urban.^{2,3} Simmons and colleagues^{4,5} had previously shown that electrical stimulation of the auditory nerve in humans could result in the perception of sound. House did his first implantation in the cochlea of a prosthesis consisting of a single electrode in 1961. These prostheses became available in 1973, and a later version was approved by the US Food and Drug Administration in 1984 for implantation in adults.

The first prostheses that were implanted in patients were primitive compared with presently available cochlear implants, but they could give totally deaf individuals their first sound awareness.⁶ An independent evaluation⁷ of 13 patients who had undergone cochlear implantation by House found that the cochlear implants improved lipreading and identification of environmental sounds.

These early endeavors were met with great skepticism by auditory physiologists and other professionals. It seemed unbelievable to most auditory physiologists that a wire inserted blindly into the cochlea and fed with electrical signals derived from sounds picked up by a microphone could replace the delicate and very complex functions of the normal cochlea.

Cochlear implants have developed radically during the nearly four decades since House performed his first implantation, and instead of a single channel, modern cochlear implants use several channels,⁸ more complex sound processing, and more refined stimulating electrodes.⁹ There has been considerable improvement in implant performance over the House single-electrode implant, and it is astonishing what modern cochlear implants can accomplish regarding speech discrimina-

tion despite the fact that even the most sophisticated cochlear implants replicate only a few of the complex functions of the normal cochlea.

Despite these major technical developments, the general principles of modern cochlear implants are the same as those of the early House type of implants, namely, electrical stimulation of auditory nerve fibers with electrical signals derived from sound waves picked up by a microphone. The original House cochlear implant stimulated all auditory nerve fibers with the same signal. In contrast, modern cochlear implants provide some frequency separation along the basilar membrane of the cochlea by using several pairs of electrodes. Each electrode pair stimulates different populations of nerve fibers with electrical impulses derived from different frequency bands of the sound reaching the microphone worn by the individual. However, cochlear implants provide only broad frequency separation because sounds within relatively broad frequency bands are applied to each electrode pair. This means that sounds within these broad frequency bands activate large populations of nerve fibers in the same way, differing from the normal cochlea, which provides continuous frequency separation along the basilar membrane and activates auditory nerve fibers accordingly. Thus, cochlear implants stimulate many nerve fibers in very much the same way; therefore, large populations of nerve fibers can be presumed to fire synchronously when activated by cochlear implants.

It is assumed that frequency discrimination and the coding of small changes in sound intensity are essential for speech discrimination. The normal cochlea provides two different codes for the frequency (or the spectrum) of sound: a place code and a temporal code. In other words, the frequency of sound is represented both in the time pattern of the discharge of individual nerve fibers and by which population of nerve fibers is activated. The temporal code is the basis for the temporal hypothesis of frequency discrimination, and the place code is the basis for the place hypothesis of frequency discrimination.

Modern cochlear implants remain relatively crude devices and are liable to similar criticisms as were the pioneering devices. The great success of modern cochlear implants has muted criticism, and there must be a physiologic explanation for this success. The physiologic basis for the speech discrimination achieved with modern cochlear implants is not completely understood, but

a review of current knowledge regarding the function of the auditory nervous system can provide some insights. The following section of this chapter discusses the normal function of the cochlea and the features that may explain the ability of cochlear implants to provide speech discrimination.

Normal Function of the Cochlea

The cochlea contains the sensory cells (hair cells*) that transduce sounds into a neural code in individual fibers of the auditory nerve. Such transduction occurs after the frequency selectivity function of the basilar membrane has transformed and filtered the sound according to frequency (or spectrum[†]).

Each point along the basilar membrane vibrates with its greatest amplitude in response to sound of a specific frequency (or within a narrow spectral range). Low frequencies are represented at the apex of the cochlea and high frequencies near the base. Thus, a frequency scale can be laid out along the basilar membrane. Each point of the basilar membrane is tuned to a specific frequency, and the basilar membrane can be viewed as a continuous spectrum analyzer that separates sounds according to their frequency (or spectrum). As the hair cells of the cochlea are located along the basilar membrane, different populations of hair cells are activated by sounds of different frequencies within the audible spectrum and different inner hair cells are tuned to different frequencies. Since the auditory nerve fibers innervate individual inner hair cells, each auditory nerve fiber becomes tuned to a particular frequency. In other words, the fre-

*There are two kinds of hair cells in the cochlea, inner and outer, with different functions. The inner hair cells transform the vibration of the basilar membrane into the discharge pattern of auditory nerve fibers. The outer hair cells participate actively in the micromechanics of the cochlea and amplify the motion of the basilar membrane; this outer hair cell action adds approximately 50 dB to the sensitivity of the cochlea and increases the frequency selectivity of the cochlea for low-intensity sounds, which, in turn, improves the ability to detect soft sounds in noisy environments. The outer hair cells have no known role in transduction of the motion of the basilar membrane into neural activity.

[†]The term "frequency" is usually used to refer to periodic sounds, such as pure tones, and the term "spectrum" is used to refer to sounds that contain energy over a broader range of frequencies, such as speech sounds.

quency selectivity of the basilar membrane is reflected in the response of individual nerve fibers.

Frequency Selectivity of Auditory Nerve Fibers

The frequency selectivity of individual auditory nerve fibers can be demonstrated in animal experiments by recording from single auditory nerve fibers and determining their response areas with regard to the frequency and the intensity of sound (Figure 5-1). The curve that delimits the response area is known as a "tuning curve." Tuning curves show the thresholds of the nerve fibers as a function of the intensity and frequency of pure tones. The threshold is lowest at a certain frequency known as the fiber's characteristic frequency (CF), that is, the frequency to which the fiber is tuned. Different auditory nerve fibers have different CFs, covering the audible frequency range of the animal in question (Figure 5-2). A nerve fiber's response to a tone that is within its response area (excitatory area) can be decreased

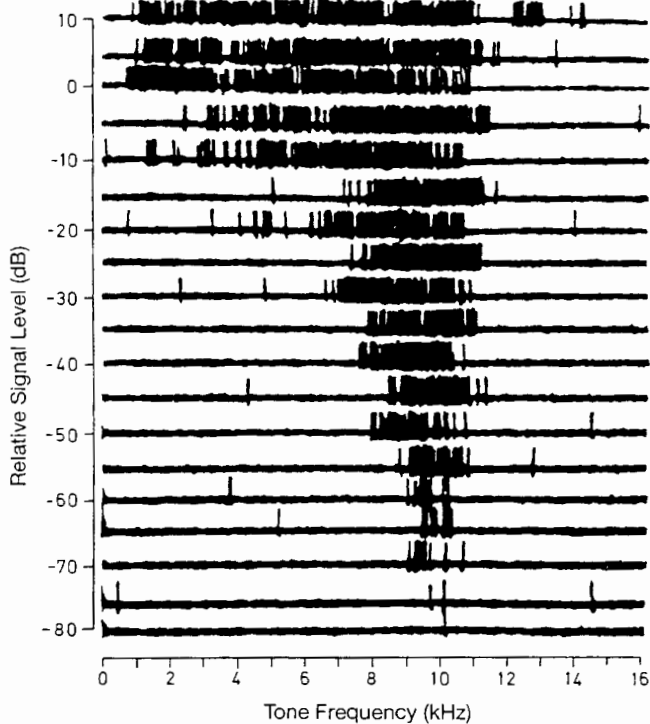


Figure 5-1 Responses of a single auditory nerve fiber in a guinea pig to tones of different frequencies and different intensities. Reproduced with permission from Evans EF.⁷²

