Paparella: Volume I: Basic Sciences and Related Principles

Section 2: Physiology

Part 1: Ear

Chapter 11: Neurophysiology of the Central Auditory and Vestibular Systems

The Central Auditory System

John F. Brugge

Structure and Organization

The major ascending auditory pathways of the brain stem and thalamus are shown schematically in Figure 1. In addition to these pathways, over which impulses originating in the cochlea reach the cerebral cortex, there are corticofugal connections and interneuronal circuits that, together with ascending projections, provide numerous opportunities at all levels of the auditory system for convergence and divergence of afferent input, serial and parallel processing of information, and feedback modulation. There are also connections between the principal auditory centers and the cranial and spinal motor nuclei, which subserve acoustic reflexes, but little is known about them. Finally, there is topographically patterned input to the superior colliculus and to the cerebellum, the latter receiving some of its input from the pontine nuclei activated by acoustic stimulation.

Cochlear Nuclei

All auditory nerve fibers terminate within the cochlear nuclei (CN), which comprise highly complex groupings of cells that together form a protuberance on the lateral surface of the brain stem at the medullopontine junction. From the cochlear nuclei, projection systems fan out in highly organized ways to reach cell groups in the medulla, pons, and midbrain (Brugge and Geisler, 1978; Aitkin, 1986; Irvine, 1986). In Nissl-stained material, three major cell groups are recognized in the cochlear nuclear complex of most mammalian species: the dorsal cochlear nucleus (DCN), which in earlier literature is referred to as the tuberculum acousticum; the anteroventral cochlear nucleus (AVCN); and the posteroventral cochlear nucleus (PVCN), the latter two nuclei forming the ventral ganglion. The relative sizes and cellular structure of these nuclei show great interspecies variation. Each of these subdivisions is heterogeneous in its cellular architecture. Lorente de No (1981), using the Golgi technique, showed some 50 different cell types distributed throughout the cochlear nuclear complex. Osen (1969a) used the Nissl and Glees methods to identify, in cat cochlear nuclei, nine morphologically distinct cell classes and a corresponding number of cell areas (Fig. 2A). Homologous cell classes have been described for human cochlear nuclei (Moore and Osen, 1979). Other studies resulted in slightly different schemes (Harrison and Feldman, 1970; Brawer et al, 1974). Thus, even though there is not unanimous agreement on the structural parcelling of the CN, the tripartite division and the simple

classification scheme of Osen, modified slightly, are in harmony with most other studies, and both have been widely accepted. The generally accepted major neuronal classes include bushy (spherical and globular), stellate, octopus, multipolar, fusiform, and granule (granular) cells.

Upon entering the CN, the eight nerve axons bifurcate in an orderly fashion; each fiber sends an ascending branch to the AVCN and a descending branch to terminate within the PVCN and DCN. This divergent projection pattern allows for *parallel processing* of information at an early stage. There are great differences in the structure of auditory nerve terminals and the patterns of contacts made with specific cell types (Morest et al, 1973; Moore, 19896). For instance, spherical bushy cells in the rostral portion of the AVCN are contacted by the large axosomatic calcine endings (end bulbs of Held) of the ascending branches of auditory nerve fibers (Brawer and Morest, 1975). This highly specialized synaptic arrangement, which is characterized by little convergence from disparate regions of the cochlear partition, is important in preserving temporal information transmitted by auditory nerve fibers. The descending branches of those same nerve fibers make contact as pericellular nests of boutons terminaux or boutons en passage neurons of different classes within PVCN and DCN, and here the transformations are quite different from those in AVCN. In addition to auditory nerve input, there is a rich network of interneurons that forms circuits within and between CN subdivisions (Lorente de No, 1981) along with a substantial set of afferents derived from neurons in other regions of the auditory brain stem. This morphologic heterogeneity of cell types, afferent endings, and interneurons is reflected in dramatic and varied transformations of the incoming afferent impulse train (Kiang et al, 1973; Young and Voigt, 1981; Young et al, 1988; Rhode, 1990).

