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Chapter 18: The Auditory System: Central Auditory Pathways

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# I. INTRODUCTION

In Chapter 17 we discussed the peripheral processing of auditory information, concluding with the discharge characteristics of auditory nerve fibers. In this chapter, we consider the processing of sound information by the central nervous system (CNS) and attempt to explain the transformations that take place between spike train activity in the 30,000 auditory nerve fibers and the perception of our rich acoustic environment.

To appreciate the difficulty of this processing task, we should reconsider the incredible versatility of our auditory capabilities. These begin with our primitive ability to detect the presence of a predator or prey in the immediate environment, independent of the illumination, direction of gaze, or wind conditions. Also we are able to use spectral and temporal variations in the acoustic energy to identify whether the intruder is close or distant, large or small, friend or foe, or a conspecific. To make such distinctions the acoustic information must be compared with stored auditory experiences, a task that requires more than the simple decoding of signals arriving on the 8th nerve. Localization of the spatial position of a sound also requires integration by CNS neurons, which must compare subtle differences in the energy arriving at the two ears. Such binaural processing, which characterizes most of our auditory pathways, is also useful for the perception of language, the highest level of human auditory processing. Here again, the raw afferent information that reaches the CNS is insufficient to account for language comprehension. Such a facility requires a stored auditory lexicon which itself, is largely independent of the specific nuances of speech sounds. A similar facility presumably underlies the understanding of complex communication signals in other species, such as whales and dolphins.

Our understanding of the CNS events that contribute to auditory detection, binaural localization and language comprehension is rather primitive. There are, however, two organizing principles that characterize auditory (and in general terms all) sensory processing.

First, auditory information is processed by many parallel pathways. We noted in the preceding chapter, that the discharge properties of the vast majority of eighth nerve fibers are quite similar, varying only in their best frequency. At the level of the cochlear nucleus where these axons terminate, this information is distributed to several subnuclei, which give rise to several ascending parallel pathways. While each pathway appears to carry the full range of frequency information, each has a different set of cell types, which themselves have a variety of different inputs, different targets, and different response properties. From these subnuclei, and probably



from subregions within each subnucleus, emanate pathways that undoubtedly transmit different kinds of information. For example, some cochlear nucleus cells drive cells that receive inputs from both ears (binaural pathways), while others contribute to pathways that remain monaural as information ascends through successive levels of neural processing. There is, however, considerable "crosstalk" between these "parallel pathways," and it is unwise to consider them as completely separate.

Second, even along a particular pathway, auditory processing cannot be considered strictly serial or hierarchical. In the preceding chapter, we saw that peripheral processing of sound is modified at the level of the middle ear by neural innervation of the tensor tympani and stapedius muscles, and further modified at the inner ear by the olivocochlear (efferent) fibers innervating the hair cells. Similarly, at each level of the CNS, ascending information can be modified by descending information from more cephalad auditory regions. Unfortunately, how these centrifugal pathways modify afferent information is largely unknown.

In this chapter, we begin with an overview of the CNS pathways involved in hearing. Ascending pathways that originate at the eighth nerve and project toward the cerebral cortex (also called centripedal projections) will be considered first, followed by a discussion of descending (or centrifugal) projections. The general principle of tonotopic organization will then be considered, as will the anatomical and physiological properties of the major auditory regions. Equipped with this knowledge of the separate elements of the auditory system, we will discuss a few examples of auditory processing, i.e. binaural interactions and the middle ear and startle reflexes. Finally, we conclude with a brief section on development and plasticity in the central auditory pathways.

# II. ORGANIZATION OF CENTRAL AUDITORY PATHWAYS

Most of our knowledge concerning the organization of nuclei and fiber tracts involved in the processing of acoustic information comes from detailed studies of the domestic cat (reviewed by Irvine, 1986). However, the basic organization appears substantially unchanged in all mammals, and the brainstem auditory pathways are similar in birds and reptiles as well. In some species, this phylogenetically conserved basic organization has been modified to accommodate their unique behavioral requirements. In this section, we first describe the basic organization, and then show how the brains of some animals provide unique opportunities to analyze particular aspects of acoustic processing.

## A. Ascending Auditory Pathways

Auditory Nerve

The auditory nerve is composed of approximately 50,000 axons in the cat (approximately 30,000 in humans), of which 90-95% are myelinated and terminate distally on the bases of the inner hair cells. The remaining 5-10% are unmyelinated and transmit information from outer hair cells. These different innervation patterns suggest that inner and outer hair cells transmit different kinds of information. This assumption is supported by several facts. First, as noted in the previous chapter, the large myelinated axons are thought to innervate a single inner hair cell while the unmyelinated axons contact a relatively large number of outer hair cells. Therefore, information from inner hair cells has a "private line" to the CNS whereas information from outer hair cells shows considerable convergence. Second, information from outer hair cells is received by the brain about 1-2 msec later than that from inner hair cells. Finally, unless the central terminations of the unmyelinated axons ramify much more profusely and widely than those of myelinated axons, responses in CNS auditory neurons should be dominated by information from inner hair cells.

The myelinated and unmyelinated fibers gather together to form the auditory nerve which courses through the internal auditory meatus. The nerve enters the brainstem at an outgrowth of neural tissue called the acoustic tubercle. The acoustic tubercle contains the cell bodies and neuropil of the cochlear nucleus where all auditory nerve fibers terminate.

Cochlear nucleus

The auditory nerve terminates in three cytoarchitectonically distinguishable subnuclei, which were named for their relative positions in the human brain. The three subnuclei, called the anteroventral, posteroventral and dorsal cochlear nuclei, seem to have gross functional differences as well. In different species the relative size of the subnuclei varies. For example, in man the dorsal cochlear nucleus is so small that it is almost vestigial. The current view is that all auditory nerve terminals are excitatory to the postsynaptic cells of the cochlear nucleus, but this is not certain. The three subnuclei of the cochlear nucleus give rise to three major fiber tracts, which constitute three brainstem pathways with apparently distinct functions.

Brainstem Pathways



Binaural brainstem pathways. One pathway originates mainly from cell bodies in the anteroventral cochlear nucleus (ACVN) and dives down into the ventral part of the brainstem to form a large fiber bundle, the trapezoid body, which runs across the base of the brain (Figure 18-1) to provide the major input to the superior olivary complex. The input from the anteroventral cochlear nucleus has two projection sites, which can be differentiated according to their preferred auditory frequencies; one, the medial superior olivary nucleus (MSO) receives input predominantly from the apical and middle turns of the cochlea (i.e. lower frequencies) whereas the other, the lateral superior olivary nucleus (LSO), receives inputs from the middle and basal turns (i.e. higher frequencies).

(Figure 18-1 near here)

The superior olivary complex is the first site for binaural interactions. Single axons from the anteroventral cochlear nucleus are thought to innervate cells at corresponding positions in both the ipsilateral and the contralateral medial superior olivary nucleus. These neurons , therefore, receive input from both ears. The lateral superior olivary nucleus also receives binaural input. Neurons in the anteroventral cochlear nucleus not only make excitatory connections in the ipsilateral lateral superior olivary nucleus but also send an axon across the midline in the trapezoid body to a group of large cells near the midline called the medial nucleus of the trapezoid body (Figure 18-1, MNTB). From this nucleus axons project to the ipsilateral lateral superior olive. Thus, each lateral superior olive neuron receives a direct input from the ipsilateral ear via the cochlear nucleus and an indirect input from the contralateral ear through an intervening synapse in the medial nucleus of the trapezoid body.

The major targets of axons from the medial and lateral superior olivary nuclei are the dorsal nucleus of the lateral lemniscus (Figure 18-1: DLL) and the inferior colliculus (IC) in the midbrain. The medial superior olivary nuclei project primarily ipsilaterally while the lateral superior olivary nuclei projects to both the ipsilateral and contralateral inferior colliculus as well as to the lateral lemniscal nuclei. In addition, some axons from the anteroventral cochlear nucleus, which cross in the trapezoid body, continue up to the contralateral nuclei of the lateral lemniscus or all the way to the inferior colliculus.

Intermediate brainstem pathway. The second pathway, which is relatively poorly understood, originates primarily in the posteroventral cochlear nucleus (Figure 18-2, PVCN) with some contribution from the anteroventral cochlear nucleus. Axons from these nuclei (dashed lines) travel in the intermediate acoustic stria to innervate both the ipsilateral and contralateral periolivary

nuclei, which surround the superior olivary complex. Additional axons ascend in the contralateral lateral lemniscus to innervate the lateral lemniscal nuclei and inferior colliculus.

(Figure 18-2 near here)

Monaural brainstem pathway. The third pathway originates in the dorsal cochlear nucleus (DCN) whose axons course across the midline in the dorsal acoustic stria on the dorsal aspect of the brainstem (Figure 18-2). They then join the contralateral lateral lemniscus and terminate in the inferior colliculus; some also terminate in the lateral lemniscal nuclei. Thus this pathway sends information from one ear directly to the contralateral inferior colliculus.

Auditory forebrain projections (Figure 18-2). As indicated in Figures 18-1 and 18-2, the three brainstem pathways converge at the inferior colliculi, which communicate with each other via their commissure. From there, information ascends ipsilaterally in the brachium of the inferior colliculus to the main thalamic auditory area, the medial geniculate body. Axons from the medial geniculate body terminate in the ipsilateral temporal regions of the cerebral cortex. In lower mammals the auditory areas are primarily on the lateral surface of the cortex; in primates, they are buried in the lateral fissure on the superior aspect of the superior temporal gyrus. Cortical auditory regions in the two hemispheres are interconnected through the corpus callosum.

## B. Descending Auditory Pathways

Sensory processing is often described as a hierarchical process with specific functions attributed to specific neural structures. This model is particularly inappropriate for describing auditory processing. The transmission of information from lower to higher structures is dramatically influenced by information flowing in the opposite direction. As we pointed out in Chapter 17, these descending influences are evident from the very beginning of auditory information processing, including the middle ear and inner ear.

Four major descending pathways are shown in Figure 18-3. At the brainstem level, the periolivary nuclei project to both the ipsilateral and contralateral inner ear. This olivocochlear pathway is composed of two relatively distinct components (Guinan, et al., 1983). One component originates in cell bodies lying lateral to the medial superior olivary nucleus and sends axons ipsilaterally to synapse on the distal dendrites of spiral ganglion cells just under the inner hair cells. The second originates in cell bodies situated in olivary and periolivary nuclei medial to the medial superior olive. It provides axons that synapse primarily on the base of contralateral



outer hair cells. The functions of the olivocochlear projections were discussed in the previous chapter. A second descending system originates

(Figure 18-3 near here)

in the periolivary nuclei but ends in the cochlear nucleus. Cell groups situated lateral to the medial superior olive send axons primarily to the ipsilateral cochlear nucleus while cells medial to the medial superior olive terminate mainly in the contralateral cochlear nucleus. A third descending pathway originates in the inferior colliculus and lateral lemniscal nuclei. The lateral lemniscal nuclei project to the superior olivary complex and the cochlear nucleus whereas the inferior colliculus projects to a variety of brainstem, auditory structures such as the superior olivary complex, as well as some regions that are not considered part of the primary auditory pathways, such as certain pontine nuclei which transmit auditory information to the cerebellum and superior colliculus (see Chapter 20). Lastly, the auditory cortex gives rise to at least two descending pathways. Axons descend to the divisions of the medial geniculate nucleus from which ascending cortical connections originate. Other cortical cells project to the ipsilateral inferior colliculus.

## C. Summary

This sketch of the major connections of the central auditory pathways serves to illustrate two points. First, the ascending auditory pathways consist of multiple independent, parallel processing networks that extract, encode and transmit information about different aspects of the acoustic energy reaching the two ears. Second, the descending pathways allow each structure up to and including the cerebral cortex to modulate the information in the ascending pathways.

# III. TONOTOPIC ORGANIZATION

In Chapter 17 we noted that peripheral auditory processing is governed by the principle that micromechanical properties of the inner ear transform sound energy into a unique pattern of hair cell excitation. Hair cells in the apical cochlea respond best to low frequencies, basal hair cells prefer high frequencies and cells in the middle of the cochlea prefer intermediate frequencies. Since this place code is a major factor in the discrimination of sounds of different spectral content, we might expect that the spatial encoding of frequency would be retained in the central auditory pathways.

Indeed, when Rose, et al. (1959), played pure tones to a cat, they discovered that each neuron of the cochlear nucleus was excited optimally by a single frequency (its best frequency), and that within each subdivision of the cochlear nucleus the best frequencies were organized in a regular order; neighboring cells preferred similar but slightly different frequencies. Figure 18-4 shows one of their recording electrode tracks through part of the cochlear nucleus and identifies the best frequencies of the neurons that were encountered. Within each subnucleus (e.g. Dc), best frequencies were encountered in a descending ordered sequence; as the electrode tip crossed the boundary into another subnuclear region (e.g. Pv), there was an abrupt change in frequency and the beginning of a new ordered sequence. This classic experiment showed that within each region of the cochlear nucleus there is an orderly representation of the cochlea.

In order to achieve a tonotopic organization in the cochlear nucleus each point on the cochlea must be represented as a two-dimensional sheet of neural tissue. This principle is illustrated in Figure 18-5. Several ganglion cells receive input from each position on the cochlea. This information can then be distributed to a lamina sheet-like area at the level of the cochlear nucleus. These "isofrequency lamina" are then stacked to form the complete tonotopic representation of the cochlea.

(Figure 18-4 & 5 near here)

The principle that the receptor surface is spatially "mapped" onto different areas of the brain is not unique to the auditory system. The same organizational principle has been seen in the somatosensory system (where it is called somatotopic organization, Chapter 15) and will be seen in the visual system (where it is called retinotopic organization, Chapter 20). In the auditory system the orderly anatomical arrangement of neurons according to their best frequencies is called Tonotopic Organization.

Tonotopic organization has now been demonstrated in each of the auditory nuclei from the cochlear nucleus to the cerebral cortex and in a large variety of species, including both vertebrates and invertebrates. For vertebrates with elongated cochleas, such as reptiles, birds and mammals, the following rules seem to govern the organization:

1. Connections between auditory nuclei are always in tonotopic register, regardless of whether the connections are ascending, descending or at the same levels of the neuroaxis (i.e. cortical-cortical connections), and irrespective of their sign (excitatory or inhibitory).



2. When an auditory region is subdivided into subnuclei, each contains an entire tonotopic organization. For example, each sub-region of the auditory cortex has a complete representation of the cochlea.

3. In binaurally activated areas, such as the medial superior olive, the tonotopic representation of each ear is in register so that each neuron is most sensitive to the same frequency played to either ear.