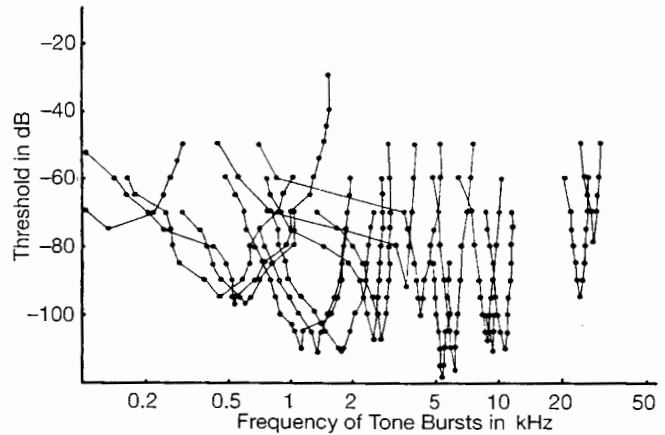


Figure 5-2 A family of auditory nerve tuning curves obtained in a cat. Reproduced with permission from Kiang NYS and colleagues.⁷³

(inhibited or suppressed) by a second tone that lies outside its excitatory area. This fact implies that auditory nerve fibers have inhibitory response areas bordering these excitatory response areas (Figure 5-3). This inhibition depends on the micromechanical properties of the cochlea and is referred to as a "two-tone suppression" to distinguish it from inhibition caused by synaptic activity.

The transduction process in the hair cells is sufficiently fast to allow the waveform of the vibration of the basilar membrane to be coded in the discharge pattern of individual auditory nerve fibers (Figure 5-4). Such temporal coding has been demonstrated in experimental animals by recording from auditory nerve fibers for

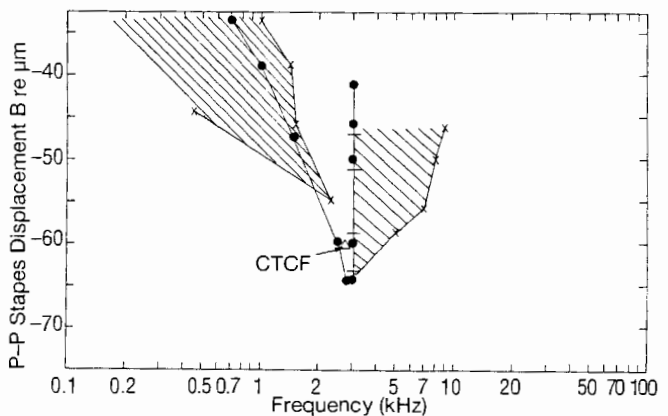


Figure 5-3 Two-tone inhibition in an auditory nerve fiber in a cat. Tones within the shaded areas decrease the response to a tone within the tuning curve (the excitatory response area) (CTCF). Reproduced with permission from Sachs MB and colleagues.⁷⁴

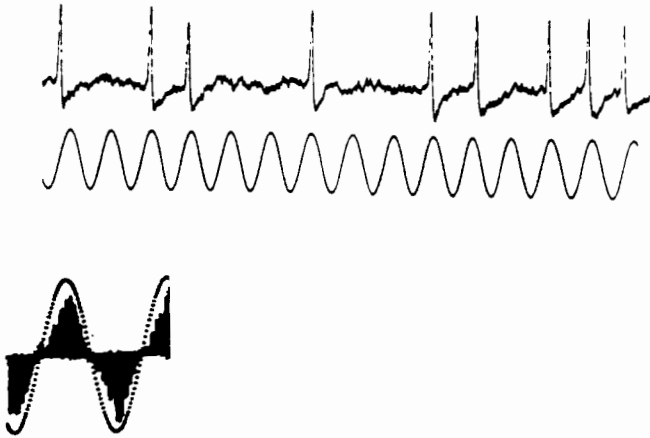


Figure 5-4 Phase-locking in an auditory nerve fiber showing that the probability of a discharge is related to the waveform of the sound. Reproduced with permission from Arthur RM and colleagues.⁷⁵

sounds up to 5 kHz. Since the temporal coding of high-frequency sounds is limited, it is thought that timing information is degraded in the cochlea.¹⁰ The upper cutoff frequency[†]) for temporal coding has been found to be different in two commonly used experimental animals, the cat and the guinea pig. The cutoff frequency for the cat cochlea is 2.5 kHz,¹¹ whereas that of the guinea pig cochlea is 1.1 kHz¹²—a considerable difference. It is not known what the frequency limit is for the human cochlea.

Auditory nerve fibers thus communicate two different codes for the frequency of sound to the central auditory nervous system: a place code that is a result of the basilar membrane separating sounds according to their frequencies and a temporal code that reflects the frequency of the vibration of each individual point along the basilar membrane. This coding means that discharges of individual nerve fibers are phase-locked to the frequency of the vibration of individual segments of the basilar membrane.

The place code for frequency is the basis for the place hypothesis for frequency discrimination. The place code is preserved throughout the auditory nervous system in a tonotopic organization that begins in the auditory nerve and includes neurons in the nuclei of the ascending auditory nervous system, which are anatomically organized according to their CF.

Since each point on the basilar membrane acts as a bandpass filter that is centered at a specific frequency, the temporal code in individual nerve fibers communicates information about the waveform and the periodicity of the bandpass-filtered version of sound. Thus, discharges of auditory nerve fibers that respond best to the frequency of the first formant of a vowel are phase-locked to the periodicity of the first formant and communicate the frequency of the first formant to the central nervous system in the form of a temporal code. The temporal code of the discharges of nerve fibers that are tuned to the higher-order formants communicate the frequency of these formants in their discharge pattern (Figure 5-5).

The temporal coding of frequency on which the temporal hypothesis of frequency discrimination is based can be regarded as an “object” code, that is, one that provides information about the properties of sound. Place coding provides (one-dimensional) spatial information. It is possible that these two codes for sound—spatial and object—are processed in different parts of the central nervous system and exemplify stream separation.

Which Code Is the Basis for Frequency Discrimination: Place or Temporal?

Cochlear implants can code the temporal pattern of sound in the evoked discharge pattern of auditory nerve fibers but are much less effective in providing the place representation of the spectrum of sounds. The following discussion therefore focuses on the relative importance of the temporal and place coding for frequency discrimination.

The fact that the frequency (or spectrum) of sound is represented in the auditory nervous system both by a place code and by a temporal code does not mean that these are both necessary for all forms of frequency discrimination. The question of how one (or both) of these two codes is used in sound discrimination has historically been an academic matter. Since the introduction of cochlear implants, this question has assumed practical interest as cochlear implants mainly deliver temporally coded sound, and their ability to provide place-coded frequency information is limited by the number of available channels.

[†]The cutoff frequency is defined as the frequency at which the reproduction of the waveform of a pure tone in the discharge pattern of an auditory nerve fiber has fallen by 3 dB compared with what it was for low-frequency tones.