Studies of cellular activity in vitro have provided new information on the synaptic events and intrinsic electrical properties that underlie integrative action in the cochlear nuclei (Oertel, 1985; Oertel et al, 1988). From this work we now know that transformation of the incoming auditory nerve signal is governed both by the spatiotemporal interactions of afferent input and by the intrinsic membrane properties of the postsynaptic neuron. Both the in vitro approach and neuropharmacologic studies of single neurons in vivo (Caspary, 1986; Caspary and Finlayson, 1990) have been important for probing the nature of the chemical events in neural transmission that take place in the cochlear nuclei. Also, although the identity of the auditory nerve neurotransmitter is not yet known, it is thought to be an excitatory amino acid (Wickesberg and Oertel, 1989).

Regardless of the terminal structure, however, auditory nerve fibers distribute in an orderly way within each subdivision. Fibers that innervate the basal coil of the cochlea project dorsally within each subdivision of the CN, whereas more apical regions of the cochlea reach targets located more ventrally (Osen, 1970). Each of the subdivisions is said to be *cochleotopically organized.* Single neurons at all levels of the auditory pathways are responsive to tones within a limited range of stimulus frequencies and intensities called the *response area.* For each cell, there is usually a single frequency to which the neuron is most sensitive. This is referred to as the *best* or *characteristic frequency (CF).* For a single auditory nerve fiber, this frequency selectivity is determined by the mechanical tuning properties of the basilar membrane. Because the tuning characteristics of the basilar membrane change as a function of distance along

the membrane, a relationship between fiber CF and cochlear place is established (Liberman, 1982). For some central auditory neurons this filter shape is retained, whereas for others the response area takes on a complex form as the result of convergent excitatory and inhibitory inputs, but it still retains a CF. Figure 3 illustrates five classes of CN neurons based on the structure of the response area. In this figure, dashed lines outline the inhibitory regions, whereas stippled areas designate excitatory areas. These complex response areas result from excitatory-inhibitory interactions between activity of directly projecting afferents and that of interneurons.

The *tonotopic (or cochelotopic) organization* of the basilar membrane and auditory nerve array is preserved within the cochlear nuclei and other principal synaptic stations of the auditory pathway (Aitkin, 1976). The results of an experiment in which the distribution of CF, and hence cochlear loci, was mapped within the CN are seen in Figure 2B. A microelectrode penetrating the AVCN encounters neurons whose CFs make an orderly high-to-low sequence. On the basis of a large number of such experiments, it is clear that precise tonotopic arrangements exist in each of the three major subdivisions and that within each frequency representation, high frequencies (cochlear base) are found dorsally and low frequencies (cochlear apex) are found ventrally, in agreement with the cochlear projection pattern (Rose et al, 1960). Tonotopy is, thus, considered to be a "place" mechanism by which frequency information is preserved in the central auditory system.

Axons of second-order neurons in the CN, in addition to making inter- and intranuclear contacts, form three main bundles: the dorsal acoustic stria (stria of Monakow), the intermediate acoustic stria (stria of Held), and the ventral acoustic stria (trapezoid body). The dorsal stria is essentially a crossed pathway by which cells in the DCN project to the nuclei of the lateral lemniscus and the central nucleus of the inferior colliculus. The intermediate stria originates mainly in the PVCN and projects to preolivary cell groups bilaterally, whereas the trapezoid body, arising from cells in the AVCN and PVCN, reaches the major cell groups of the superior olivary complex. Some fibers of both striae terminate in or send collaterals to the nuclei of the lateral lemniscus; the remainder terminate in the central nucleus of the inferior colliculus (Irvine, 1986).