4. Although the frequency range varies from species to species, the basic tonotopic map is the same within a class of vertebrates, and is virtually identical for individuals of the same species. The similarity of maps between animals of the same species is often so precise that a formula which predicts the best frequency of a neuron on the basis of its anatomical location can be accurate to within 200-300 Hz (e.g. Rubel and Parks, 1975).

Each frequency does not necessarily have an equal anatomical representation. Within a structure, the actual number of neurons devoted to a given frequency depends on the number of receptors responding to that frequency. When an animal is specialized to use a particular frequency band, both the cochlea and the central nervous system have a relatively larger amount of tissue devoted to that band and the neural representation actually becomes magnified as one ascends the central pathways to the auditory cortex. For example, the mustache bat uses biosonar to navigate, and its auditory system is specialized to use 60 kHz echoes for this behavior. Its cochlea has a specialized region of high receptor density to encode this frequency. While this region accounts for about 20% of the cochlea, its central representation covers almost 50% of the auditory cortex. While this is an extreme example it is likely that other species that utilize specific frequencies for behavioral adaptations also show a neural "magnification factor" as one ascends the auditory pathways. A similar phenomenon characterizes other sensory systems. For example, the fovea has an increased representation in the central visual pathways (Chapter 20) as do the perioral regions and tips of the digits in the central somatosensory pathways (Chapter 15).

## IV. THE COCHLEAR NUCLEUS

As the cochlear nerve enters the brain, each axon divides into two main branches; one courses anterior to terminate in the anteroventral subdivision of the cochlear nucleus. The other branch runs posterior through the posteroventral subdivision where it usually synapses via en passant synapses and short collaterals. Most of these axons finally terminate in the dorsal cochlear nucleus. The tonotopic organization of each subdivision of the cochlear nucleus is established by

the branching patterns of entering auditory nerve axons. Low frequency fibers enter ventrally and branch immediately while high frequency fibers enter dorsally and branch later. The transmitter used by auditory nerve terminals has not been unequivocally identified; it is probably an excitatory amino acid, probably an aspartate-like compound.

While we describe the cochlear nucleus as being composed of three main subdivisions, several investigators have further subdivided each region on the basis of cell types or other anatomical features. In addition, there are marked variations between species in the relative sizes of each division.

To appreciate the contribution of the cochlear nucleus to auditory processing, we must briefly review the discharge properties of its inputs from the auditory nerve as revealed by several analysis techniques (Figure 18-6). The discharge patterns of the vast majority of eighth nerve axons differ only in their best frequency. Most axons have a high rate of spontaneous activity (Figure 18-6A), and sharp excitatory tuning curves (Figure 18-6B). Those responding to frequencies under 5-6 kHz preserve the temporal characteristics of the stimulus by phase-locking (Figure 18-6F). Rate-intensity functions at a neuron's best frequency are usually monotonic and saturate at 30-40 dB above threshold (Figure 18-6C). The temporal response characteristics of an auditory nerve axon to a tone burst are obtained by repeating a stimulus many times and grouping the action potentials into sequential time bins. The action potentials in each time bin are then added for all the stimuli to produce a post-stimulus-time-histogram (PSTH). The typical form of a PSTH for an auditory nerve fiber is shown in Figure 18-6D. Finally, one can determine the entire frequency "response area" (or frequency "receptive field") of an auditory neuron by plotting its discharge rate as a function of frequency at a number of stimulus intensities. Such a plot characteristic of all auditory primary afferents is shown in Fib 18-6E.

(Figure 18-6 near here)

In contrast to the similarities in the discharge properties of primary auditory afferents, cochlear nucleus neurons display a wide variety of response properties. For example, Figure 18-7 compares PSTHs in the auditory nerve with those found in the cochlear nucleus. Some cochlear nucleus responses are virtually identical to those of the nerve fibers (lowest cell) while others respond to only the onset of sound (second cell) and still others show distinct temporal patterns of excitation and inhibition (first and third cells). These differences in the response properties of cochlear nucleus neurons are associated with particular subdivisions and with cell types with unique morphologies (Kiang, 1975).



(Figure 18-7 near here)

Anteroventral nucleus. The anteroventral subdivision of the cochlear nucleus contains two cell types that can be differentiated on morphological grounds. One type is large, round or globular-shaped, with a few short, stubby dendrites that branch repeatedly. These are usually called "bushy cells" or spherical cells. The second type is large and stellate with several tapering dendrites of medium length.

The responses of bushy cells to tone bursts are strikingly similar to those described for auditory nerve fibers and, therefore, are called "primary-like" responses (Figure 18-7, lowest cell). A tone elicits a large initial response followed by a decline to a steady-state firing rate for the duration of the tone; when the tone is turned off, there is a short period of inhibition. These cells exhibit phase-locking, monotonic rate-intensity functions with a dynamic range of 20-40 dB, and tuning curves resembling those of auditory nerve fibers. The only consistent difference between the responses of auditory nerve fibers and bushy cells is that the latter often show "inhibitory sidebands"; i.e., inhibition of spontaneous activity when tones are presented at frequencies and intensities adjacent to the excitatory tuning curve. Therefore, at this level, there is some integration of the events occurring in surrounding cells.

The striking similarity of neuronal responses in the anteroventral cochlear nucleus to those of the auditory nerve can be understood by considering the morphology of auditory nerve terminals. Auditory nerve fibers provide 2-4 large calyx-type endings onto the soma and primary dendrites of the bushy cells. These end bulbs of Held provide input from one or only a few hair cells. In vitro experiments using tissue slices containing the auditory nerve root and the cochlear nucleus indicate that bushy cells fire one action potential for each spike in the nerve up to very high rates of simulation (Hackett et al., 1982; Oertel, 1983); therefore, the synapse is extremely secure.

The second cell type of the anteroventral cochlear nucleus also has response characteristics similar to those of eighth nerve fibers, except that it discharges rhythmically after the initial transient portion of the PSTH (Figure 18-7, 4th trace). This discharge pattern, which has been called a "chopper" response, is often associated with stellate cells (Rhode, et al., 1983; Rouillier and Ryugo, 1984).

It should not be concluded that no integration occurs in the anteroventral cochlear nucleus. Both primary-like and chopper cells receive several other synaptic connections which include gabaergic and noradrenergic inputs, which are presumed to be inhibitory, a cholinergic input, and probably other peptaergic inputs (Wenthold and

Martin, 1984). The sources of most of these other inputs have not been identified and their roles in information processing remain obscure.

Posteroventral nucleus. The most common type of neuron in the posteroventral subdivision of the cochlear nucleus responds best to the onset of a stimulus. Thus, it faithfully phase-locks to low frequencies or rapid clicks (below 1 kHz) but responds only to the onset of a higher frequency tone. The neural network responsible for the dramatic cessation of activity in these neurons following the onset of a stimulus is not known, but must include only one or two interneurons since the response is inhibited very rapidly. These cells also often have broad tuning curves, suggesting that they receive inputs from cells located over considerable distances along the cochlea. Altogether, their response characteristics suggest that they can faithfully code rapid temporal changes in a complex acoustic stimulus or in the envelope of a complex stimulus. These response characteristics have been attributed to a cell whose soma and dendritic morphology resemble an octopus (Figure 18-7, second cell); thus, it is called an octopus cell.

Other response types similar to those described in the anteroventral cochlear nucleus (i.e. chopper cells and primary-like cells) also exist in the posteroventral cochlear nucleus but the cellular morphology associated with these responses is unknown (Rhode, et al. 1983; Rouillier and Ryugo, 1984).

Dorsal nucleus. The dorsal cochlear nucleus is the most complex of the cochlear subnuclei. It has been subdivided into a number of regions with heterogeneous cell morphologies and, as noted above, receives descending inputs from a variety of other brainstem regions including the inferior colliculus.

The response patterns of cells in the dorsal cochlear nucleus show a considerable variety, including the simple pattern characteristic of primary afferents and each of the other patterns shown in Figure 18-7. A consideration of the inhibitory responses further complicates the number of possible patterns (Young, 1984). For example, Figure 18-8 shows the inhibitory and excitatory regions for a neuron in the dorsal cochlear nucleus. At moderate sound pressure intensities (80 dB; dashed line), the cell is inhibited by low frequencies. Then as the frequency is increased it is excited, then inhibited again and then excited again as the frequency is raised. At higher or lower intensities, the response pattern is different. Furthermore, responses of dorsal cochlear nucleus cells are dramatically altered by barbiturate anesthesia (Young and Brownell, 1976), further complicating our understanding of information processing in this region.



(Figure 18-8 near here)

## V. UTILITY OF BINAURAL INFORMATION

In all the structures discussed so far, neural discharge has been influenced by either one ear or the other. Beginning with the superior olive, however, many neurons are influenced by stimuli delivered to both ears. Before examining such discharge patterns it is useful to consider the use we make of our binaural capabilities in order to better understand the binaural responses of neurons.

Binaural hearing allows us to perform two well-known auditory feats. First, we can localize sound in space. Binaural hearing is essential for the localization of a brief sound that varies in position around the horizontal meridian (measured in degrees azimuth). Some animals, such as the barn owl also can use binaural cues to localize the position of a sound in 3 dimensional space. Second, we can attend selectively to sound emanating from a particular location such as the conversation of one person in a crowded, noisy room, i.e. the "cocktail party effect." Both these feats are accomplished by using either differences in the timing or differences in the intensity of the sounds reaching the two ears.

Interaural time differences occur because sound travels relatively slowly and there is a finite distance between the ears. The speed of sound in air is 340 m/sec and the diameter of the human head is about 17.5 cm. Thus, a sound emanating from 90º azimuth (i.e. along a line intersecting the ears) reaches the far ear approximately 660 µsec after it reaches the near ear. For sound positions between 0 (the saggital midline plane) and 90º the time differences will be proportionally less. This timing difference provides two related binaural signals. First, the onset of stimulation of the two ears will occur at slightly different times; this is important when sound undergoes an abrupt change in frequency or intensity. Second, a constant sound emanating from a single source will be phase-delayed to the far ear. For example, at the 90º azimuth, a pure tone of 500 Hz will be shifted in phase by about 120 º and a 740 Hz tone by about 180º. Thus, for a steady, complex sound, different frequency components will be shifted in phase by different amounts even though the interaural time delay is constant. Interaural time delays are significant only at lower frequencies (i.e. less that 2 kHz).

Interaural sound pressure (or intensity) differences occur at higher sound frequencies because part of the sound energy is reflected when its wavelength is short compared to the size of the head; i.e. the head is said to cast a "sound shadow." Therefore, when the sound source is displaced to one side of the head, the sound intensity at the far ear is less than that at the near ear.

In other words, the spectral properties of complex sounds will differ at the two ears. In humans, interaural intensity differences can be as much as 20 dB at frequencies above 5 kHz. Below about 1 kHz, interaural intensity differences are quite small or nonexistent.

Thus, interaural time differences provide effective spatial information about low frequency sound components while interaural intensity differences provide information about high frequency components. This dichotomy is called the "duplex theory" of sound localization.

The timing or intensity of sounds at the two ears depend not only on the location of the sound source but the position of the head and pinna. Thus, the activity of neurons associated with the neck and pinna musculature ultimately must influence the responses of neurons with binaural sensitivities.

## VI. THE SUPERIOR OLIVARY COMPLEX

The superior olivary complex consists of the medial and lateral superior olivary nuclei and the medial nucleus of the trapezoid body. The more diffusely organized periolivary nuclei are poorly understood and will not be considered in this chapter. Since the superior olivary nuclei are the first regions of the central auditory pathways to receive substantial input from both ears, they are thought to play an important role in sound localization and binaural processing. Both their anatomical organization and response characteristics of their neurons are consistent with this suggestion.

Medial superior olive. The neurons of the medial superior olive lie in a thin sheet that is oriented dorso-ventral and rostro-caudal in the ventral brainstem. In cross section, it appears as a stack of loosely aligned cells (Figure 18-9C). The major cell type has a bipolar dendritic tree; one dendrite extends toward the midline while the other extends toward the lateral surface of the brainstem. Axons from the ipsilateral anteroventral cochlear nucleus innervate the lateral dendrites, while axons from the contralateral anteroventral cochlear nucleus cross the midline in the trapezoid body to terminate on the medial dendrites (Figure 18-9A). In the mammal, it is not known whether a neuron in the anteroventral cochlear nucleus sends a collateral to each medial superior olive, but such a pattern does exist in the bird (Young and Rubel, 1982).

(Figure 18-9 near here)

Binaurally responsive cells are designated by two letters according to the sign of their responses (i.e. excitatory, E; inhibitory, I). The first letter is the sign of the response produced by



stimulation of the contralateral ear, and the second is the sign produced by stimulation of the ipsilateral ear. Thus, an IE cell is inhibited by the contralateral ear and excited by the ipsilateral ear. Most cells in the medial superior olive are of the EE type. Their excitatory best frequency is the same for stimulation of either ear.

When tested with monaural stimuli, neurons in the medial olivary nucleus have primary-like responses similar to those in the anteroventral cochlear nucleus. Binaural stimulation, however, reveals that they also are sensitive to differences in the time at which sound arrives at the two ears. Figure 18-10 shows how the average discharge rate of a cell in the medial superior olive varies when a pure tone at the cell's best frequency is first presented to one ear and then is delayed by varying amounts before being delivered to the other ear. The highest discharge rate for this cell occurred when the stimulus to one ear occurred about 0.7 msec or 1.7 msec later than the stimulus to the other. Delaying one stimulus was more effective than presenting both simultaneously or presenting the stimulus monaurally, even at an increased sound intensity. Finally, when the two ears were stimulated at the least favorable delay, the response was less than when the contralateral ear was stimulated alone. Different cells are responsive to different characteristic delays between stimuli presented to the two ears. Since an auditory stimulus reaches the two ears at different times whenever a sound comes from anywhere off the midline plane (i.e. 0° azimuth), neurons with different characteristic delays are thought to code the position of sound. When the temporal difference in binaural stimuli matches the characteristic delay of a neuron in the medial superior olive, a large response will occur; other neurons with different characteristic delays will be less active or inhibited.

(Figure 18-10 near here)

Since we use interaural time differences to localize low frequencies neurons in the medial superior olive seem uniquely suited to participate in low frequency sound localization. Generally, animals that have a low auditory frequency range have a large medial superior olive while those that hear predominantly high frequencies have a small one.