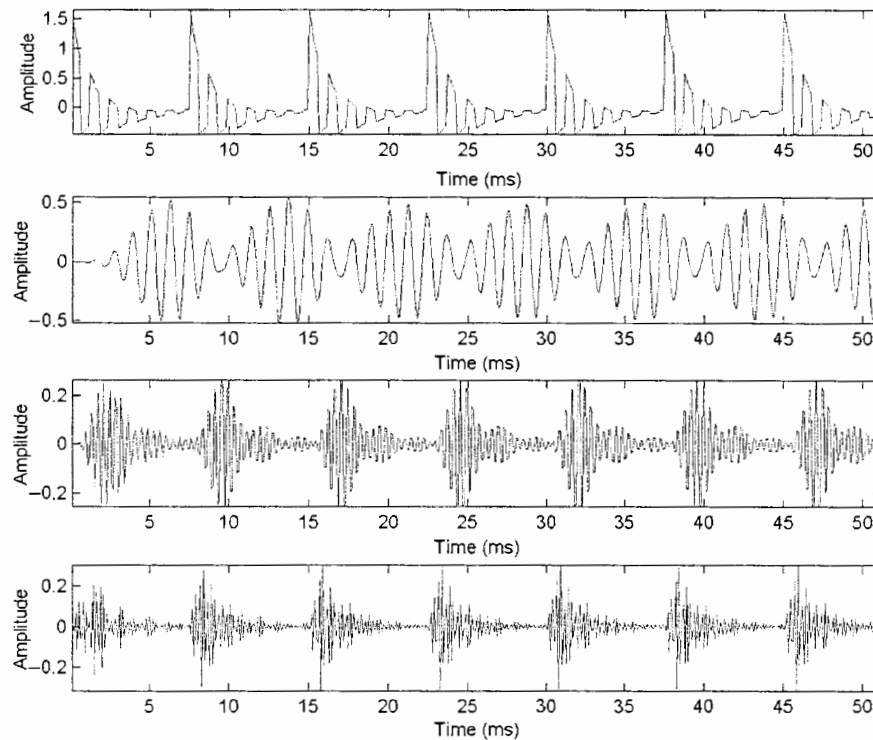


Figure 5-5 Illustration of how the output of bandpass filters that are centered at the formant frequencies of a synthetic vowel resemble damped oscillations, the frequencies of which are equal to the formant frequencies. (The formant frequencies of the synthetic vowel were 500, 1,000, and 1,500 Hz.) Courtesy of Drs. Peter Assmann and Ginger Stickler.

The fact that a tonotopic organization is maintained throughout the auditory nervous system and that individual neurons in the nuclei of the ascending auditory pathways, including those of the cerebral cortex, are specifically tuned with regard to the frequency of audible sound has contributed to the focus on the place hypothesis of frequency discrimination over the temporal hypothesis. The temporal hypothesis has been regarded as less important because of skepticism that temporal coding could be preserved through synaptic transmission and a lack of understanding of how the temporal code may be interpreted in the nervous system.

Experimentation to determine which of the two codes is used for frequency discrimination is hampered by the limited ability to manipulate a sound's time pattern without also changing its spectrum and vice versa. A few psychoacoustic studies in which such manipulations have been done favored the temporal hypothesis for frequency discrimination.¹³ Manipulations of speech sounds that remove most of the spec-

tral properties cause little changes in intelligibility.¹⁴ These studies also provided some insight as to how many channels may be necessary to obtain good speech discrimination.

The fact that disorders affecting neural conduction time in the auditory nerve affect speech discrimination more than similar threshold shifts caused by cochlear dysfunction also indicates that timing in the auditory nerve is important for speech discrimination.

Other methods can provide some insight regarding the relative importance of temporal and spectral coding to frequency discrimination. It is known that frequency discrimination is nearly independent of sound intensity, which means that the code (place or temporal) that is the basis for frequency discrimination must also be robust with regard to sound intensity. Further, the neural code used for frequency discrimination must be preserved through the ascending auditory pathways until it is decoded. The place and the temporal codes fulfill these requirements to differing degrees.

It has been shown in many studies that the frequency to which a point of the basilar membrane is tuned depends on the intensity of the sound.^{15,16} It has also been shown that the frequency tuning of individual auditory nerve fibers shifts when the intensity of the stimulus sound changes.^{17,18} These findings suggest that the place code may not be sufficiently robust to account for the ability to discriminate sound frequency as documented in psychoacoustic studies.^{19,20}

Temporal coding is little affected by sound intensity, that is, the shortest interval between nerve impulses in a population of auditory nerve fibers is unaffected by changes in the intensity of the sound. With increased sound intensity, more nerve fibers phase-lock to the sound wave, but the shortest interval is unaffected as it always equals the inverse of the frequency of the vibration of the basilar membrane. Thus, temporal coding is robust with regard to sound intensity.

One reason it has been assumed that temporal coding would be less likely to be the basis for frequency discrimination is that it was thought that synaptic "jitter" would impair transmission of temporal information in the nuclei of the ascending pathways. Studies of directional hearing, however, have shown that a high degree of temporal precision can be preserved through synaptic transmission in the auditory system. Many psychoacoustic studies have shown that humans can detect interaural time differences in the order of 10 microseconds.²¹ These results mean that short time intervals must be preserved accurately in neural transmission to the superior olivary complex (SOC), at which point the interaural time difference in the arrival of sound is decoded by neurons serving as coincidence detectors. This transmission of information involves at least two synapses in addition to the synaptic transmission in the hair cells, which proves that auditory temporal information can indeed be preserved through transmission (at least two synapses in addition to that at the hair cells) with a high degree of precision.

The high degree of temporal precision observed in synaptic transmission can be explained by the fact that neurons receive many synaptic inputs. Neurons perform spatial averaging similar to the signal averaging used, for instance, in the recording of evoked potentials to reduce the level of background noise. Experiments using models of neurons have shown that the variability (jitter) of the firing of neurons that receive many synaptic inputs

decreases with increasing number of inputs and that the variability of the output of a neuron that receives many inputs is less than that of the inputs.²² That such a high degree of temporal accuracy can occur in the auditory system has been confirmed by recording the response of neurons in the cochlear nucleus to "click" stimulation.²³

The other presumed obstacle to the use of temporal coding involves the decoding of the time pattern to recover the periodicity of sound. There is evidence that such decoding can be done by neural circuits similar to those that decode interaural time differences in the arrival of sound.

Importance of the Frequency Selectivity of the Basilar Membrane

The frequency selectivity of the basilar membrane facilitates the temporal coding of sound by separating the spectral components of complex sounds. It would not be possible to code the waveform of a vowel in the discharge pattern of auditory nerve fibers directly, but separating the spectrum of a vowel results in a series of waveforms that are similar to damped sinusoidal oscillations, the frequency of which is (exactly) the frequency of the formants of the vowel in question (see Figure 5-5). This separation makes it possible to code individual formants in separate populations of auditory nerve fibers. The center frequencies of the three filters shown in Figure 5-5 are equal to the formant frequencies of the synthetic vowel, the waveform of which is depicted (500, 1,000, and 1,500 Hz). The output of each of these filters is a damped oscillation, the frequency of which is equal to the respective formant frequencies. The auditory nerve fibers can phase-lock to these damped oscillations as they do to pure tones. It is difficult to imagine that the complete waveform of a vowel could be coded accurately in the temporal pattern of auditory nerve fibers, but it can be seen that the bandpass filtering has reduced the task of communicating the formant frequencies of vowels through temporal coding of the firing of auditory nerve fibers. The cochlear spectral analyzer acts as a series of bandpass filters that separates the spectral components of sound before converting the waveform into a neural code and may therefore be the most important function of the cochlea. This function can be emulated by a bank of relatively few bandpass filters as is done in modern cochlear implants.