Superior Olivary Complex

The superior olivary complex (SOC) includes a number of closely grouped nuclei that span the ventrolateral region of the pons. Cells in these nuclei receive massive input from the AVCN and PVCN, form local circuits, and send axons to the midbrain via the lateral lemniscus (Irvine, 1986). Four of the nuclei are easily recognized in Nissl-stained material in most mammalian species. The most conspicuous of these nuclei in the cat is the S-shaped *lateral superior olivary nucleus (LSO).* Nearby is a curved band of spindle-shaped cells, the *medial (accessory) superior olivary nucleus (MSO).* These two cell groups are both prominent in nonprimate species, but in monkeys, and humans, the MSO constitutes a major part of the SOC, and the LSO is relatively small (Moore and Moore, 1971; Strominger and Hurwitz, 1976; Strominger, 1978). A third cell group, lying within the fibers of the trapezoid body, is the *medial nucleus of the trapezoid body (MNTB),* referred to in the earlier literature simply as the nucleus

of the trapezoid body. The *preolivary nuclei* comprise a broad band of cells that curves around the MSO and LSO. Scattered groups of cells around the MSO and LSO are collectively referred to as the *periolivary nuclei.* It is within the SOC that binaural convergence first occurs and that neural mechanisms for sound localization are first established.

Cells of the LSO are multipolar, with flattened, two-dimensional dendritic fields that run for considerable distances in the rostrocaudal direction (Scheibel and Scheibel, 1974). The LSO receives bilateral innervation. The ipsilateral input comes via the trapezoid body from the AVCN (Stotler, 1953; Warr, 1966). In the cat, the small spherical cells of AVCN are the major contributors to this pathway (Osen, 1969a). The ipsilateral pathway is almost exclusively excitatory, and the projection is highly organized tonotopically, as shown in Figure 4B (Tsuchitani and Boudreau, 1966; Guinan et al, 1972b; Tsuchitani, 1977). It appears that neurons within the LSO are most sensitive to stimulus frequencies greater than about 5 kHz, in contrast to the MSO, which has a prominent low-frequency representation. The contralateral pathway originates from globular bushy cells in the caudal AVCN and the rostral PVCN (Tolbert et al, 1982) and reaches the LSO via an inhibitory interneuron in the MNTB. There is now considerable evidence to support the hypothesis that glycine is the neurotransmitter of MNTB neurons mediating inhibition in the LSO (Caspary and Finlayson, 1990). The principal cells within the MNTB receive the large axosomatic calyces of Held that stem from the largest fibers of the trapezoid body (Morest, 1973). Each principal cell receives one calyx, and each calyx embraces only a single principal cell. The electrophysiologic characteristics of this region indicate secure short-latency transmission at this synapse so that the onset times for direct ipsilateral excitation and indirect contralateral inhibition of the LSO are the same.

Bushy cells within the contralateral and ipsilateral AVCN project directly upon the medial and lateral dendrites, respectively, of MSO neurons in the cat (Stotler, 1953; Warr, 1966), rat (Harrison and Feldman, 1970), dog (Goldberg and Brown, 1968), and rhesus monkey (Strominger and Strominger, 1971). In an arrangement similar to that found in the LSO, incoming axons branch predominantly within horizontal layers between the elongated and flattened MSO neurons (Morest, 1973; Scheibel and Scheibel, 1974; Schwartz, 1984). Most binaurally activated MSO cells are excited by stimulation of either ear (Yin and Chan, 1990), and the available data suggest that an excitatory amino acid is the neurotransmitter at these synapses (Caspary and Finlayson, 1990). The nucleus is tonotopically organized (Fig. 4A), and the single-cell discharge patterns in many ways resemble those of the large bushy cells of the rostral AVCN, which are believed to be the sources of MSO input (Goldberg and Brown, 1969; Guinan et al, 1972a).

The AVCN and PVCN are the principal sources of afferent input to the medial (MPO) and lateral (LPO) preolivary nuclei. The LPO is activated almost exclusively by ipsilateral stimulation, whereas the MPO probably receives it input from the CN of both sides. The MPO also receives descending inputs from the inferior colliculus and possibly the nuclei of the lateral lemniscus (Rasmussen, 1964; Moore and Goldberg, 1966).