The avian nucleus laminaris, which is believed to be the homologue of the mammalian medial superior olive, has a unique anatomical organization that apparently causes interaural time differences to be represented topographically. As shown in Figure 18-11, nucleus laminaris is a sheet of neurons, each of which has a distinct bipolar dendritic configuration; one dendritic tree extends dorsally and one ventrally. The dorsal dendrites receive input from the ipsilateral ear while the ventral dendrites receive input from the contralateral ear. As seen in Figure 18-11, the

ipsilateral input reaches the dorsal dendrites across the sheet of cells at the same time [all ipsilateral axons from the nucleus magnocellularis (NM) have the same length). In contrast, an axon from the contralateral NM innervates the ventral dendrites sequentially via short axon collaterals, such that the most lateral cell in nucleus laminaris will be excited approximately 30 μsec after the most medial cell. This anatomical arrangement of afferents could provide the substrate for differential stimulation of nucleus laminaris cells as a function of the position of a sound source in the contralateral hemifield. When a sound emanates from the midline, medial cells in nucleus laminaris receive coincident dorsal and ventral activation. When a sound is moved to the 90° azimuth, the delay in the sound waves reaching the ear farthest from the sound source will be matched by the delay of action potentials from the ear closest to the sound source. Under these circumstances, coincident activation will occur only on the lateral neurons of the nucleus laminaris contralateral to the sound source.. Thus, each sound location will produce a coincident arrival of action potentials to the dorsal and ventral processes at only one location in the contralateral nucleus laminaris.

(Figure 18-11 near here)

Lateral superior olive and medial nucleus of trapezoid body. We will consider these two nuclei together because they appear to constitute one functional system in the mammalian brain.

The medial nucleus of the trapezoid body serves primarily as a high fidelity relay nucleus between the contralateral anteroventral cochlear nucleus and the lateral superior olive. The response properties of its neurons seem virtually identical to those of anteroventral cochlear nucleus neurons (i.e. they have V-shaped frequency tuning curves and primary-like or chopper type PSTHs; recall Figure 18-7). This dominance of the cochlear nucleus input on responses in the medial nucleus of the trapezoid body is probably due to the fact that axons from the anteroventral cochlear nucleus are of extremely large diameter (i.e. rapidly conducting) and terminate in hugh calyces that envelope the postsynaptic neuron (Figure 9A).

The postsynaptic neurons in the medial nucleus of the trapezoid body, in turn, send their axons to the ipsilateral lateral superior olive where they make inhibitory synapses using glycine as the neurotransmitter (Wenthold and Martin, 1984). In addition to this inhibitory input from the contralateral ear, most cells of the lateral superior olive also receive an excitatory input from the same frequency region of the ipsilateral anteroventral cochlear nucleus. Therefore, lateral superior olive neurons are of the IE type. Neurons in the lateral superior olive are extremely sensitive to the intensity differences of sounds presented to the two ears. Figure 18-12A shows that the response of an IE cell increases dramatically as ipsilateral sound intensity is increased (0 curve). When



tones of the same frequency are delivered at increasing intensity to the contralateral ear, the rate-intensity curves become less steep and reach lower maximum values, reflecting the increased contralateral inhibition. By varying the frequency of the tone applied to the contralateral ear while the ipsilateral ear is being stimulated at its best frequency, investigators have shown that the best frequency of the inhibitory input is identical to that of the excitatory (Boudreau and Tsuchitani, 1970; Sanes and Rubel, 1988). Since the discharge rates of lateral olivary neurons are exquisitely sensitive to small differences in sound intensity between the two ears but rather insensitive to absolute intensities of sound delivered to the two ears (Figure 18-12B), the discharge rates of lateral superior olivary neurons seem to encode the location of a sound source rather than its absolute intensity.

(Figure 18-12 near here)

The superior olivary complex appears to be the level of the auditory system at which information is distributed to the contralateral side of the brain. In this respect, the superior olivary complex functions somewhat like the optic chiasm (Glendering et al., 1985). Lesions of the superior olive entirely eliminate the ability to localize sounds, while lesions above this level (lateral lemniscus, inferior colliculus, medial geniculate or auditory cortex) disrupt sound localization only in the opposite hemifield (Jenkins and Masterton, 1982).

## VII. NUCLEI OF THE LATERAL LEMNISCUS

The dorsal and ventral nuclei of the lateral lemniscus are embedded in the ascending and descending axons of the lateral lemniscus. These nuclei, which are not well studied (Irvine, 1986), belong to two different ascending pathways. The major sources of afferent input to the dorsal nucleus are the nuclei belonging to the ventral binaural system, including the ipsilateral medial superior olive, both lateral superior olives and the contralateral anteroventral cochlear nucleus. The response properties of dorsal nucleus cells reflect all of these inputs. In addition, they respond best to binaural stimuli. Ventral nucleus cells, on the other hand, receive their major afferent input from the contralateral ventral cochlear nucleus and respond accordingly. The dorsal and ventral nuclei project to many common nuclei including the medial geniculate, the midbrain reticular formation and the superior colliculus. One difference is that the dorsal nucleus projects to both inferior colliculi whereas the ventral nucleus does not project to the contralateral inferior colliculus.

## VIII. INFERIOR COLLICULUS (IC)

The inferior colliculus serves as the major integration and transmission relay for information ascending in the central auditory pathways. Because it is more accessible than other brainstem auditory nuclei, it has received the most experimental attention. This attention, however, has revealed it to be an immensely complicated area, which has been divided into 10 or more subdivisions on the basis of morphological criteria (e.g. Morest and Oliver, 1984). Here, we distinguish just the three traditional subdivisions and consider only the physiological properties of cells in the largest subdivision, the central nucleus.

Most cells in the central nucleus are excited by contralateral stimuli. They have sharp tuning curves, display increasing responses over a range of 20-40 dB above threshold, and show relatively poor phase locking. However, there is considerable variability. Some cells, for example, exhibit very broad tuning curves while others have unusually sharp tuning curves.

Most cells in the central nucleus of a variety of species are excited by contralateral stimuli. In the best studied animal, the cat, about 25% of the cells respond exclusively to stimuli delivered to the contralateral ear, and the other 75% are binaural. Of the latter, the majority with best frequencies above 3 kHz are excited by the contralateral ear and inhibited by the ipsilateral ear (EI) while the majority with low best frequencies are excited by both ears (EE) (Irvine, 1986). The relative proportions of the two cell types vary widely between species according to the frequency range of their hearing. Thus, most rodents have a higher proportion of EI units while the kangaroo rat, which has excellent low frequency hearing, has a higher proportion of EE units.

Two kinds of evidence indicate that EE cells code the absolute temporal delay of stimuli reaching the two ears rather than the phase relationship between stimuli. First, the characteristic delay is independent of frequency (Yin and Kuwada, 1984). Second, a characteristic delay can be demonstrated by adjusting the delay between noise bursts presented to the two ears; in this situation the characteristic delay reflects the delay between noise bursts rather than the relative phase shift, which varies as a function of frequency (see Irvine, 1986). EE neurons respond best when stimulation of the ipsilateral ear lags that of the contralateral ear, the situation that occurs when a sound is in the contralateral hemifield. These neurons respond not only to the initial time disparity produced by the onset of sound, but also to ongoing time disparities produced by a continuous sound located on one side of the head.

EI cells in the inferior colliculus behave like IE cells in the lateral superior olive (LSO). That is, almost all EI cells in the inferior colliculus are completely suppressed if the ipsilateral



stimulus is of equal or greater intensity than the contralateral stimulus. Therefore, like the EE cells discussed above, EI cells respond when a sound source is in the contralateral hemifield where it is louder to the contralateral ear.

To localize the rustling sound of its prey (e.g. mice) while it is perched or in mid-flight, the barn owl uses both interaural time and intensity differences (Konishi, 1983). The inferior colliculus of the barn owl contains neurons that respond selectively to stimuli emanating from specific spatial locations in the contralateral hemifield and are relatively unresponsive to signals from any other location (Figure 18-13). The space specific neurons respond only when both the interaural time and interaural intensity differences are appropriate for the particular location. Space-specific neurons are distributed so that the inferior colliculus has a topographical representation of all positions in the owl's auditory space. Successive cells encountered on an electrode penetration prefer progressively adjacent positions in auditory space (Figure 18-13). As a stimulus is moved from the midline plane to the 90° azimuth, neurons at progressively more posterior positions in the inferior colliculus are activated and as the stimulus is elevated, progressively more dorsal neurons are excited.

(Figure 18-13 near here)

The inferior colliculus is the main source of sensory input to the auditory forebrain which is thought to be responsible for the conscious perception of sounds. The auditory forebrain is composed of thalamic regions receiving auditory input and the cortical areas with which they are reciprocally connected. This organization has been investigated most thoroughly in the cat.

In addition to serving as the major hub for ascending and descending auditory information, the inferior colliculus also delivers auditory information to structures outside of the main auditory structures. Such structures include the deep layers of the superior colliculus, which also receive directional information from the visual system (see Chapter 20), and the pontine nuclei which transmit auditory information to the cerebellum.

## IX. MEDIAL GENICULATE BODY

The medial geniculate body is the major thalamic relay for ascending auditory information (recall Figure 18-2). It is usually subdivided into 3 main divisions (ventral, medial and dorsal), each of which has a different cytoarchitecture and different auditory and non-auditory inputs (Winer, 1985).

The ventral division, which is the most thoroughly studied, has neuronal discharge characteristics that are similar to those of the auditory nuclei that have already been discussed (Calford, 1983). Most neurons have sharp tuning curves, firing rates that increase monotonically with increasing stimulus intensity, and binaural inputs (either EE or EI). Most respond primarily to the onset of a pure tone, suggesting that they are more sensitive to dynamic than static acoustic information. Therefore, the ventral division faithfully transmits the frequency, intensity and binaural characteristics of the acoustic stimulation. A strict tonotopic organization is also preserved in the ventral division, which seems to result from the laminar organization of its cells and the dendrites as shown in Figure 18-14. Morest (1964) suggested that each lamina represented an isofrequency band whose elements exhibit little overlap with neighboring bands. Single neuron recording studies have confirmed this suggestion. The major ascending input to the ventral nucleus is from the central nucleus of the ipsilateral superior colliculus.

(Figure 18-14 near here)

The dorsal division is a heterogeneous group of as many as 10 subnuclei with vague boundaries. The response patterns of its neurons are equally diverse. Although many can be driven by acoustic stimuli, their responses tend to be more irregular, their latencies more variable, and their tuning curves broader than those of neurons in the ventral division (Calford, 1983). A consequence of the broad tuning is that the tonotopic organization is imprecise. Nevertheless, a complete frequency representation is repeated several times within this division. The activity of many cells are only inhibited by auditory stimulation. Also, the activity of some cells is influenced by other sensory modalities, particularly somesthetic. Their variable auditory responses and responses to other sensory modalities reflect the fact that inputs to these cells originate from the area surrounding the central nucleus of the inferior colliculus and from non-auditory areas of the midbrain tegmentum and cortex.

The auditory responses of neurons in the medial division are also diverse. Response latencies range from 7 to 70 msec, both broad and sharp tuning can be found, and all combinations of binaural interactions are observed. Many neurons have two distinguishing characteristics (Calford, 1983): 1) they are maximally excited by sounds of a particular intensity and suppressed by more intense sounds and 2) they continue to respond for the duration of an auditory stimulus rather than only to its onset. These characteristics suggest that neurons of the medial division signal the relative intensity and duration of an auditory stimulus rather than its spectral and temporal content. Finally, many medial division neurons are polysensory.



The medial division receives its auditory input from regions surrounding the superior olivary nucleus or the lateral lemniscal nuclei. It also receives a variety of other sensory and non-sensory inputs [e.g. from the spinothalamic tract, vestibular nuclei, superior colliculus and the thalamic reticular nuclei (Winer, 1985)].

## X. AUDITORY CORTEX.

Woolsey and his colleagues first mapped the auditory areas in the cat cerebral cortex by describing the cortical areas where electrical stimulation of the auditory nerve produced evoked potentials (a similar strategy is described for the visual system, Chapter 20). Figure 18-15A shows Woolsey's (1960) summary, indicating 5 tonotopically-organized cortical regions (AI, AII, SF, EP and Ins) with other "auditory responsive" areas surrounding them. The tonotopic organization of each subdivision is indicated grossly by a "B" for the representation of the basal (i.e., high frequency) cochlea and an "A" for the apical (i.e., low frequency) region. Intermediate frequencies are represented in between. More recent studies based on single unit data and anatomical connections (Figure 18-15 B, C) suggest 4 tonotopically organized cortical auditory areas (A, AI, P, VP)), again surrounded by a belt of "auditory responsive cortex."

(Figure 18-15 near here)

The auditory cortex in primates, although not as well studied, has essentially similar features (Brugge, 1975). The primary auditory cortex is buried in the depths of the Sylvian fissure on the superior aspect of the temporal gyrus. It has a tonotopic organization with low frequencies represented rostrally and high frequencies caudally. The auditory cortex of man can be distinguished by its densely packed, small cells in layer IV. Both clinical observations and modern imaging techniques indicate that high frequencies are represented deep in the Sylvian fissure while lower frequencies are located more toward the top of the temporal gyrus (Brugge, 1975; Romani, et al, 1982).

When microelectrodes are driven through the cat auditory cortex perpendicular to its surface each neuron encountered has a similar best frequency. Thus, like other sensory cortices (see Chapters 15, 20), there is a columnar organization of certain stimulus attributes, in this case frequency. If the microelectrode is driven perpendicular to the frequency columns and parallel to the cortical surface, the best frequencies either increase or decrease progressively until the boundary between one cortical area and another is reached. At the boundary, the orderly progression stops and may reverse. If the electrode moves along a frequency column but parallel

to the cortical surface, similar best frequencies are again recorded, indicating that a band of cortex oriented perpendicular to the tonotopic progression receives input from the same place on the cochlea; i.e. it is an isofrequency band.

1. Connections of Auditory Cortex.

The organization of the auditory areas of the cat cortex has been extensively studied by a combination of microelectrode recording and anatomical techniques (Imig, et al., 1982; 1986; Merzenich, et al., 1979; Morel and Imig, 1987; Winer, 1985). While cortical organization may be somewhat different in primates, the main principles are similar. In the cat, each of the four tonotopic cortical areas receives a major input from a subregion of the tonotopically organized ventral division of the medial geniculate body. This input presumably confers the tonotopic organization on the cortical areas. Each cortical area, in turn, sends a point-to-point projection back to the same thalamic region from which it received its frequency-specific innervation. These connections, therefore, form a frequency-specific geniculo-cortico-geniculate loop. In addition to its major cortical projection, each tonotopic region of the thalamus sends a minor projection to one or more of the other cortical auditory areas. Each cortical area also is reciprocally connected with one or more non-tonotopic area in the medial or dorsal division of the medial geniculate body. Figure 18-16 illustrates these complex feed-forward and feedback connections. For example, a 1 kHz region of the cortical field A1 makes a point-to-point reciprocal connection with a 1 kHz area in the ventral division of the medial geniculate body which also has a minor projection to field A. The non-tonotopic areas of the thalamus also project to the A1 cortical fields, but this projection is more diffuse as is the reciprocal cortico-thalamic projection.