How to apply such filtering to cochlear implants is a design question that involves the number of channels necessary to accomplish such spectral separation.^{9,14} A similar question does not arise with respect to the normal cochlea because cochlear frequency analysis is continuous; therefore, there are always populations of hair cells (and thus nerve fibers) that are tuned to each of the formants of a vowel.

The size of the population of nerve fibers that is activated by the normal cochlea depends on the spectrum and the intensity of the sound. The discharges of members of populations of nerve fibers that are activated by the same sound are phase-locked to the same waveform, namely, the bandpass-filtered sounds. Thus, the discharges in such a population of nerve fibers are phase-locked to each other.²⁴ Such phase-locking of neural activity in populations of nerve fibers may be important for the detection of sound²⁵ and for the coding of complex sounds such as speech.

Other Functions of the Cochlea

The frequency selectivity of the cochlea is emulated by a set of bandpass filters in cochlear implants. However, the excitatory response area of an auditory nerve fiber is bordered by two inhibitory areas (known as two tone inhibition; see above) (see Figure 5-3). These areas of suppression are a function of the cochlea and are thus a feature of normal cochlear function. The sound processors of cochlear implants do not include suppression. The importance of such suppression for sound discrimination is unknown, but it may be assumed that they may sharpen frequency resolution just as lateral inhibition in the visual system enhances contrast.

The cochlea also provides amplitude compression, which is essential for neural coding of sound within the intensity range of hearing. Amplitude compression means that an increase in sound intensity by 10 dB results in an increase in the excitation of hair cells that is (much) less than 10 dB. There are several sources of amplitude compression in the cochlea. One such source is the amplification resulting from action of the outer hair cells. As that amplification is greater for sounds of low intensity than for sounds of high intensity, the amplitude of the vibration of the basilar membrane is compressed. The transduction process in the inner hair cells is another

source of amplitude compression. The acoustic (stapedius) reflex provides some amplitude compression for sounds above approximately 85 dB HL. Amplitude compression can be achieved electronically in cochlear implants.

Auditory Brainstem Implants (Cochlear Nucleus Implants)

Auditory brainstem implants (ABIs) were developed for use in patients whose auditory nerve has been destroyed bilaterally, as may occur with the removal of the vestibular schwannomas of neurofibromatosis 2.²⁶ Bilateral absence of cochlear nerve function is also found in children with auditory nerve aplasia,⁵ and the use of ABIs in such patients has recently been described.²⁷

Auditory brainstem implants electrically stimulate the cochlear nucleus, thus bypassing both the cochlea and the auditory nerve. Auditory brainstem implants are placed in the lateral recess of the fourth ventricle, the floor of which is the dorsal surface of the ventral and the dorsal divisions of the cochlear nucleus²⁹ (see Chapter 33 for additional details of ABI placement).

There are considerable technical obstacles to the implementation of ABIs. Only recently has it been possible to place the electrode array in such a way that stable and constant function is achieved. Ideally, the electrode array should probably be placed on the surface of the ventral cochlear nucleus, but precise positioning of the array is difficult as it is inserted "blindly." Intraoperative recording of auditory evoked potentials is used to check the position of the electrode array.³⁰ Furthermore, it is not known which orientation of the electrode array on the surface of the cochlear nucleus gives optimal results. It seems logical to presume that the array should be oriented according to the tonotopic organization of the cochlear nucleus; however, the tonotopic organization of the human cochlear nucleus is not well characterized and is likely to be individually variable.

⁵Auditory nerve aplasia is a rare condition that may not always be distinguished from deafness that is caused by cochlear injury. The hearing loss of neural aplasia may mistakenly be diagnosed as a cochlear disorder. A child with auditory aplasia may therefore get a cochlear implant, which will not be of any help.²⁸

Normally, each auditory nerve fiber connects to neurons of all three main divisions of the cochlear nucleus—the first manifestation of parallel processing in the auditory system. The fact that ABIs can stimulate only one of the three main divisions of the cochlear nucleus means that they cannot replicate such parallel processing. Thus, there is more work to be done before ABIs are perfected. Nonetheless, although limited, the results with ABIs are encouraging.

Importance of Neural Plasticity in Cochlear Implant Patients

Cochlear implants and ABIs emulate only some of the functions of the cochlea, and the neural activity generated in the auditory nerve differs in many respects from that generated by the normal cochlea.

The sound discrimination achieved with cochlear implants benefits from changes in the way in which the central auditory nervous system processes signals received from the auditory nerve. Neural plasticity allows neural processing to adapt to abnormal situations (eg, cochlear implants) through more or less extensive “rewiring” of parts of the central nervous system. Such reorganization can result from sprouting of axons and from adjusting the efficacy of specific synapses, the latter probably being the most important factor in the adaptation to cochlear implants and ABIs.

Neural plasticity is a form of unconscious learning. The plasticity of the central nervous system is greatest during childhood development, which emphasizes the importance of early implantation. The extensive capability of the adult central nervous system to adapt to abnormal situations has only recently become evident. Neural plasticity can thus be assumed to play an important role in achieving the high degree of speech discrimination seen in implant recipients. Naturally, learning in the normal sense also plays an important role in achieving optimal results with implants.

Although the auditory nervous system can change in response to abnormal situations, adequate stimulation is important for normal development of the nervous system in childhood. This fact again points out the importance of early implantation. The changes needed for good results from ABIs during childhood are therefore more extensive than those needed for adaptation to cochlear implants in postlingually deafened adults.

NEUROPHYSIOLOGIC BASIS FOR CENTRAL AUDITORY DISORDERS[†]

The symptoms and signs of disorders of the auditory nervous system reflect changes in the neural conduction of the auditory nerve or changes in synaptic efficacy in the central auditory nervous system. Altered function of the auditory nerve causes hearing loss, typically with greater impairment of speech discrimination than seen with similar threshold shifts caused by conductive or cochlear dysfunction and tinnitus. Auditory nuclear injury resulting from destruction of their fibers or cells causes more complex clinical manifestations.

Changes in the function of the auditory nervous system sufficient to cause clinical manifestations can occur despite the absence of any detectable morphologic abnormalities. Thus, neural plasticity can alter organization and function by changing synaptic efficacy, outgrowth of new connections (sprouting), or interruption of normal connections. Recently, plasticity in the auditory nervous system has been implicated in disorders such as tinnitus, hyperacusis, and phonophobia (with involvement of the nonclassic auditory system with activation of limbic structures, especially the amygdala^{31,32}). Neural plasticity has also been linked to the hearing loss caused by noise exposure and presbycusis.^{33,34} Presbycusis may represent neural plasticity caused by deprivation of auditory input. It is clear that disorders traditionally ascribed solely to cochlear dysfunction (loss of hair cells) may, in fact, emanate from a combination of dysfunction of the cochlea and of the central auditory nervous system.