The periolivary nuclei comprise as many as six separate cell groups that receive afferent input from the PVCN and the DCN over the three acoustic striae (Warr, 1966, 1969; Fernandez

and Karapas, 1967; Morest, 1968, 1973). One of these cell groups, the dorso-medial periolivary nucleus (DMPO) receives afferent input not only from the CN but also from the MNTB and the inferior colliculus. There is a great variety of neuronal response patterns in this area, perhaps because of the overlapping afferent input from different cell types within the CN (Guinan et al, 1972b; Tsuchitani, 1977). Anatomic tracer studies have shown that many neurons in this territory, which surrounds the LSO and MSO, project back to the cochlea as two systems, medial and lateral, to the regions beneath the inner and outer hair cells (Warr, 1975; Guinan et al, 1983). These observations agree with the electrophysiologic findings that single-cell discharges in this region are often similar to those of olivocochlear fibers (Guinan et al, 1972b). Moreover, some periolivary neurons also send axons to the CN.

In summary, all auditory nerve fibers terminate within the cochlear nuclei, the first synaptic stations in the ascending auditory pathways. Here all information encoded in trains of all-or-none action potentials in first-order afferent fibers is received and recorded. Neurons of the SOC are principal targets for cells located throughout the AVCN and are among the first to receive and process binaural input. Reciprocal connections between these two brain stem neuronal complexes are the bases for feedback loops, and a pathway from the SOC to the cochlear hair cells provides a route for central control of peripheral sensory coding.

Nuclei of the Lateral Lemniscus

The lateral lemniscus is a pathway coursing rostrally in the lateral part of the brain stem that connects second- and third-order neurons of the CN and SOC with the inferior colliculus of the midbrain. Intermingled with fibers of this pathway are two distinct cell groups, the *dorsal* (DNLL) and *ventral* (VNLL) nuclei of the lateral lemniscus. Within the VNLL, several overlapping subdivisions may be identified on the basis of cytoarchitecture and connectivity patterns (Irvine, 1986).

The major sources of input to the DNLL are the ipsilateral MSO and the ipsilateral and contralateral LSO. The ascending afferents to the VNLL, in contrast, arise mainly from the contralateral AVCN and PVCN, with smaller contributions being derived from the SOC (Glenndening et al, 1981). Axons of neurons in the DCN that cross the brain stem in the dorsal acoustic striae occupy a medial position in the lateral lemniscus. Some of these axons terminate on cells in the VNLL, whereas others, on their way to the inferior colliculus, give off collaterals to cells in the DNLL. Along with axons of some cells in the dorsal nucleus, lemniscal fibers cross the midline in the intercollicular commissure (of Probst) to end in the DNLL or inferior colliculus of the opposite side (Goldberg and Moore, 1967).

Aitkin and colleagues (1970) have shown that the great majority of neurons in the DNLL are affected by binaural stimulation, whereas most cells in the VNLL are affected only by stimulation of the contralateral ear. Both the dorsal and ventral nuclei are organized tonotopically. Within each nucleus, cells with a low best frequency are located dorsally and those with a high best frequency are situated ventrally (Fig. 5). Because of the structural complexity of the VNLL, however, there is some question about how the available tonotopic data on that nuclear complex

should be interpreted (Irvine, 1986).

Inferior Colliculus

The inferior colliculi are imposing bilaterally symmetric structures that form a part of the midbrain tectum (Aitkin, 1986; Irvine, 1986). The main cell mass of the inferior colliculus is the *central nucleus* (ICC), which is an obligatory relay station on the lemniscal pathway between the lower brain stem and the forebrain (Fig. 5). The ICC is composed of two basic neuronal types, based on observations in Golgi-stained material: neurons with disc-shaped dendritic fields and stellate neurons with dichotomously branched, spherical-shaped dendritic fields (Oliver and Morest, 1984). On the basis of its cytoarchitecture and fiber connections, the ICC can be further subdivided into dorsomedial and ventrolateral regions (Geniac and Morest, 1971; Rockel and Jones, 1973a and b; FitzPatrick, 1975). The dorsomedial division consists mainly of large multipolar cells and receives fibers from the auditory cortex, lateral lemniscus, and contralateral inferior colliculus. The ventrolateral division, conversely, contains small to medium-sized neurons and is the major recipient of lemniscal afferents. Cells in the ventrolateral division have disc-shaped dendritic fields, which tend to be oriented in such a way that in Golgi-stained material they give this region a pronounced laminar appearance.