(Figure 18-16 near here)

Each cortical region also connects reciprocally with its homotopic area in the opposite hemisphere, with one or two other areas of the opposite hemisphere, and with all of the other tonotopic areas in the same hemisphere. Like the thalamic connections, one or two of these connections are very strong and precisely tonotopic while others are more sparse and diffuse.

Recently, the functional organization of auditory cortex has been further elaborated by the discovery of "binaural bands," which extend parallel to the tonotopic gradient (perpendicular to each isofrequency band). If an electrode penetration is run perpendicular to an isofrequency band, the response of each neuron to contralateral ear stimulation may be enhanced by stimulation of the ipsilateral ear. If an electrode penetration is run adjacent to the first track, the responses of these



cells to contralateral ear stimulation are suppressed by ipsilateral ear stimuli (Figure 18-17). These summation and suppression bands are reminiscent of the ocular dominance columns in the visual cortex (Chapter 20). Concomitant anatomical studies show that cells in bands that receive dense projections from the opposite cortex display summation and that cells in interposed bands, which receive projections from the same hemisphere, show binaural suppression (Figure 18-17).

(Figure 18-17 near here)

In summary, the anatomical and physiological organization of the cat auditory cortex suggests that multiple pathways emerge from separate areas of the thalamus to reciprocally innervate separate regions of their auditory cortex, and that each pathway processes different types of information. However, while each pathway has its own unique, dominant connections, each also communicates with the others.

2. Organization of Bat Auditory Cortex

The idea of separate cortical areas, each processing different functionally related signals, has been best revealed by making use of the unique prey-locating system of the mustache bat (Suga and his colleagues, 1984 a, b). During flight, the mustache bat emits a series of highly directional, ultrahigh frequency, echo locating pulses. Each pulse is composed of harmonically-related constant frequency portions followed by a short, frequency-modulated (FM) component. The second harmonic at 61-63 kHz is the most intense part of the vocalization. Obstacles or prey (flying insects) in the path of the bat cause a reflection (an echo) of the biosonar pulse. This echo has several interesting properties, which the bat is able to detect. For example, the delay between the pulse and the echo is proportional to the distance of the object. The echo also contains slightly different frequency components than the vocalizations because of a Doppler shift caused by the bat and target (e.g. insect) moving at different velocities. If the bat is closing in on his target, the echos will contain slightly higher frequencies than the pulse; if he is flying away from the target the echos will be at slightly lower frequencies.

The mustache bat's auditory system has several specializations that allow it to optimize its tracking performance. Although its total frequency range is from around 7 kHz to 120 kHz, about 30% of its primary auditory cortex is tuned to the narrow band of sounds between 61 and 63 kHz, the range that is crucial for the detection of the most intense part of its vocalizations. Second, another cortical area contains neurons whose responses depend on the precise frequency difference of the pulse and the echo i.e., on the Doppler shift. Neurons sensitive to different Doppler shifts

are topographically organized so as to represent systematic changes in the relative velocities of the bat and its target. Finally, neurons in a third area are differentially sensitive to the delay between the FM portions of the pulse and echo. These neurons respond poorly to the FM portions of either signal alone, but when the FM portion of the pulse is paired with the FM part of the echo at a particular delay a vigorous response occurs. Thus, this area seems to contain neurons that respond to targets at specific distances.

Based on their work in the bat, Suga and his colleagues have proposed 4 rules for cortical processing: 1) cortical neurons are specialized for processing different parameters of a complex acoustic stimulus; 2) neurons specialized for processing different parameters are clustered in separate areas; 3) within the clusters, different neurons respond best to different values of the parameter and are arranged topographically according to systematic variations in the parameter; and 4) the components of an auditory signal that are most important to the organism have an expanded cortical representation. It is not yet known whether these rules provide general principles for auditory cortical organization in other mammals.

### 3. Lesion Studies of Auditory Cortex

Over the past 50 years, many investigators have attempted to determine the role of auditory cortex by removing it and examining the resulting deficits in behavior. This approach has allowed us to draw important conclusions about the functional importance of different regions. These conclusions, however, must be tempered by certain shortcomings that plague all ablation experiments. First, studies that destroy part of the brain test the capabilities of an animal without that brain area rather than the function of that area per se. Second, the deficit could be due to an absence of appropriate sensory integration, but might equally well be due to deficits in sensory-motor integration, motivational factors or purely motor capabilities. While the latter deficit is relatively easy to demonstrate, the others are more difficult to dissociate from purely sensory dysfunction. Third, lesions of a given brain area produce effects beyond the tissue that was damaged. Other areas of the brain receiving direct, secondary or tertiary connections from the lesioned area, also will be affected. For example, regions supplying afferents to the damaged area will undergo some degree of retrograde degeneration and the targets of the lesioned area may undergo anterograde transneuronal atrophy or cell loss. In addition, sprouting of terminals from other afferents to the damaged area is likely to occur. Finally, it is difficult to remove specific auditory cortical regions without damaging neighboring ones. In view of these caveats, behavioral deficits produced by lesions serve only to implicate a region in the regulation of the affected



behavior. Nevertheless, it is of interest to examine those behaviors that are disrupted by lesions of auditory cortex.

In general, after removal of the entire auditory cortex, animals can still learn simple frequency and intensity discriminations but are unable to identify the position of a particular stimulus within a more complex pattern (e.g. distinguish a tone burst pattern of high-low-high frequencies from one containing low-high-low frequencies). Cortical lesions also disrupt tasks that require temporal discriminations such as determining the number of tone bursts in a series or distinguishing acoustic stimuli of barely different durations (Neff, 1975). Finally, cortical lesions affect behaviors based on stimuli delivered to the contralateral ear more than those to the ipsilateral ear. Although humans who have suffered unilateral cortical damage exhibit some improvement with time after the lesion, a moderate hearing loss in the opposite ear remains. In monkeys, bilateral lesions of the auditory cortex also produces a persistent 30-40 dB hearing loss of the middle frequencies (Hefner and Hefner, 1986).

The anatomical and physiological data presented above suggest that the primary auditory cortex is involved in the localization of sound in the opposite hemifield. This suspicion has recently been confirmed by experiments in which cats were trained to localize the precise position of sound emanating from one of seven speakers positioned within $\pm 90^{o}$ of the midline plane (Jenkins and Masterton, 1982; Jenkins and Merzenich, 1984). Unilateral lesions of the entire auditory cortex permanently disrupted the cat's ability to choose the correct speaker in the contralateral hemifield, although localization in the ipsilateral hemifield was unaffected. Furthermore, cats with removals of A1 cortex along isofrequency strips (say between 6-12 kHz) could not localize stimuli at those frequencies in the contralateral hemifield while sound localization was normal at other frequencies. These experiments reveal that the ability to accurately localize sound requires an intact primary auditory cortex on the opposite side of the brain, and that this involvement is frequency specific. Sound location seems to be independently represented within each frequency representation of primary auditory cortex.

Other areas of the "auditory cortex" and surrounding "auditory association areas" have received relatively little attention. Physiological investigations reveal a variety of responses to acoustic as well as other sensory stimuli, but these are likely to be dramatically influenced by anesthesia and other "state" variables. Behavioral studies have also failed to yield a coherent picture of functional roles for these regions.

## XI. MOTOR CONSEQUENCES OF AUDITORY STIMULI: AUDITORY REFLEXES

A. Acoustic Middle Ear Reflex.

As discussed in the Chapter 17, contraction of the two muscles in the middle ear, the stapedius and the tensor tympani, limits movement of the tympanic membrane and the stapes, thereby damping the transmission of sound to the inner ear. This middle ear reflex protects the inner ear from intense sounds and attenuates loud sounds to improve discrimination. In addition, contraction of the middle ear muscles occurs prior to vocalizations in humans, probably to attenuate the low frequency components of our own vocalizations so that our own speech is more intelligible. Contraction of the middle ear muscles is always bilateral and can be evoked by acoustic stimulation of either ear. Thus, in its bilateral action, the acoustic middle ear reflex resembles the pupillary light reflex (Chapter 19). Finally, this reflex is useful clinically to separate peripheral from central dysfunction.

The neuronal pathways involved in the middle ear reflex involve a 3 or 4 neuron circuit from the cochlea to the motor neurons in the facial and trigeminal nuclei, which innervate the stapedius and tensor tympani muscles, respectively. The principal components of this pathway are: 1) primary auditory nerve fibers; 2) neurons in the ventral cochlear nucleus; 3) neurons in or around both superior olivary nuclei and; 4) the motor nuclei of the facial (VII) and trigeminal (V) nerves. In addition to these direct pathways, there are longer latency pathways involving brainstem auditory nuclei and the reticular formation and/or the red nucleus, which, in turn, project to the motor nuclei of V and VII. The relative roles of the direct and indirect pathways are unknown.

B. Acoustic Startle Reflex.

Another important auditory reflex is the acoustic startle response which usually causes us to react to a loud sound. Activation of the startle reflex produces a short latency motor response that travels down the spinal cord, beginning with muscle contraction in the neck and shoulders and culminating with contraction of muscles in the distal segments of the forelimbs and legs. In rats, the reflex time from the onset of the acoustic stimulus to electromyographic responses in the hindlimbs is only 7-8 msec. The descending input, which elicits the motor response, involves projections from the primary auditory neurons to the ventral cochlear nucleus and then to the contralateral lateral lemniscal nuclei (Davis, et al., 1982). Neurons in or near the lateral lemniscal nuclei project into the caudal portion of the pontine reticular formation, which sends axons down the reticulospinal tract to innervate spinal interneurons and occasionally motor neurons directly.



Like the middle ear reflex, therefore, the startle reflex can involve a direct pathway of as few as 4 or 5 neurons. At each level, from the cochlear nucleus to the motor neurons, the direct pathway can be influenced by inputs from other neural networks. Indeed, the startle reflex can be modified by a variety of factors such as learning, state of the animal or other "competing" sensory events. The startle reflex also produces a chain of autonomic responses whose neural substrate is largely unknown.

## XII. DEVELOPMENT AND PLASTICITY OF THE CENTRAL AUDITORY SYSTEM.

Several properties of the auditory system make it well suited for understanding the factors that regulate both normal neuronal development and neural plasticity. First, the coding properties of auditory neurons can be precisely and quantitatively described on the basis of sound frequency, sound intensity and binaural interactions. Second, the cell bodies that represent successive levels of processing (e.g. cochlear nucleus,. superior olive, inferior colliculus, etc.) are spatially segregated, making them individually accessible. Third, there is extensive literature on the normal development of both peripheral and central structures with which to compare the results of experimental manipulations (Rubel, 1978; Willott, 1984; Romand, 1983).

The age at which individuals begin responding to sound varies considerably from specie to specie. Some animals, such as humans, guinea pigs and precocial birds begin responding in utero or in ovo. For example, the human fetus responds to loud sounds by the beginning of the third trimester (25-26 wks). Other species, such as most carnivores, rodents and atricial birds do not respond until after birth. Mice and rats, for example, first respond about 10-12 days postnatal. Electrical stimulation of the auditory nerve can evoke cortical responses before sound elicited responses are obtained. Therefore, the onset of auditory function is dependent on peripheral maturation, rather than the establishment of CNS connections.

Peripheral maturation can be documented. Very soon after central connections are established. First, the cochlear microphonic response is obtained by very loud, relatively low frequency stimuli. Within 1-2 days an eighth nerve compound action potential is obtained. As the middle ear and inner ear matures, response thresholds recorded from the auditory nerve or cerebral cortex drop and responses can be obtained to a broader range of frequencies. Tuning curves become progressively sharper over this same period, indicating that the ontogeny of frequency selectivity is primarily due to peripheral maturation.

Subtle changes in physiological properties however, also can be attributed to the CNS maturation. For example, response latency decreases with CNS myelination, and neurons are better able to follow rapidly repeating stimuli,as synapses mature. In addition, recent evidence suggests that immature tuning curves recorded from CNS neurons are, in part, due to the maturation of CNS connectivity (Sanes and Rubel, 1988). In contrast, the topographic representation of frequency is established prior to the onset of auditory function. For example, Sanes and Rubel (1988) showed that IE neurons in the neonatal gerbil lateral superior olive have matching excitatory and inhibitory best frequencies.

There is, however, ample evidence that normal input from the inner ear is required for normal maturation at all levels of the auditory system. For example, Levi-Montalcini (1949) showed that removal of the embryonic anlagen of the inner ear (the otocyst) in the chick results in severe cell loss in the maturing cochlear nuclei. This loss is correlated with the age when auditory nerve activity first activates postsynaptic responses in the CNS (Jackson, et al., 1982). Similarly, removal of the cochlea or silencing the electrical activity of the auditory nerve of neonatal chicks can cause a large number of CNS changes, including cell death, decreased protein synthesis, cell atrophy, alterations of enzyme activity and dendritic atrophy (Rubel et al., 1984; Born and Rubel, 1988). Figure 18-18 shows examples of the trophic influence of the inner ear on cochlear nucleus cells. The low power photomicrographs (A&B) show considerable neuron loss in the cochlear nucleus (NM in Figure 18-11) ipsilateral to inner ear removal in neonatal chicks. The cells that are destined to degenerate can be identified by loss of staining within 24 hours (18-18C) and by reduced protein systhesis (18-18D; cells without black grains over cytoplasm) within 3-6 hours after elimination of auditory nerve activity. Dramatic effects of peripheral manipulations on CNS auditory pathway development also have been shown in neonatal rats, mice, gerbils and cats. In some cases, neonatal rearing with a 30-40 dB conductive hearing loss produces atrophy of cells in the brainstem auditory nuclei presumably because of the reduction of afferent activity during development (Webster and Webster, 1979).

(Figure 18-18 near here)

Peripheral influences on auditory system development are not limited to anatomical atrophy in the brainstem auditory nuclei. Changing the balance of inputs from the two ears can cause marked physiological alterations. For example, stimulation of the ipsilateral ear, which normally produces inhibition of inferior colliculus neurons produces excitatory responses if the contralateral ear is removed soon after birth (Nordeen, et al., 1983).



These and other examples of peripheral influences on the structure and function of the auditory system are most clearly demonstrable in the immature organism. Similar manipulations on adult animals produce either less dramatic or no effects. There seems to be a restricted period during development, beginning at the time of synapse formation, when the establishment of normal mature central pathways depend critically on the amount or pattern of synaptic activity. An understanding of the biological basis of these "critical" or "sensitive" periods which also have been demonstrated for vision (Chapter 20) will emerge through examining how the genome of the developing neuron is expressed and how expression can be modified by changes in the ionic fluxes that occur in the environment of developing neurons.