This section first discusses the neurophysiologic basis for the typical symptoms and signs of disorders of the auditory nerve and the auditory nervous system that are caused by morphologic changes and then discusses

[†]The term “auditory neuropathy” has recently been introduced to describe what were previously referred to as central auditory disorders. It describes a hearing impairment in which patients have normal otoacoustic emissions (indicating normal function of the outer hair cells) but absent or extremely abnormal auditory brainstem response (ABR). Such patients have a greater impairment of speech discrimination than seen in cochlear disorders with the same pure-tone threshold. The word neuropathy means disorders affecting the nervous system, but neurologists commonly use the term neuropathy for describing disorders of peripheral and cranial nerves. The use of the term auditory neuropathy is not yet established; presently, it is a loosely defined term for hearing disorders that are not caused by dysfunction of the cochlea or the sound-conducting apparatus.

disorders that reflect plasticity of the auditory nervous system.

Anatomy and Physiology of the Auditory Nervous System

The ascending auditory nervous system has two parts: classic and nonclassic ascending pathways. Classic ascending pathways are the youngest phylogenetically and are also the best understood with respect to their anatomy and physiology.

Classic Ascending Auditory Nervous System

The first nucleus of the classic ascending auditory pathway (Figure 5-6) is the cochlear nucleus in which the information in all auditory nerve fibers is relayed by synaptic transmission. The cochlear nucleus has three main parts: the anterior ventral cochlear nucleus (AVCN), the posterior ventral cochlear nucleus (PVCN), and the dorsal cochlear nucleus (DCN). The afferent fibers of the auditory nerve bifurcate with one branch terminating in the AVCN; the other branch bifurcates, with one branch terminating in the PVCN and the other in the DCN. Each of the three divisions of the cochlear nucleus connects to the inferior colliculus (IC) via the three acoustic striae and the lateral lemniscus (LL). Some fibers of the acoustic stria synapse in one or more of the several nuclei of the SOC, whereas some fibers of the LL make synaptic contacts in the dorsal or the ventral nuclei of the LL (DNLL and VNLL). All fibers of the LL make synaptic contacts with neurons in the central nucleus (ICC) of the IC. The ICC projects to the ventral part of the medial geniculate body (MGB) (the thalamic nucleus of the classic auditory system). Neurons in the ventral portion of the MGB project to the primary auditory cortex (AI).

Nonclassic Ascending Auditory System

The nonclassic ascending auditory pathway is thought of as an "adjunct" to the classic pathway. It receives its auditory input through connections with the ICC, the external nucleus of the IC (ICX), and the dorsal cortex of the IC (DC) (Figure 5-7).

Ascending fibers from the ICX and the DC connect to neurons in the medial and dorsal MGB. These neu-

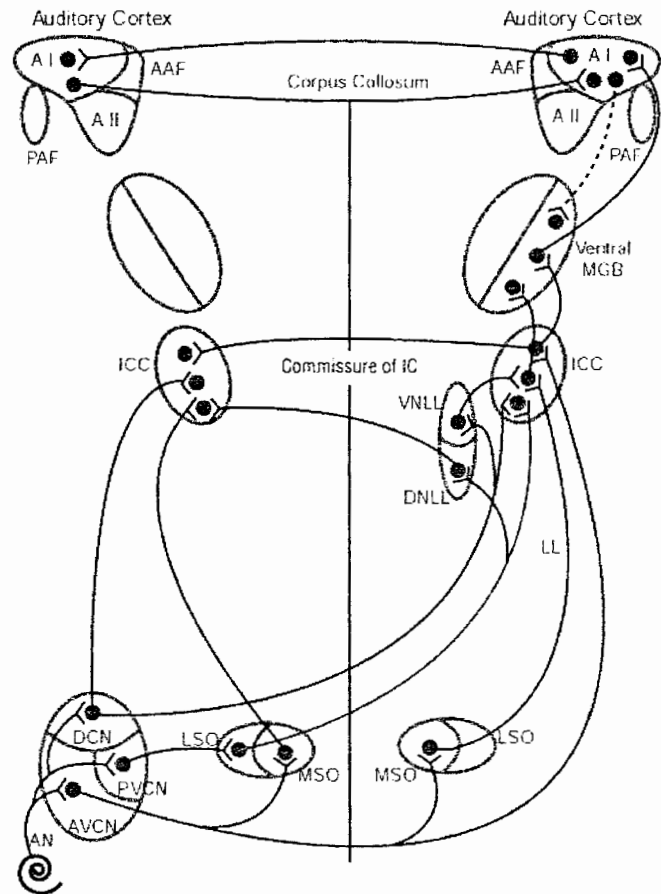


Figure 5-6 Classic ascending auditory pathways. AN = auditory nerve; DCN = dorsal cochlear nucleus; PVCN = posterior ventral cochlear nucleus; AVCN = anterior ventral cochlear nucleus; LSO = lateral superior olivary nucleus; MSO = medial superior olivary nucleus; LL = lateral lemniscus; DNLL = dorsal nucleus of the lateral lemniscus; VNLL = ventral nucleus of the lateral lemniscus; IC = inferior colliculus; ICC = central nucleus of the inferior colliculus; MGB = medial geniculate body; PAF = posterior auditory field; AI = primary auditory field; AII = secondary auditory field; AAF = anterior auditory field. Reproduced with permission from Møller AR.⁷⁶

rons project to association cortex and to structures of the limbic system, such as the ventrobasal division of the amygdala, which is involved in affective reactions such as fear. The ICX and DC also project to motor systems; some of these connections involve the superior colliculus (SC).

Much less is known about the nonclassic pathway than the classic pathway. Whereas the classic ascending auditory system receives input only from the cochlea, the nonclassic auditory system also receives input from other sensory systems. The connections of the somatosensory system to the nonclassic auditory pathways are the best understood.

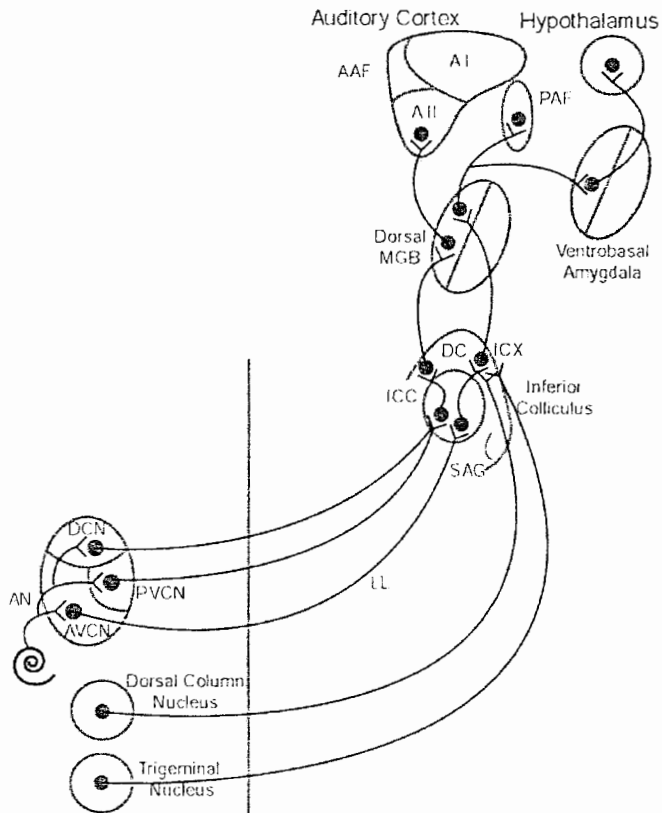


Figure 5-7 Nonclassic ascending auditory pathways. (Superior olivary nuclei are not shown.) AN = auditory nerve; DCN = dorsal cochlear nucleus; PVCN = posterior ventral cochlear nucleus; AVCN = anterior ventral cochlear nucleus; LL = lateral lemniscus; ICC = central nucleus of the inferior colliculus; ICX = external nucleus of the IC; DC = dorsal cortex of the IC; SAG = sagulum; MGB = medial geniculate body; PAF = posterior auditory field; AI = primary auditory field; AII = secondary auditory field; AAF = anterior auditory field. Reproduced with permission from Møller AR.⁷⁶