Fibers of the lateral lemniscus enter the ventrolateral division parallel to the flattened disc-shaped neurons and terminate on their somata and proximal dendrites. This laminar arrangement of cells, dendrites, and incoming afferent fibers is highly correlated with the tonotopic organization of the ICC; the plane of orientation of cellular laminae is the same as that of the isofrequency planes worked out electrophysiologically (Merzenich and Reid, 1974; FitzPatrick, 1975). Multipolar cells with dendrites that lie across these laminae may form the basis for interactions among neurons located within different isofrequency planes.

Retrograde tracer studies have shown that the ICC receives afferent input from most cell types within the three subdivisions of the contralateral CN (Roth et al, 1978). Within the SOC, the major collicular afferent fibers stem from the LSO and MNTB bilaterally and the MSO ipsilaterally. The sources of cerebral cortical input are primarily layer V pyramidal cells.

The region surrounding the ICC has been divided on the basis of Nissl cytoarchitecture into two areas: the *pericentral nucleus* (ICP) and the *external nucleus* (ICX). Other, more elaborate parcelling schemes have been advanced (Morest and Oliver, 1984). In contrast to cells in the ICC, which as a rule are sharply tuned and have well-defined best frequencies, ICP and ICX neurons have very broad response areas (Aitkin et al, 1975). The ICX and ICP may be tonotopically organized (Rose et al, 1963; Aitkin et al, 1975), although neither nucleus receives significant direct lemniscal input. The ICP receives a projection from the auditory cortex (Jones and Rockel, 1973). The ICX may receive a projection from the ICC (Jones and Rockel, 1973; Goldberg and Moore, 1967) as well as from the dorsal column nuclei (Hand and Van Winkle, 1977). Aitkin and his colleagues (1979) showed that within the ICX there is a sizeable number of cells that are activated by both somatosensory and auditory input and thus are concerned with the integration of information pertaining to two sensory modalities. It is also known that auditory

information is relayed via multisynaptic pathways to the spinal cord (Buser et al, 1966; Wright and Barnes, 1972). Thus, integration of auditory and somatic information may be necessary to coordinate body movements toward or away from a sound source of significance to the behaving animal.

Ascending projections of the inferior colliculus can be divided into two major components. One of them, the intercollicular commissure, arises mainly from the dorsal part of the ICC. Many of its fibers terminate in the dorsal part of the opposite ICC, whereas others enter the contralateral inferior brachium. The second major component is the brachium of the inferior colliculus, a large ipsilateral pathway, which runs from the inferior colliculus to the medial geniculate body (MGB) of the thalamus, giving off fibers along the way to the ICX, the parabrachial region of the midbrain tegmentum, and the interstitial nucleus of the inferior colliculus. The MGB projection is bilateral and highly organized topographically (Anderson et al, 1980).

Superior Colliculus

The superior colliculus (SC) is a midbrain structure that receives sensory input from a wide range of sources. The superficial layers are almost exclusively visual, whereas neurons in the deep and intermediate layers exhibit multimodal response properties. Auditory input converges from auditory cortex, inferior colliculus and its brachium, periolivary groups, and the ventral nucleus of the lateral lemniscus. The output pathways mediate movements of the eyes, ears, head, and neck. Thus, the SC is considered to be a coordinator of movement direction in response to a sensory stimulus. Neurons in the intermediate and deep SC respond to tones and noise delivered monaurally or binaurally (Wise and Irvine, 1983, 1984; Hirsch et al, 1985). At high frequency they exhibit IID sensitivity and at low frequency they exhibit ITD sensitivity similar to that recorded in other regions of the auditory system. The role of the SC in possible visuo-auditory integration is not well understood. Nonetheless, electrophysiologic studies suggest a possible topographic organization of IID sensitivity in SC and a representation of auditory space (Palmer and King, 1985; Middlebrooks, 1988).