FIGURE CAPTIONS

Figure 18-1. Summary of primary auditory nuclei in the CNS on both sides of the brain. Connections of the binaural brainstem auditory pathways are shown by solid lines. For simplicity we have only shown the projections from the left cochlear nucleus. The connections from the other cochlear nucleus would form a mirror image. Abbreviations: AVCN, anteroventral cochlear nucleus; PVCN, posteroventral cochlear nucleus; DCN, dorsal cochlear nucleus; LSO, lateral superior olive; MSO, medial superior dive; MNTB, medial nucleus of the trapezoid body; VLL, ventral nucleus of the lateral lemniscus; DLL, dorsal nucleus of the lateral lemniscus; IC, inferior colliculus; MG, medial geniculate nucleus; corp. call., corpus callosum. (Redrawn from Thompson, 1983).

Figure 18-2. Connections of the intermediate brainstem pathway and monaural (solid lines) and monaural brainstem pathway (dotted lines). As in Figure 18-1, for simplicity, only projections from one side are shown. Forebrain auditory pathways are shown as broken lines (____ .. ____). Abbreviations as in Figure 18-1.

Figure 18-3. The major descending auditory pathways are shown for one side of the brain. Abbreviations are the same as in Figure 18-1.

Figure 18-4. Sagittal section through the cochlear nucleus of the cat showing an electrical penetration through the dorsal cochlear nucleus (Dc) and posteroventral cochlear nucleus (Pv). The best frequency (in kHz) of neurons encountered at successive points along the electrode tract are indicated to the right. Note that there is a systematic decrease in best frequencies until the electrode enters Pv. At this point a new decreasing sequence is started again.

Figure 18-5. Schematic showing the topographic representation of points on the cochlear in the ventral cochlear nucleus. Many spiral ganglion cells (G) contact each region of the cochlea. Their central axons then terminate on as a sheet of cells in the cochlear nucleus, forming an isofrequency lamina. The tonotopic organization is formed by stacking these isofrequency lamina in order of their cochlear innervation.

Figure 18-6. Response pattern of typical auditory nerve fiber as seen from extracellular recording. A-F show typical analyses used to describe the response patterns of auditory neurons to simple acoustic stimuli.A. Spontaneous activity in the absence of acoustic stimuli. Spikes



per second (S/S) is displayed as a function of time trace shows representative discharge pattern in 100 msec. B. Tuning curve plots the threshold for an increase in activity above the spontaneous rate as a function of the frequency of a pure tone acoustic stimulus. Note that the neuron has a "best frequency", indicated by the tip of the tuning curve, and at higher or lower frequencies a louder stimulus is required to elicit a response. C. Rate-intensity function plots spikes per second as a function of the intensity of a pure tone stimulus. Most auditory nerve fibers show monotonic rate-intensity functions as shown here. D. Post-stimulus-time-histogram (PSTH) shows the pattern of discharges as a function of time. It is typically constructed by repeating a short pure-tone stimulus (shown under graph) many times and averaging the number of discharges in successive time bins following onset of the stimulus. Note that the response pattern shows a high rate of activity immediately after onset of the stimulus. The activity rate then drops to a level which is maintained until the stimulus is turned off. There is then a brief period of inhibition before th activity returns to spontaneous discharge rate. This pattern of discharges is termed "primary-like" because it is typical of auditory nerve fibers. E. Response are. Average discharge rate is plotted as a function of stimulus frequency. The family of curves represent different stimulus intensities from 20 to 60 dB. F. Phase-locking of auditory nerve fibers can be seen by plotting an interspike interval histogram. The interval between each successive discharges is computed during a stimulus. The frequency of intervals is then plotted against the time between each pair of discharges. The dots below the abscissa represent the time of 1, 2, etc. periods of the tone. Note that discharges tend to be spaced at the period of the tone or at multiples thereof.

Figure 18-7. Relationship of response types in the cochlear nucleus to cell types. A diagrammatic representation of unit types as defined by typical responses to moderate intensity, short (25- to 50-msec) tone bursts at the best frequency and the cell types to which the unit types are believed to correspond. The PST histogram above the auditory-nerve fiber shows its typical response pattern to tone bursts. The envelope of one tone burst is shown below the fiber. (From Kiang, 1975)

Figure 18-8. Complex tuning curve typical of one type of cell in the dorsal cochlear nucleus. Black areas show frequency-intensity combinations which are excitatory. Enclosed white areas show frequency-intensity combinations which inhibit spontaneous activity. The dotted horizontal line at 80 dB SPL is referred to in the text. (Redrawn from Young, 1984).

Figure 18-9. RC. Ramon y Cajal's classical illustrations of A the afferent axonal plexus, and of cell types in B lateral and C medial superior olivary nuclei, based on Golgi material from young kittens. Labeling in figures has been modified from Ramon y Cajal (1909), and identification of regions uses modern terminology. In A: *A* medial nucleus of trapezoid body (note calyces of Held); *B* periolivary cell region; *C* medial superior olivary nucleus; *D* lateral superior olivary nucleus; *E* lateral nucleus of trapezoid body; *F* fibers of trapezoid body (Reproduced from Irvine, 1986)

Figure 18-10. Discharge rates of a cell in the medial superior olive of a dog as a function the interaural delay of a 444.5 Hz stimulus presented to both ears at 70 dB SPL. Point of the left indicates response to contralateral (C) and ipsilateral (I) monaural stimulation, and in the absence of stimulation (SPON). Note that the unit's discharge rate is a cyclic function of the interaural delay with the maximum rate occurring when the stimulus to the ipsilateral ear delayed approximately 500 μsec or the contralateral ear delayed about 1.5 msec. (Redrawn from Goldberg & Brown, 1969.)

Figure 18-11. Schematic diagram of primary auditory pathways in the avian brain stem. Auditory nerve fibers (VIIIn) terminate in nucleus angularis (NA) and nucleus magnocellularis (NM). Axons from NM, the avian homolog of the mammalian anteroventral cochlear nucleus, terminate bilaterally in nucleus laminaris (NL). Note that the terminal arborizations of these axons on the two sides of the brain differ. The ipsilateral axon is the same length across the medio-lateral extent of NL while the contralateral axon forms a serial delay-line from medial to lateral.

Figure 18-12. Family of binaural intensity functions for an IE cell in the lateral superior olivary nucleus of the cat showing sensitivity to interaural intensity difference (IID). Each function was generated by presenting a contralateral tone at the characteristic frequency of the neuron (31.0 kHz) at the fixed level indicated (in dB SPL) on the function, varying the level of the simultaneously presented ipsilateral tone of the same frequency in 5-dB steps. Function marked *Off* is for monaural ipsilateral stimulation. It is apparent that for any given level of stimulus to the ipsilateral (excitatory) ear (on abscissa), the response declines with increases in the level of the stimulus to the contralateral (inhibitory) ear. B Data in A have been replotted to show variation in response as a function of IID (contralateral intensity relative to ipsilateral intensity) at different levels of the ipsilateral stimulus (as indicated in *key*). The *horizontal line* at the top of the figure indicates the broad azimuthal



ranges corresponding to the IID ranges on the abscissa. (Data from Boudreau & Tsuchitani, 1970; Figure from Irvine, 1986).

Figure 18-13. A neural map of auditory space. Upper left: Coordinates of auditory space are depicted as a globe surrounding the owl. Projected onto the globe are the best areas (solid-lined rectangles) of 14 units that were recorded in four separate penetrations. The large numbers backed by the same symbols (dart diamonds, triangles, etc. represent units from the same penetration; the numbers themselves denote the order in which the units were encountered. Penetrations were made with the electrode oriented parallel to the transverse plane of the auditory midbrain positions indicated in the horizontal section by solid arrows. Below and to the right of the globe are illustrated three histological sections through MLD in the horizontal, transverse, and sagittal planes. The stippled portions corresponds to the space-mapped region. Isoazimuth contours, based on field centers, are shown as solid lines in the horizontal and sagittal sections; isoelevation contours are represented by dashed lines in the transverse and sagittal sections. On each section, dashed arrows indicate planes of the other two sections. Solid, crossed arrows to the lower right of each section define the orientation of the section: a anterior, d dorsal, l lateral, m medial, p posterior, v ventral, OT optic tectum (from Knudsen and Konishi, 1978)

Figure 18-14. Drawing from transverse section of the ventral division of the cat medial geniculate. The section was stained by the Golgi method to show cell bodies and dendrites. Note the laminar appearance with the dendrites oriented parallel to the lamina. These lamina form isofrequency sheets and the tonotopic organization is perpendicular to the lamina. (From Morest, 1965).

Figure 18-15. Auditory cortical fields in the left hemisphere of the cat. A. Summary diagram from Woolsey (1960) showing five tonotopically organized cortical regions; SF, A1., A4, EP and Ins. The tonotopic organization of each area is indicated by "A" representing apex (low frequency) of the cochlea and "B" representing base (high frequency) of the cochlea. Other regions which respond to sound but are not tonotopically organized are also shown. B & C show more recent parcelation of tonotopic cortical regions based on microelectrode recording and anatomical connections. Four tonotopic regions are defined; A, A1, VP and P. In C the sulcus and the tonotopic organization of each area is shown from "high" to "low" frequency. (from Imig, et al., 1982).

Figure 18-16. Schematic diagram of cortical gyros showing patterns of connections between cortical field A1 and both tonotopic and non-tonotopic areas of the medial geniculate nucleus (MGB). Note that there is a heavy reciprocal point-to-point connection between field A1 and the same frequency region of the tonotopically organized area of MGB. There is also a sparser projection from the tonotopically organized area of MGB to field A. Fields A, A1 and non-auditory cortical areas project diffusely into the non-tonotopic area of MGB.

Figure 18-17. Schematic representation of cortico-cortical connections thought to be responsible for binaural summation (shaded) and binaural suppression (unshaded) bands in the cerebral cortex. The 10 kHz band of field A1 on the left side receives alternating projections from the 10 kHz region of field A1 on the right side and the 10 kHz region of the ipsilateral field A. This pattern is repeated for each frequency. Recordings from the regions of A1 receiving ipsilateral input (from A) reveal "suppression" and recordings from the regions receiving contralateral A1 input reveal "summation". These response characteristics are shown at the bottom. In each graph the response to contralateral stimulation alone is indicted by "C: and the lack of an excitatory response to ipsilateral ear stimulation is indicated by I. When the contralateral stimulus is paired with an ipsilateral stimulus the response depends on the intensity of the ipsilateral stimulus. For "suppression" neurons the response becomes progressively inhibited while summation neurons are showing increasing discharge rates when the ipsilateral ear stimulus intensity is increased.

Since the suppression regions and summation regions of field A1 are roughly aligned across frequencies there are binaural suppression bands and binaural summation bands oriented parallel to the tonotopic organization.

Figure 18-18. Photomicrographs showing rapid changes in nucleus magnocellularis (NM) of the chick (avian homolog of the mammalian anteroventral cochlear nucleus; see figure 18-11) following destruction of the cochlea. A & B show low magnification views of NM on the ipsilateral side (A) and contralateral side (B)B of the brain just 2 days following the removal of the cochlea. Note that approximately half of the neurons in A are gone or very pale staining. Scale bar = 0.2mm. C. High power view of the ipsilateral side showing that neurons in the process of transneuronal degeneration (arrows) have lost cytoplasmic staining for Nissl substance, indicating that cytoplasmic RNA has been severely depleted. Scale bar = 10mm. D. In this animal $^{3}H$ leucine was injected 1/2 hour prior to death in order to study protein synthesis by NM neurons following elimination of eighth nerve



activity three hours earlier. The cells without black silver grains (arrows) have already ceased protein synthesis and are the one that will degenerate. (A-C from Born & Rubel, 1985).

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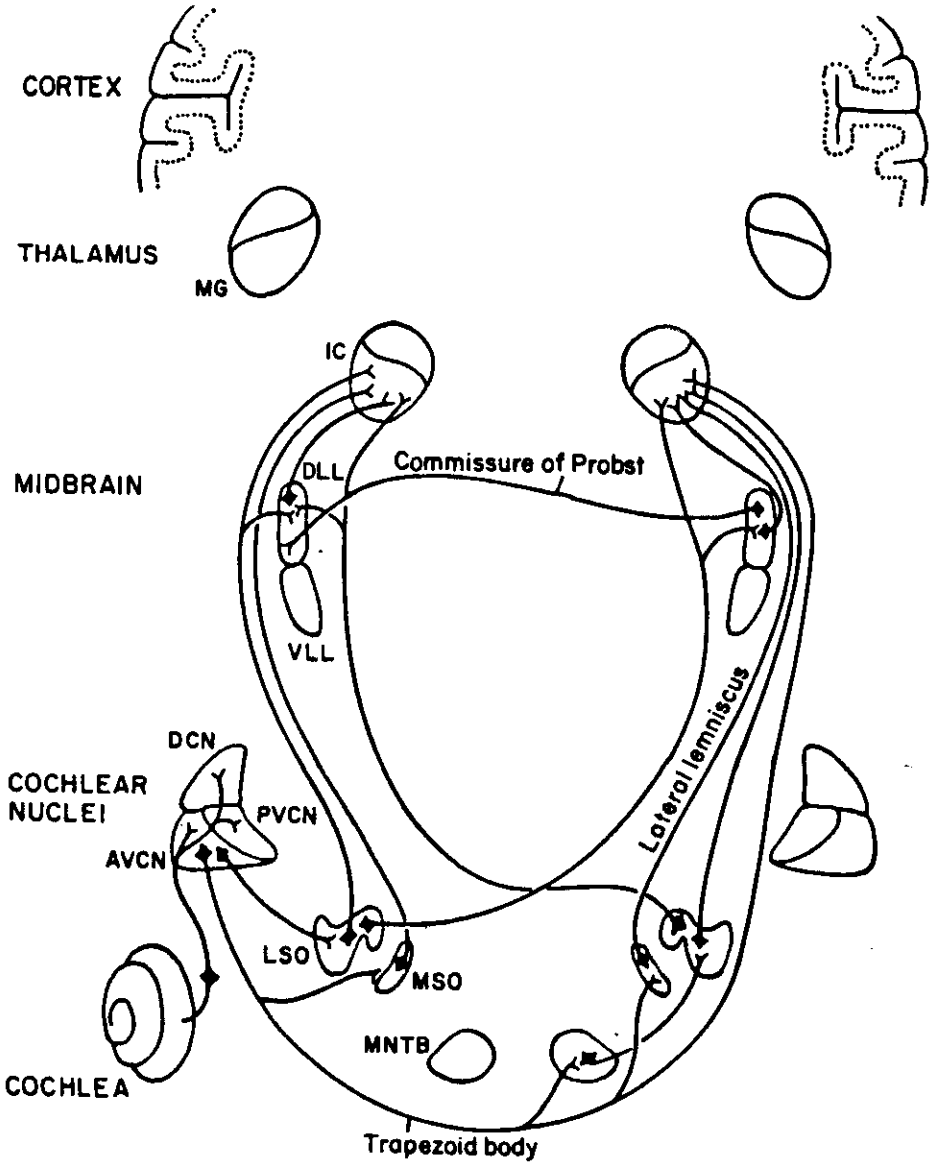