Thus, the ICX receives input from the somatosensory system (dorsal column nuclei), and the dorsal cortex of the IC sends axons to motor systems. There is also evidence that dorsal column neurons connect to neurons of the cochlear nucleus.^{35,36} Some neurons of the trigeminal nucleus also connect to the cochlear nucleus.³⁷

The nonclassic auditory system is phylogenetically older than the classic system. Responses recorded from single neurons of the nonclassic ascending pathway show broader tuning and less distinct responses than those of the classic pathway. This difference in response pattern is more pronounced in some studies^{38,39} than in others.⁴⁰ These differences in response patterns may reflect the fact that different studies used different animal species. There is also some doubt regarding the def-

inition of the border between the ICC, the ICX, and the DC, which means that some recording presumed to be from neurons in the ICX might, in fact, have been from neurons in the ICC. Animal experiments have shown evidence of input, which can be inhibitory or excitatory, from the somatosensory system to the auditory system at the midbrain level.⁴¹

Disorders of the Auditory Nervous System

Auditory nervous system dysfunction may be caused by tumors, infection, bleeding, stroke, and functional changes of neural plasticity. The most well-recognized disorders are those affecting the auditory nerve, and only recently has it been appreciated that neural plasticity plays an important role in provoking auditory system dysfunction.

Disorders of the Auditory Nerve

Acoustic tumors (vestibular schwannomas) are probably the most common lesions of the auditory nerve that cause auditory nerve dysfunction, but viral infection and vascular compression can also affect auditory nerve function. The symptoms and signs of auditory nerve dysfunction are poor speech discrimination, tinnitus, irregularly shaped pure-tone audiograms (with small dips that can appear at any frequency), elevated acoustic reflexes and/or poor growth of the reflex response above threshold. There is an increased interval between peaks I and III and between I and V on ABR testing. Speech discrimination is typically poorer than that seen in cochlear injuries with similar audiograms.

These manifestations may be caused directly by altered function of the auditory nerve alone or in combination with functional changes of more centrally located auditory nervous system structures, such as those caused by neural plasticity from a change (decrease) in input. Deprivation of input is a strong promoter of neural plasticity; animal experiments have shown that deprivation of input causes auditory hypersensitivity and altered temporal integration.^{42,43}

Congenital disorders of the auditory nerve, such as auditory nerve aplasia, may cause severe hearing loss with an absent ABR but with normal otoacoustic emissions. A rare disorder of the cochlea in which the inner hair cells

cannot activate auditory nerve fibers in a temporally coherent way demonstrates a similar response to testing.

DECREASED CONDUCTION VELOCITY IN THE AUDITORY NERVE.

Injury or disease of nerves and fiber tracts almost universally causes a decrease in conduction velocity. Decreased conduction velocity (prolonged delay) is the most prominent sign of dysfunction of the auditory nerve and is seen with acoustic tumors or stretching of the auditory nerve as may occur during operations in the cerebellopontine angle.⁴⁴ Decreased conduction velocity within the auditory nerve can be identified as an increased latency of a response that depends on conduction through the nerve in question (such as the ABR). Auditory brainstem response findings of decreased conduction velocity consist of an increase in the latency of peak II as well as all subsequent peaks. The latency of peak I is normal because it is generated in the peripheral portion of the auditory nerve and is unaffected by neural conduction in the auditory nerve. Similarly, electrocochleographic potentials are unaffected by auditory nerve injury.

TEMPORAL DISPERSION IN INJURED NERVES.

With increasing neural injury, conduction in some fibers of the nerve is blocked, and if very severe, all fibers may cease conducting impulses. Impairment of temporal coherence of the auditory nerve is believed to be the cause of the reduced speech discrimination common to auditory nerve injury. Temporal coherence of neural activity is important in auditory nerve fibers because frequency discrimination depends on the temporal coding of sounds. If the arrival time of neural impulses from different parts of the cochlea to the cochlear nucleus is altered (because some auditory nerve fibers conduct more slowly than normal), discrimination of speech is impaired.

The ABR reflects the conduction in the entire auditory nerve but does not provide information regarding individual nerve fiber latencies, which would have greater clinical utility.

ABNORMAL DISCHARGE PATTERN.

The discharge pattern of a nerve may be altered, and subsequent to injury, nerve fibers may fire in bursts instead of in their normal continuous pattern. The receiving neuron is likely to respond differently to burst firing even though the average firing rate may be normal. Burst firing can cause

synapses that are normally not conducting to open (unmasking of dormant synapses[#]).

INJURED NERVES AS IMPULSE GENERATORS.

Injured sensory nerves may become impulse generators and generate neural discharges with an abnormal temporal pattern in the absence of sensory stimulation. Since most auditory nerve fibers have spontaneous activity, such impulse generation entails increased spontaneous activity or an altered pattern of spontaneous activity.

Synapses may be nonconducting (dormant) because the excitatory input is too infrequent to exceed the threshold of the neuron, because temporal summation of excitatory postsynaptic potentials is insufficient to reach threshold, or because inhibitory postsynaptic potentials prevent membrane potential from reaching firing threshold.

EPHAPTIC TRANSMISSION BETWEEN NERVE FIBERS.

Injury to their myelin may make direct communication, known as "ephaptic" transmission, between nerve fibers possible. Ephaptic transmission has been implicated in facial and auditory nerve (facial nerve) abnormalities.²⁵ It can synchronize (lock together) the discharge pattern of many nerve fibers and thus cause the normal spontaneous activity in a population of auditory nerve fibers to become phase-locked, resembling the activity generated in response to sound stimulation. Such neural activity could result in the perception of sound despite the absence of any sound reaching the ear (eg, tinnitus). However, no study has been able to demonstrate the etiologic relevance of ephaptic transmission to specific disorders.

Disorders of the Central Auditory Nervous System (Excluding the Auditory Nerve)

The most common disorders of the central auditory nervous system (excluding the auditory nerve) are tumors, stroke, and hemorrhage. When such disorders are located in the temporal lobe, the auditory cortex may be affected.

[#]Synapses that are normally not conducting may become conducting in several ways: by a decrease in inhibitory influence, by an increase in the firing rate of the input to excitatory synapses, or by a change in the pattern of input from random firing to burst firing.