Medial Geniculate Body

The medial geniculate body (MGB) is the main auditory relay station of the thalamus. It is parcelled into three major divisions based on its cellular and fiber architecture (Morest, 1964). They are the *ventral*, *dorsal*, and *medial* divisions (Fig. 6). The ventral division is further divided into a pars ovoidea and pars lateralis, and the dorsal division is divided into dorsal, deep dorsal, and suprageniculate nuclei. Through its brachium, the inferior colliculus reaches the medial and ventral divisions as well as the lateral part of the posterior nuclear group.

The ventral division, sometimes referred to as the caudal portion of the *pars principalis*, is composed of only two neuron types, geniculocortical (principal) cells and short-axon Golgi type II neurons. The ventral division receives a massive input from the inferior colliculus and projects tonotopically, in turn, to the auditory cortex. The projection to the MGB is tonotopically

organized in a highly complex way (Aitkin and Webster, 1971; Calford and Webster, 1981; Imig and Morel, 1985, 1988). Morest (1975) has analyzed some of the synaptic organization of the ventral division by light and electron microscopy (Fig. 7). Ascending axons from the inferior colliculus end directly upon dendrites and somata of geniculocortical neurons and reach these same cells indirectly via intermediate Golgi type II cells. Most ascending axons terminate on intermediate dendrites within "synaptic nests", which are special aggregations of axonal endings and dendritic processes that are partially separated from the surrounding neuropil by glial lamellae. The geniculocortical projection is reciprocated by a point-to-point corticogeniculate pathway (Merzenich et al, 1982). Corticofugal fibers enter the ventral division in distinct parallel order between curved cell laminae and terminate upon dendrites of geniculocortical neurons in the neuropil between the synaptic aggregates formed by axodendritic and axoaxonal contacts of fibers arising in the brachium of the inferior colliculus (Jones and Rockel, 1971). They also terminate on dendrites and somata of Golgi type II cells (Morest, 1975).

Cells within the dorsal division of the MGB receive relatively little colliculogeniculate input. Rather they receive ascending input through a lateral tegmental system from diffusely arranged nuclei in the midbrain in the vicinity of the brachium of the inferior colliculus (Morest, 1965) and project to nonprimary auditory cortex (Morest, 1965). Like the ventral division, the dorsal division receives corticogeniculate input. However, it contains four different neuron types and a highly complex synaptic organization. Aitkin and Webster found very little tone-evoked activity in the dorsal division of anesthetized cats (Aitkin and Webster, 1972; Aitkin, 1973).

The medial division of the MGB (MGm) also receives a strong projection from the inferior colliculus and, in the cat, some colliculogeniculate fibers end in the lateral part of the posterior thalamic group as well (Moore and Goldberg, 1963, 1966). The MGm is part of a pulvinar-posterior (Pul-PO) complex that also includes the pulvinar, nucleus posterior, and nucleus lateralis posterior, along with the remainder of the posterior nuclear group. Responsive neurons in the PO are generally sharply tuned to tonal stimuli, whereas neurons recorded in the MGm are typically broadly tuned (Aitkin, 1973; Phillips and Irvine, 1979). Some cells in the MGm are excited by somatosensory, auditory, and vibratory stimuli, and some are driven by electrical stimulation of the vestibular nuclei. Thus, the medial division of the MGB appears to integrate information from several sensory modalities, and because of strong binaural input to this region, this information may be useful in localizing the sources of biologically significant sounds. The Pul-PO is considered part of a "lemniscal adjunct" system standing alongside the lemniscal pathways.