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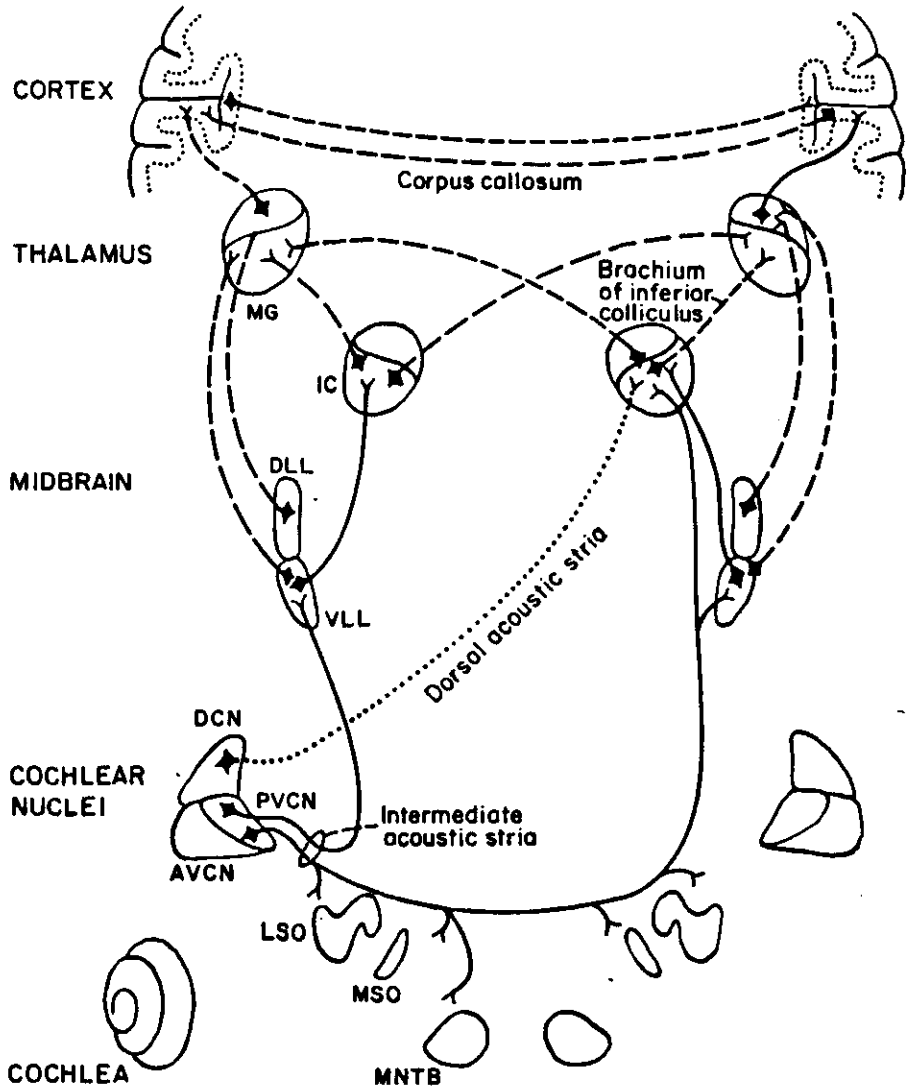


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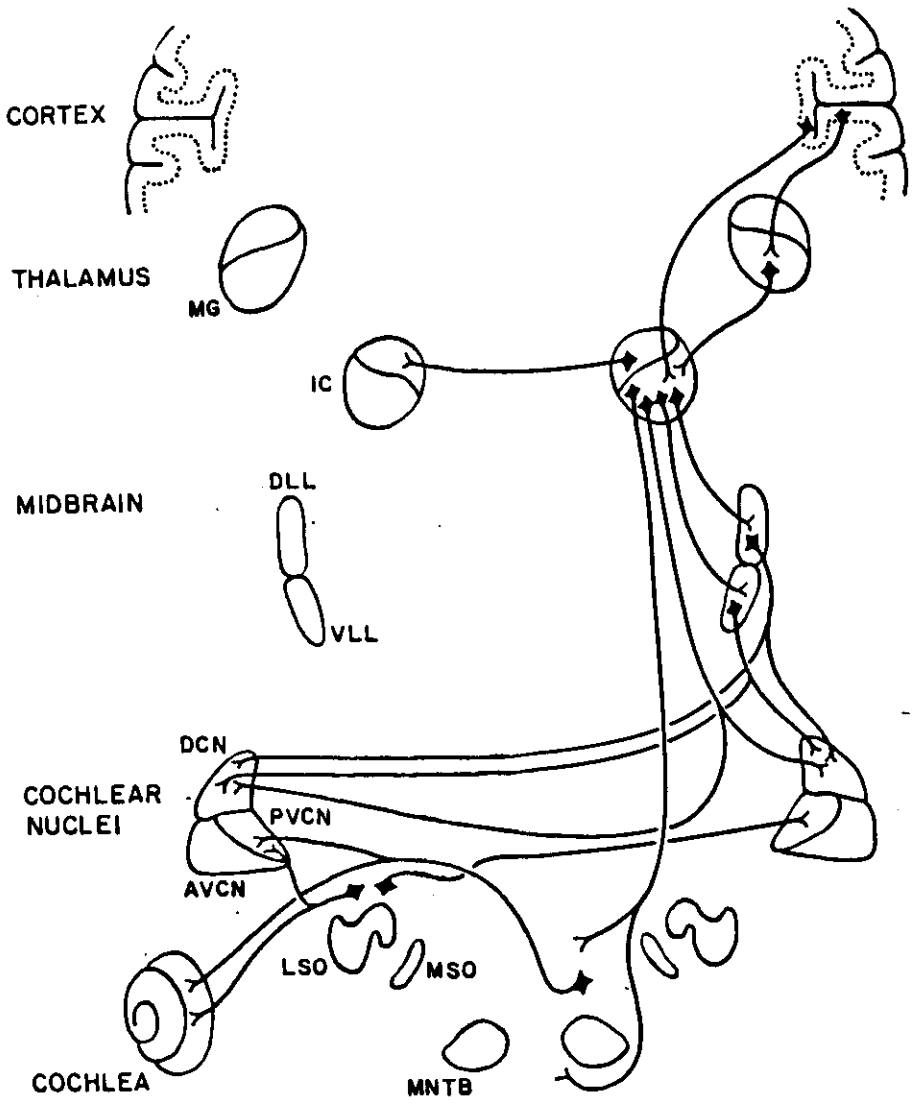


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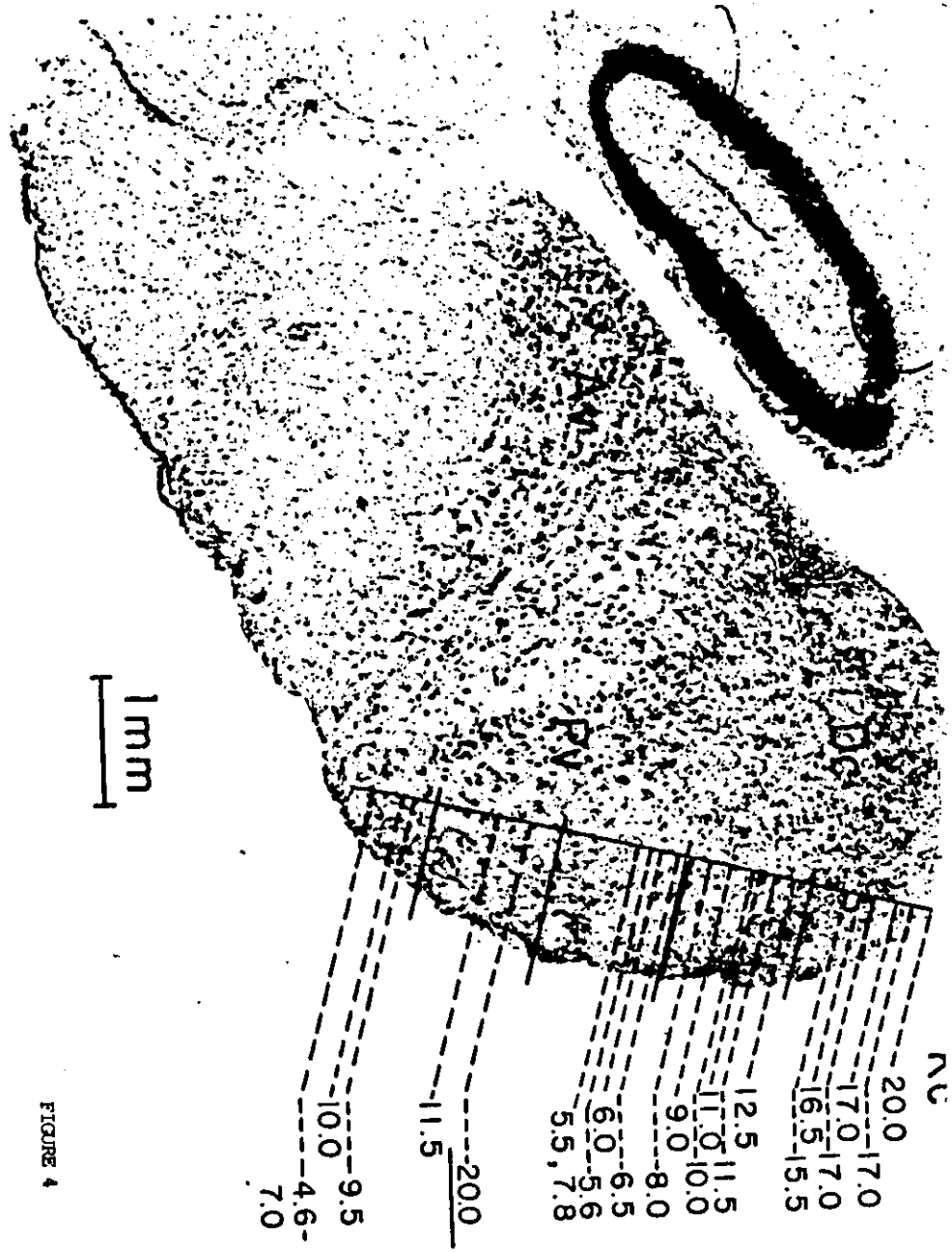


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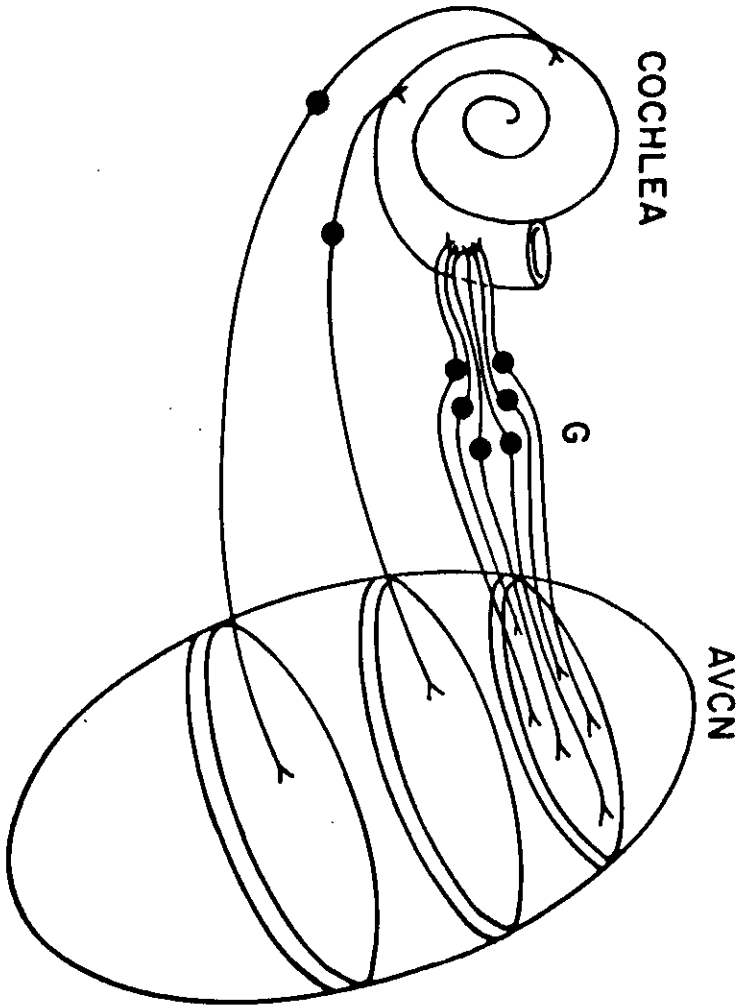


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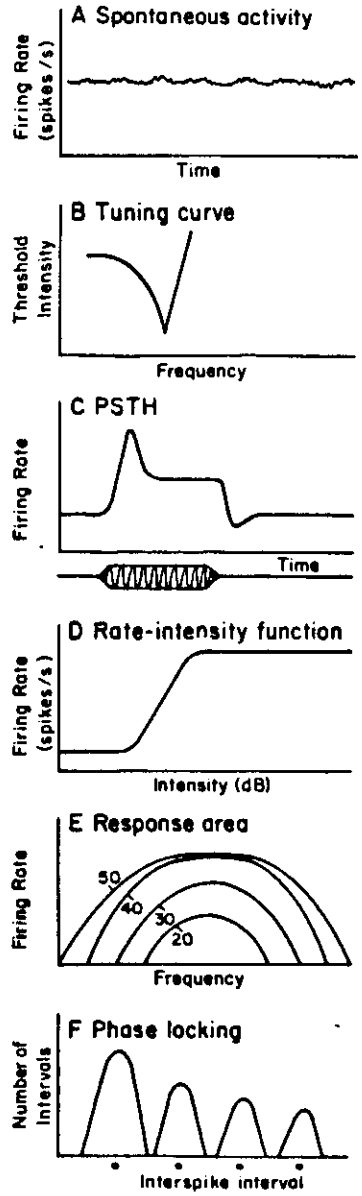