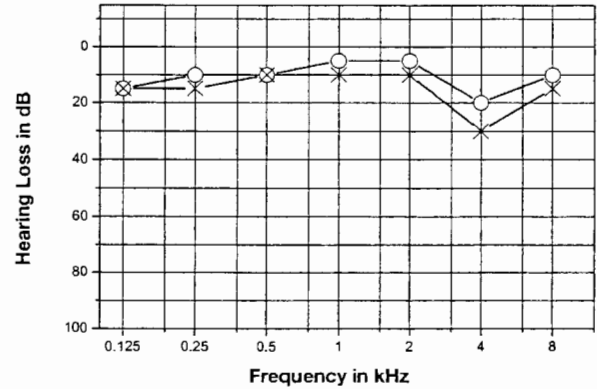
Disorders of the brainstem auditory pathways are very rare and usually present with symptoms and signs from many systems. Chemical insults can preferentially affect the nuclei of the auditory system; thus, hyperbilirubinemia seems to affect the cochlear nucleus to a greater degree than other parts of the auditory system. Tumors, strokes, and bleeding all share the feature of causing structural changes, and such changes can be detected by imaging techniques. Specific symptoms and signs are related to the observed morphologic changes.

LESIONS OF THE AUDITORY CORTEX. Tumors or other lesions of the temporal lobe affecting the auditory cortex on the one side have few obvious effects on hearing. Pure-tone thresholds are little affected, and speech discrimination is usually normal bilaterally when tested using standard methods. Therefore, the auditory cortex on the unaffected side must receive input from both ears despite findings from anatomic studies indicating that the auditory pathways are mainly crossed. Although there are uncrossed connections from the cochlear nucleus to the IC, it is assumed that bilateral representation is achieved by connections between the two primary auditory cortices through the corpus callosum. Bilateral representation is, however, not complete, as indicated by the finding that the discrimination of low-redundancy speech)** is impaired when presented to the ear contralateral to the affected side (Figure 5-8).^{45,46}

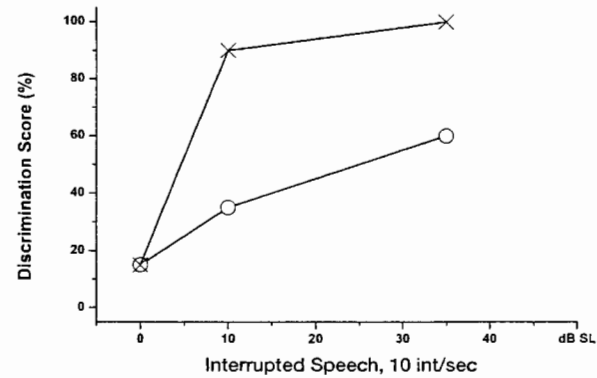
Neural Plasticity as a Cause of Symptoms and Signs

It has become increasingly evident that changes in the central nervous system caused by neural plasticity can give rise to symptoms and signs of disease. Such changes consist of altered synaptic efficacy and the creation or elimination of connections, none of which have detectable morphologic correlates.

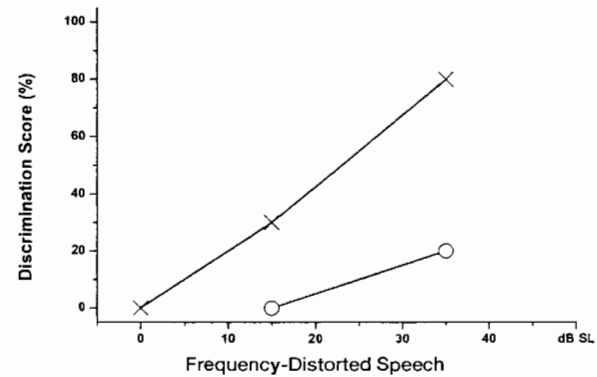
Functional changes in the central nervous system caused by neural plasticity may underlie a wide variety of symptoms and signs, most commonly chronic neu-



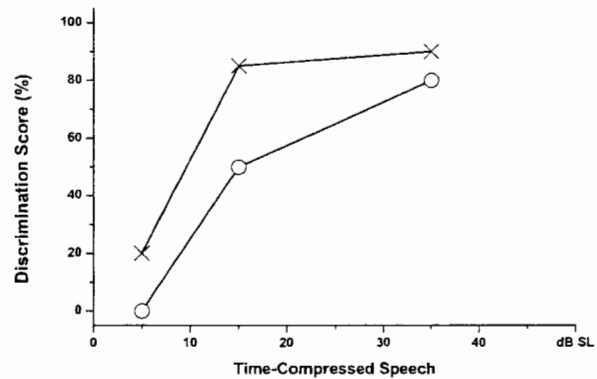
A



B



C



D

Figure 5-8 Speech discrimination in a patient with an astrocytoma in the left temporal lobe that involves the auditory cortex. A, Preoperative pure-tone audiogram; speech discrimination using B, interrupted speech; C, frequency distorted; and D, time-compressed speech. Circles = right ear; crosses = left ear. Reproduced with permission from Møller AR.⁷⁷ After Korsan-Bergtsen MAMM.⁴⁶

**Examples of low-redundancy speech include speech that is interrupted periodically (eg, 10 interruptions per second), time-compressed speech, and filtered speech (see Korsan-Bergtsen⁴⁶).

ropathic pain but also motor disorders such as facial synkinesis and hemifacial spasm.⁴⁷ More recently, it has become evident that neural plasticity explains the symptoms and signs of diseases of the auditory system and is now regarded as the etiology of some forms of severe tinnitus, hyperacusis, and phonophobia.⁴⁸ Noise-induced hearing loss is associated with morphologic changes in the cochlear nucleus^{33,34} in addition to changes in the hair cells of the cochlea. Studies in animals have documented changes (increased amplitude and/or sensitivity of auditory evoked potentials) in auditory nervous system function as a result of deprivation and overexposure. Altered temporal integration is another frequently demonstrated sign of plasticity of the auditory system^{43,49} and in the somatosensory system (pain).⁵⁰

Wall⁵¹ showed that the synapses connecting dorsal root fibers to neurons of the dorsal horn of the spinal cord, which are normally not conducting (ie, are closed or “dormant”), could be made to conduct (become “unmasked”) by severance of the afferent fibers (dorsal root) that serve as their primary input. Thus, this expression of neural plasticity was caused by deprivation of input, which is a potent inducer of neural plasticity. More recently, it has been shown^{52,53} that some forms of neuropathic pain are associated with other changes in the dorsal horn such as the outgrowth of new connections by axonal sprouting.

Whereas unmasking of dormant synapses may occur with little delay, outgrowth of new connections takes time. Changes in synaptic efficacy can be readily reversed, whereas elimination of newly created connections may be more difficult.

Unmasking of dormant synapses can be reversed by appropriate stimulation. The treatment of neuropathic pain with electrical stimulation of the skin (eg, transdermal electric nerve stimulation) is an example of reversing plastic changes in the nervous system.