Auditory Cortex

Detailed microelectrode mapping coupled with the use of powerful neuroanatomic tracer techniques has greatly expanded our knowledge of the organization of auditory fields of the cerebral cortex (Brugge, 1975; 1982; Imig et al, 1982; Brugge and Reale, 1985). Figure 8 illustrates the locations and boundaries of auditory cortical fields in cat and monkey. These recent studies build on the organizational framework of the cortical auditory system obtained by earlier work using evoked potentials in a large number of mammalian species (Woolsey, 1971).

Area AI

The core of the auditory cortex is the primary field, AI. Its essential tonotopic organization is now well established from evoked potential and microelectrode mapping studies in a wide variety of mammals (Fig. 9). In the monkey (Merzenich and Brugge, 1973; Imig et al, 1977), cat (Rose and Woolsey, 1949), and squirrel (Merzenich and Kaas, 1976), area AI has been shown to be confined to a single cytoarchitectonic field of koniocortex. The primary receiving area in primates is located on the superior temporal gyrus within the lateral fissure. Although this area has not been mapped in any detail in humans, the region of koniocortex that occupies the transverse gyrus of the superior temporal lobe (Heschle's gyrus) is most likely the homologue of area AI in the monkey. Celesia (1976) used computer averaging techniques to record evoked responses to tones and clicks in and around this region in patients during surgical treatment of temporal lobe seizures (Fig. 10). The latency of the initial component of the click-evoked complex waveform recorded on the region believed to be AI is between 8.4 and 10 msec, which is the range of latencies recorded for AI in experimental animals.

In addition to an orderly frequency representation, other spatial organizations may exist in AI. One of them may relate to the sensitivity of AI cortical neurons to stimulus intensity. Many auditory cortical neurons are maximally excited within a relatively narrow range of intensities (Brugge and Merzenich, 1973). The center of this range may be termed the "best amplitude" for that cell, and different neurons have different best amplitudes. In the bat, best amplitudes, as well as best frequencies, vary in a systematic way with the location of the neurons so that on the cortical surface there are overlapping tonotopic and "ampliotopic" representation axes (Suga, 1977).

Most neurons within a radial cell column have the same best frequency, as is shown in Fig. 11. They also respond very similarly to binaural stimulation (Imig and Adrian, 1977; Middlebrooks et al, 1980). About two thirds of cell columns identified electrophysiologically within the high-frequency representation of cat AI are classified as *summation,* or *EE,* columns, ie, neurons throughout the column respond to stimulation of each ear, and the response to binaural stimulation is greater than that to stimulation of either ear alone. The remaining one third of cell columns contain neurons that are excited by stimulation of one ear and *suppressed* by stimulation of the other (*EI* columns). Both *summation* and *suppression* columns may be composed of aggregates of smaller functional columns with special physiologic properties. The sizes and configurations of binaural interaction columns vary. Some of the occupy several square millimeters of cortex and their configuration consists of strips oriented orthogonally to isofrequency contours. A similar segregation of binaural function with the auditory cortex has been described in the bat (Manabe et al, 1978).

Auditory cortical neurons receive input from a variety of sources and send corticofugal fibers to targets in the thalamus, midbrain, and pons, as well as to cortical areas of the same and opposite hemispheres (Brugge and Reale, 1985). The circuitry of these neuronal networks is not completely known, but accumulated anatomic and physiologic evidence points to the presence of multiple reciprocal interconnections, indirect feedback loops, and interneuronal contacts.

Area AI receives a direct convergent input from several groups of all three divisions of the MGB and, in turn, AI sends reciprocal connections to these MGB nuclei (Merzenich et al, 1982; Imig and Morel, 1983, 1984). All of these reciprocal connections between AI and MGB are topographically related to the cochleotopic organization of the primary field. In addition to these pathways, there are nonreciprocal corticofugal projections to the corpus striatum, reticular nucleus, superior colliculus, parabrachial region, midbrain tegmentum, and pons.