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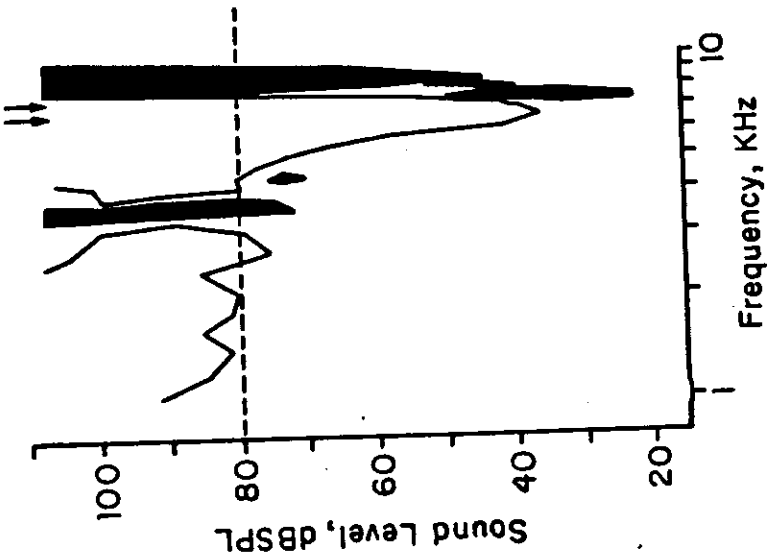


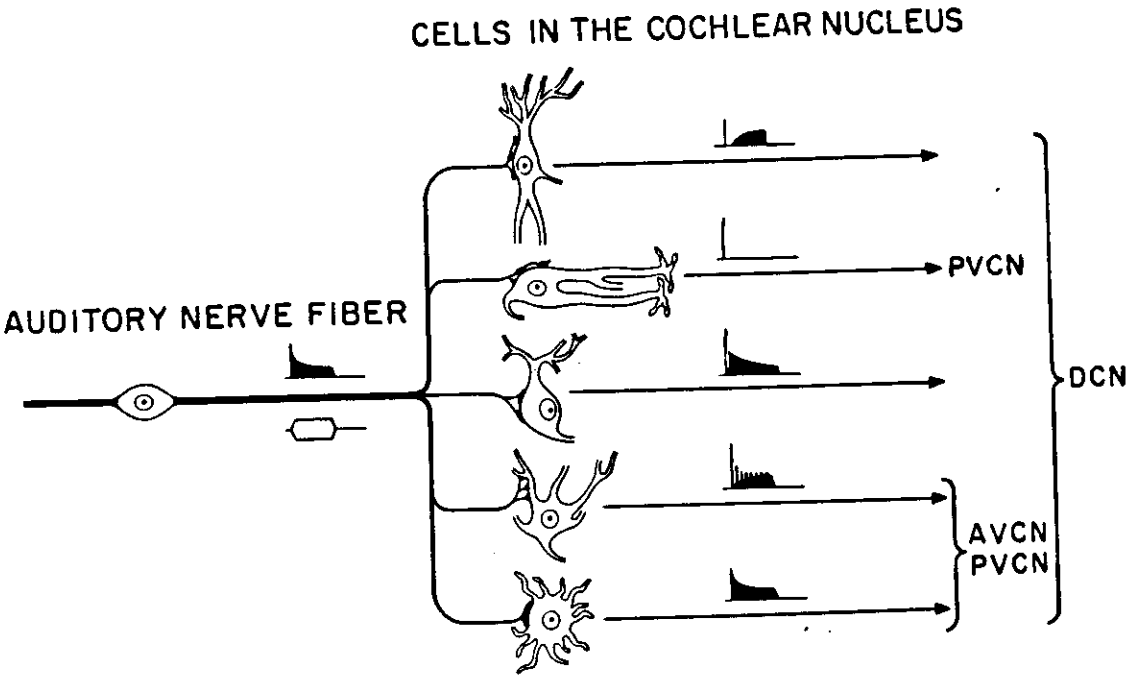


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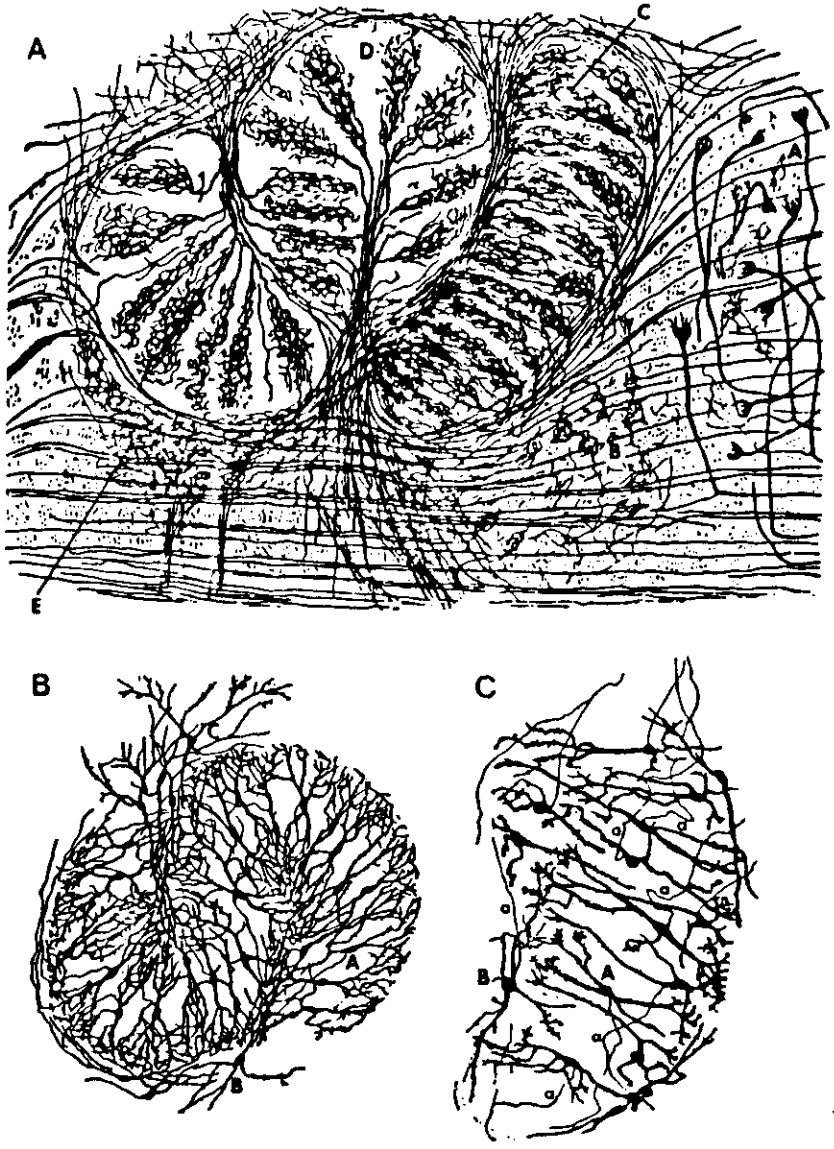


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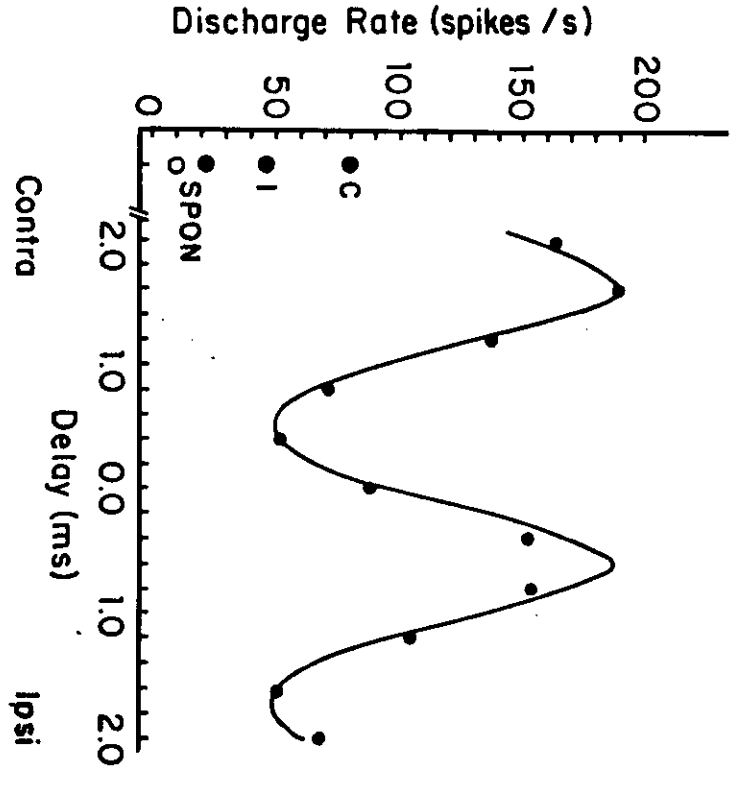


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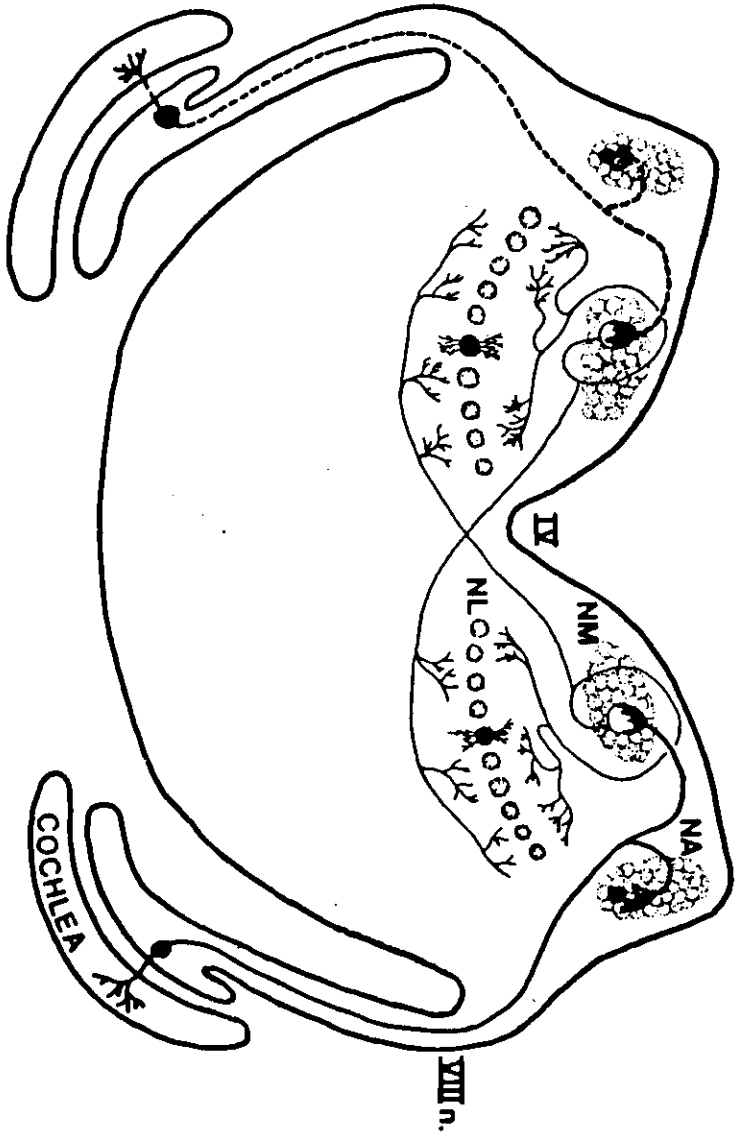


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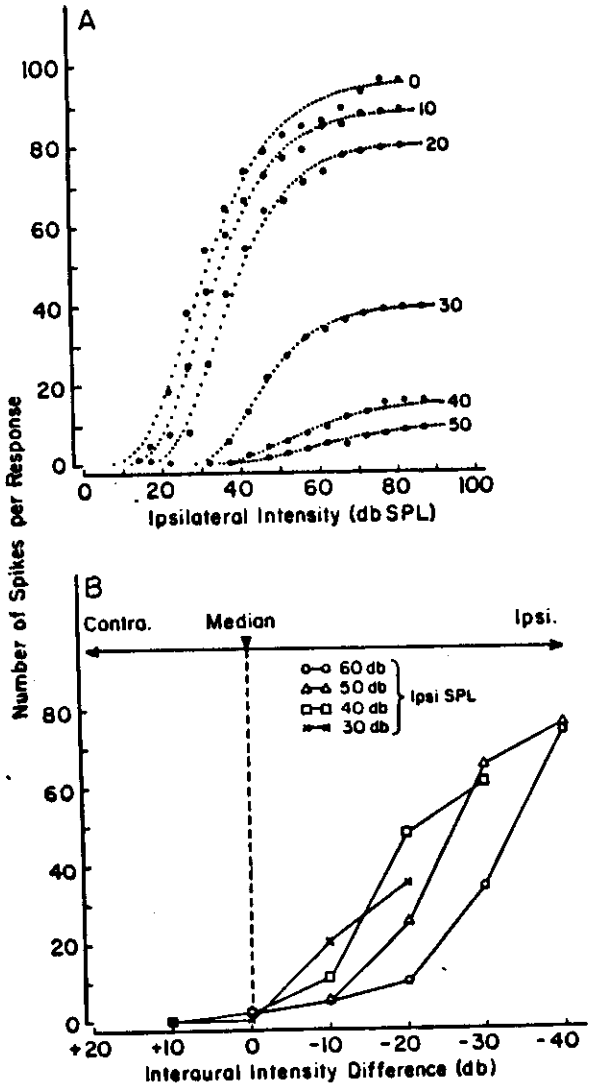