Deprivation of input and overstimulation are the most potent inducers of neural plasticity in the auditory system. Plastic changes may cause hyperactivity (tinnitus) and other dysfunction. Thus, noise-induced hearing loss may be partly caused by neural plasticity.^{33,34}

TINNITUS, HYPERACUSIS, PHONOPHOBIA, AND OTHER ABNORMAL AUDITORY PERCEPTIONS. Tinnitus is a manifestation of hyperactivity that is of particular interest to the otologist. There are many forms, and also many causes, of tinnitus. Tinnitus often occurs in con-

junction with hearing loss of cochlear origin. The deprivation of input to the auditory pathways may promote neural plasticity, hyperactivity, and hypersensitivity,⁴² which, in turn, may cause spontaneous neural activity that is perceived as sound. Tinnitus almost always accompanies acoustic neuromas and is a frequent symptom of individuals with vascular compression of the auditory nerve. Tinnitus therefore appears to be associated with injury or irritation of the auditory nerve. How tinnitus develops is not known, but observation of other forms of cranial nerve injury or irritation (such as those caused by close contact with blood vessels) has shown that such injury/irritation can lead to hyperactivity of the associated nucleus (eg, for motor systems, hemifacial spasm, and for sensory systems, trigeminal neuralgia).⁵⁴

Hyperacusis often accompanies tinnitus but may also occur without tinnitus. Phonophobia less commonly accompanies tinnitus. Hyperacusis may be the result of hyperactivity and other forms of altered sound processing. Since the incidence of tinnitus increases with age, it is thought that it may be a result of progressive deterioration of neural systems. The increase in prevalence of tinnitus with age may be specifically affected by the decrease in production of γ -aminobutyric acid (GABA),⁵⁵ an inhibitory neurotransmitter that has been implicated in tinnitus. It is known that benzodiazepines, which are GABA_A receptor agonists, can alleviate tinnitus in some individuals.⁵⁶

The abnormal sensation of sound (hyperacusis and phonophobia) that often accompanies severe tinnitus may also be mediated by the nonclassic auditory system. The subcortical connections of the thalamic auditory nucleus of the nonclassic auditory system to limbic structures such as the amygdala⁵⁷ may explain why phonophobia and affective reactions often accompany severe tinnitus. Functional imaging studies³² have shown signs of activation of limbic structures in some individuals with tinnitus.

The nonclassic auditory system also receives input from other sensory systems such as the somatosensory system, which may explain why some individuals with tinnitus note changes in their tinnitus when moving their eyes⁵⁸⁻⁶⁰ or contracting neck muscles (Levine, personal communication).

Activation of the nonclassic auditory system can explain why some individuals with tinnitus perceive

sound when touching certain regions of the skin^{††} (eg, a patient with severe tinnitus was reported to hear a sound when rubbing his back with a towel).⁶¹

The abnormal auditory sensations perceived in response to somatosensory stimulation that often accompany tinnitus may be similar to allodynia,^{‡‡} which often accompanies neuropathic pain. Allodynia is an example of rerouting of sensory information and probably occurs as a result of unmasking normally dormant synapses. Thus, there are many similarities between severe tinnitus and some forms of neuropathic pain.^{48,61}

Many patients with chronic neuropathic pain also experience hyperpathia,^{§§} which may be similar to hyperacusis in individuals with tinnitus.

It is not known how the nonclassic auditory nervous system becomes activated in individuals with tinnitus, but it seems likely that the connections between the classic auditory system and the nonclassic auditory system in adult humans, which are normally dormant,³¹ may become unmasked after abnormal external or intrinsic events (ie, are a manifestation of neural plasticity). Recently, evidence has been presented⁶² that the nonclassic pathways are active in children.

Some of the changes in the function of sensory systems that can be attributed to neural plasticity may have detectable signs in addition to the symptomatic changes in perception of the sensory stimulation. It has been shown in animal experiments that temporal integration is altered after sound deprivation.⁴³ Overstimulation can also cause altered temporal integration (as demonstrated in experiments with rats that were exposed to loud sounds—4-kHz tones at 104 dB SPL for 30 minutes),⁶³ similar to the altered temporal integration demonstrated by electrical stimulation of the skin⁵⁰ in neuropathic pain.

HEARING LOSS. Hearing loss caused by noise exposure, administration of ototoxic drugs, and aging is associated with loss of (mainly) the outer hair cells of the cochlea.

^{††}Perception of sound from stimulation of the skin is an abnormal situation that may violate the law of specific nerve energies (Johannes Muller, in his monumental *Handbook of Human Physiology*, published in the 1830s), which states that stimulation of a specific sensory nerve will result in a sensation of that sensory modality.

^{‡‡}Allodynia is the perception of a painful sensation from what would normally be considered an innocuous stimulation of skin receptors, such as touching the skin.

^{§§}Hyperpathia is an exaggerated reaction to mild and moderate pain stimulation.

There is also evidence that such hearing loss is associated with morphologic changes in the cochlear nucleus.⁵² Hearing loss from noise exposure can be reduced by prior exposure to noise (“toughening”).^{64,65} The mechanism remains unknown. It may be that such “use” of hair cells makes them less susceptible to noise injury. Since noise-induced hearing loss is assumed to result from damage to the outer hair cells, the observed reduction in hearing loss from noise exposure could be a result of neural activity in the efferent system (olivocochlear bundle) that controls the mechanical properties of the outer hair cells. Even age-associated hearing loss can be reduced by exposure to sound. Thus, Turner and Willott⁶⁶ and Willott and colleagues⁶⁷ have shown that exposure to sound of moderate intensity (“augmented acoustic environment”) can prevent or delay the progression of hearing loss in animals. The mechanism of this effect of sound exposure is also unknown; it could represent an effect on the outer hair cells, but it could also be mediated by the central auditory nervous system through the olivocochlear bundle affecting the function of the outer hair cells. Finally, presbycusis may have a neural component that can be affected by prior exposure to sound through neural plasticity.

DEFICITS CAUSED BY SOUND DEPRIVATION. It is established knowledge that sound, and probably meaningful sound, is necessary for the normal ontogenetic development of the auditory nervous system. Total congenital deafness from cochlear causes results in functional abnormalities of the auditory nervous system. Lesser degrees of hearing loss may also impair the development of the auditory nervous system and may cause more general deficits in other parts of the central nervous system because of reduced input of information. Hearing loss early in life may thus impair speech development. An important question that has been discussed often in connection with middle ear disorders is how severe does hearing loss need to be to cause noticeable deficits later in life?

Motor Disorders

Motor disorders, such as muscle spasms, may reflect neural plasticity. Evidence has been presented that hemifacial spasm is caused by hyperactivity of the facial motor nucleus, probably caused by plastic changes.^{47,68} There is also evidence that synkinesis, which often accompa-

nies hemifacial spasm, is caused by the opening of dormant connections between motoneurons that supply different muscles of the face.⁴⁷ Other studies indicate that facial spasm and synkinesis following facial nerve trauma are also caused by plastic changes in the function of the facial motor nucleus.⁶⁹

Animal experiments have confirmed that repeated stimulation of the facial nerve can lead to spasm of the facial muscles.⁷⁰ This phenomenon is similar to the Kindling phenomenon, which was first demonstrated by stimulation of the amygdala of rats⁷¹; after weeks of daily stimulation for short periods, the rats developed seizures. It has been hypothesized that the spasm of hemifacial spasm is caused by a similar mechanism, and animal experiments have supported this hypothesis.

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