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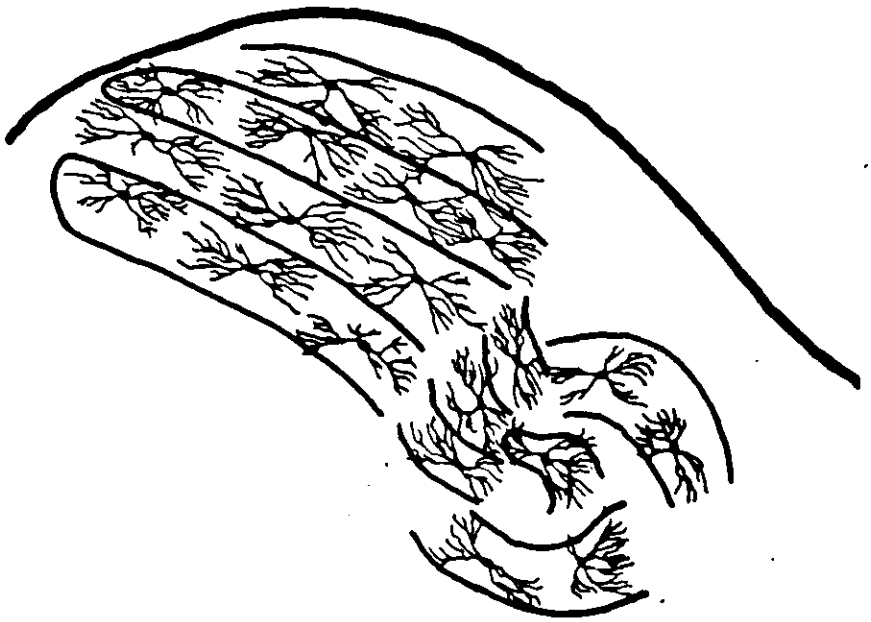

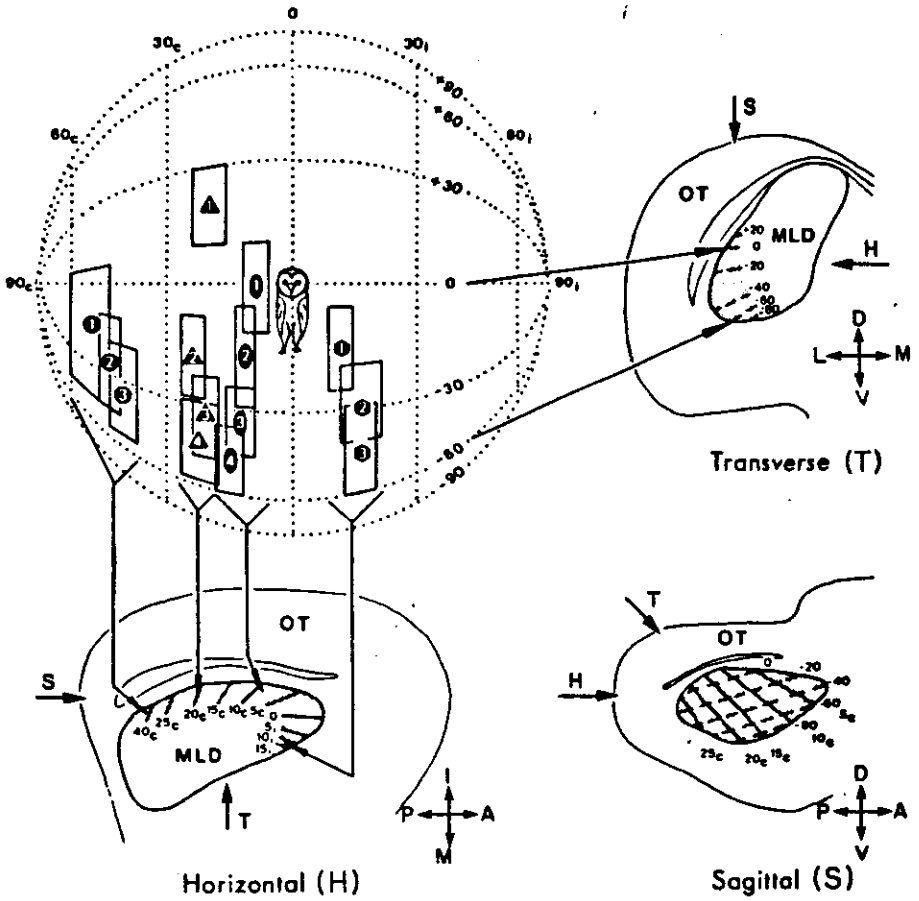


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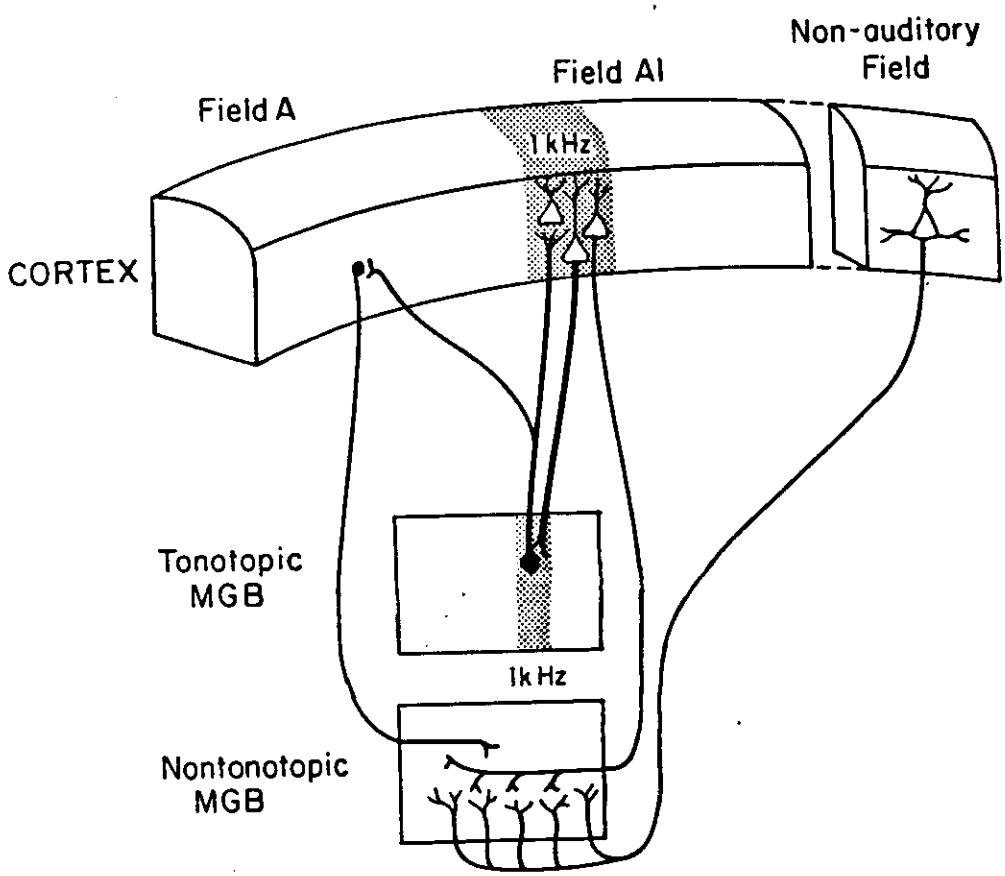


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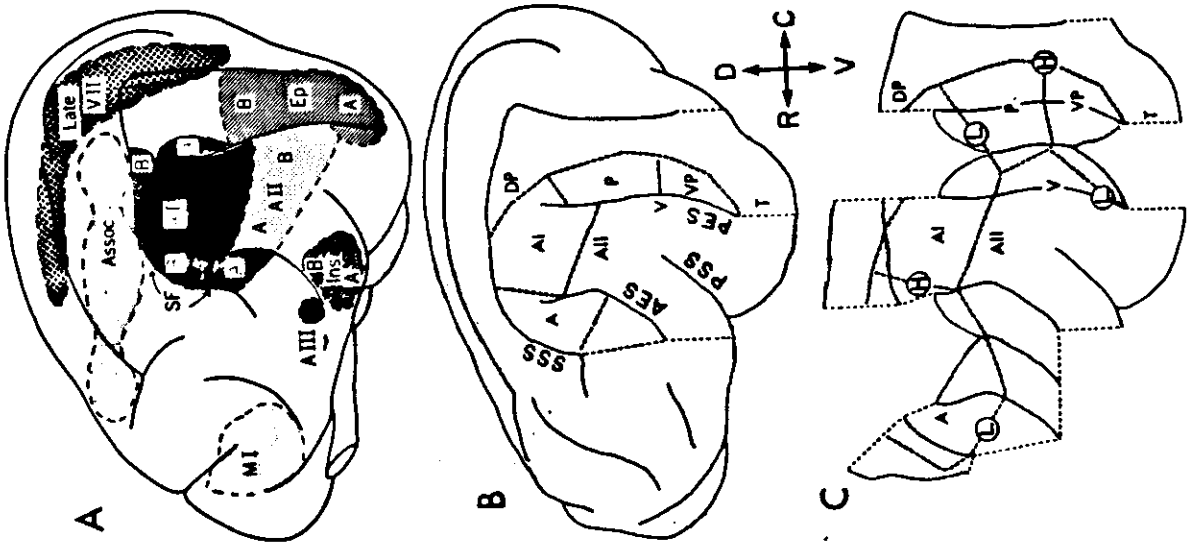

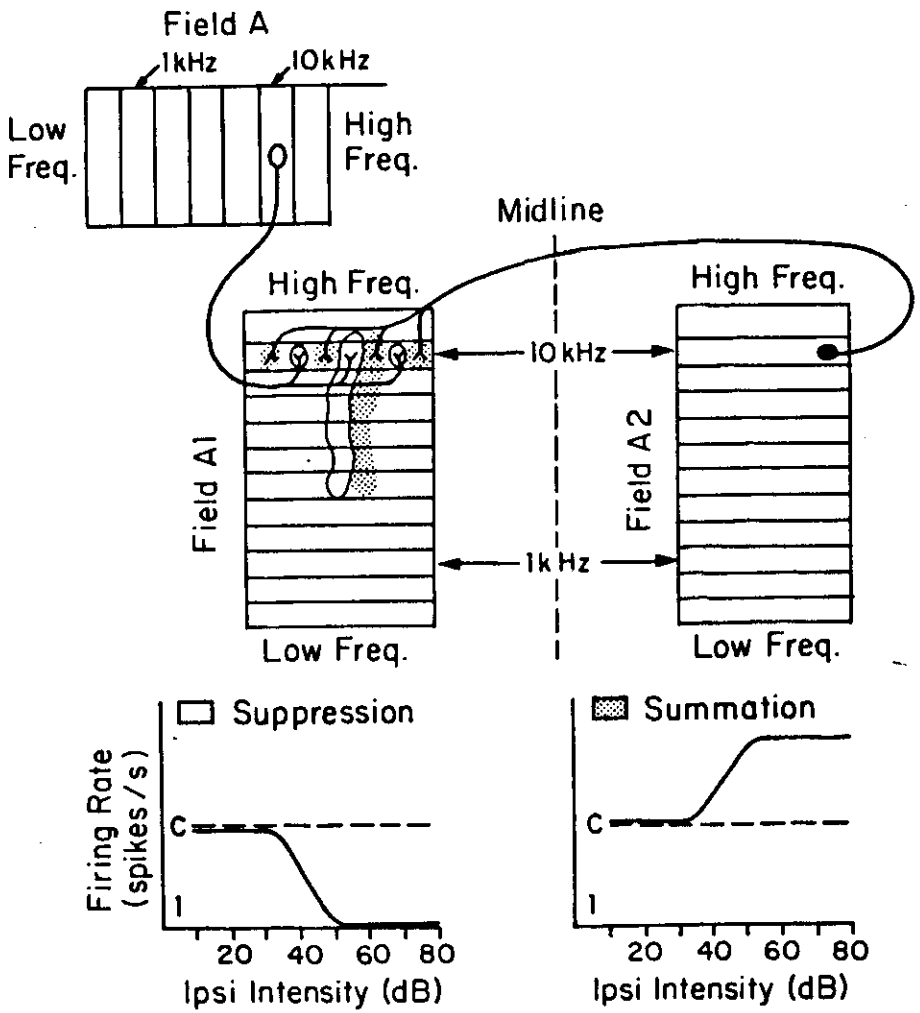


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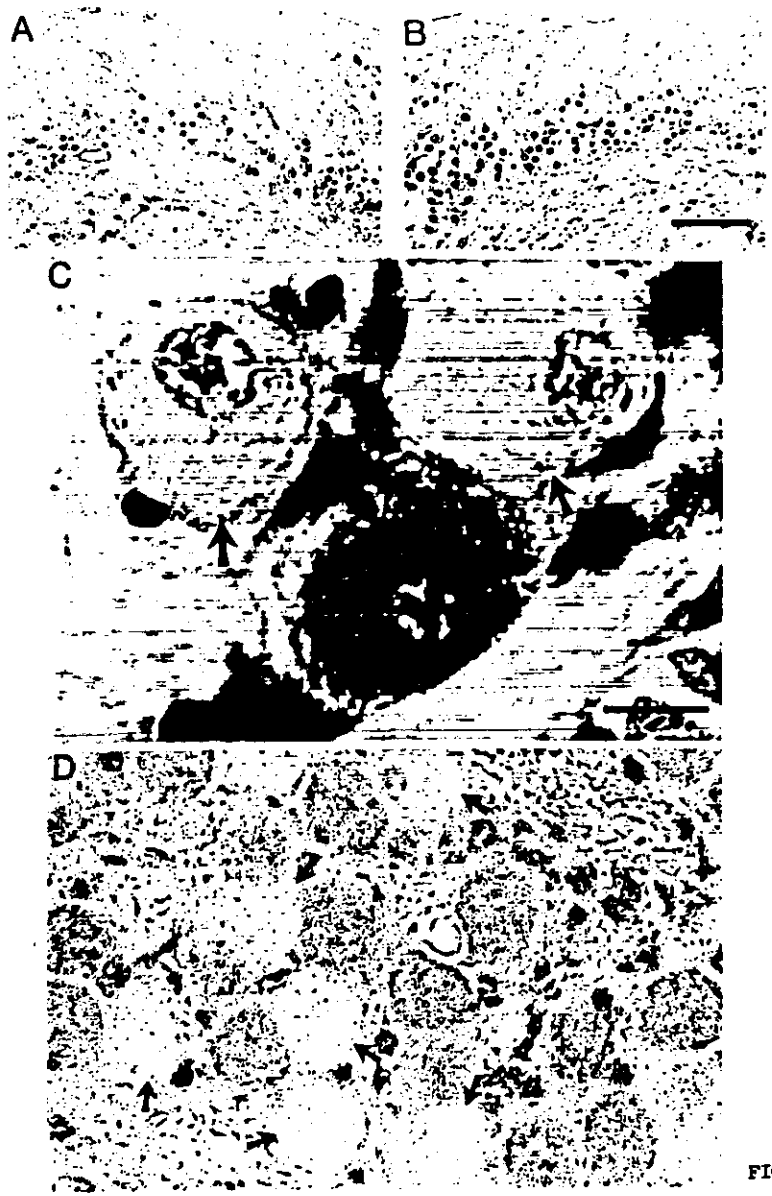


FIGURE 18