Auditory corticofugal fibers also terminate within the ICC and ICP of the inferior colliculus of the same and opposite sides (Diamond et al, 1969; Jones and Rockel, 1973; Rockel and Jones, 1973a and b; Merzenich et al, 1982). The laminated ventral division of ICC, which is an obligatory synaptic station in the ascending lemniscal pathway, receives a sparse corticofugal input, whereas the dorsomedial division receives a relatively heavy input from the auditory cortex. Thus, the MGB, the posterior nuclear group of the thalamus, and the inferior colliculus form links in a chain of descending pathways to lower auditory centers and, possibly, to the cochlea.

Auditory area AI makes topographically organized corticocortical connections with auditory fields of the same and opposite hemispheres (Imig et al, 1982; Brugge and Reale, 1985). Interhemispheric connections of the two primary fields are made largely via layer III pyramidal cell axons within the corpus callosum. The entire frequency spectrum is represented in the projection. However, different cell columns within AI contribute differently to the callosal pathway. Cells in binaural summation columns contribute significantly more axons to the corpus callosum than do cells in binaural suppression columns. Suppression columns contain high concentrations of cell coding for sound source location in the opposite hemifield. Thus, each cerebral hemisphere contains a representation of one auditory hemifield relatively independent of the representation of the other.

Auditory Areas Surrounding AI

A belt of auditory responsive cortex surrounds AI, as seen in Figure 8. In the cat and monkey, several tonotopically organized areas have been identified by microelectrode mapping and neuroanatomic tracer methods (Imig et al, 1982). Like AI, these fields make complex topographically organized interconnections with the MGB, ICC, and auditory cortical fields on the same and opposite hemispheres.

Outside this central zone of auditory cortex are the insular and temporal areas and, in the dog, the third auditory area (AIII) of Tunturi. In the suprasylvian and anterolateral gyri and in the sensorimotor cortex of the cat, evoked responses to clicks are not abolished by removal of all auditory cortex below the suprasylvian sulcus or by interruption of the brachium of the inferior colliculus. Thus, these cortical fields are activated over pathways independent of those leading to the classic auditory fields. Neurons in these regions may provide convergent auditory, visual, and somatic sensory system, hence the names polysensory and nonspecific have been applied to them (Irvine and Phillips, 1982). Typically cells here have high thresholds to pure tones and are broadly tuned. These and other properties identify them with input from medial

intralaminar nuclei or the posterior-pulvinar complex of the thalamus, which are part of a nonlemniscal, or "lemniscal adjunct" system of pathways ascending to cortex from the brainstem.

Experiential Response of Humans to Activation of the Auditory Cortex

It has been known for a long time that auditory hallucinations in humans sometimes accompany seizures resulting from lesions of the temporal lobe. Auditory auras may take the form of crude or vague sounds, such as the ringing bells, hissing of steam, or rumbling of a train. Some may be more highly elaborated and extensive, such as the sound of voices or music. Furthermore, they may be recognized by the patient as coming from the past and may include the sight, sound, and accompanying emotions of a past time. Penfield and Perot (1963) refer to these latter phenomena as "experiential hallucinations", and they have produced many types of them by electrically stimulating small regions of the temporal lobes of humans undergoing neurosurgical operations under local anesthesia. Most auditory hallucinations are evoked on the lateral and superior surfaces of the first temporal lobe (Fig. 12). None is brought out by stimulation of the anterior transverse gyrus, the presumed site of the primary auditory field, in which only crude auditory sensations, eg, buzzing or whistling, are evoked. Stimulation within the large speech area of the temporal lobe of the dominant hemisphere never produced experiential responses, although such responses, mostly visual in nature, are numerous on the nondominant side.

Information Processing

Timing of Afferent Volleys in the Auditory Nerve

The vibration pattern set up on the cochlear partition reflects the temporal and spectral properties in an acoustic waveform reaching the inner ear. The discharge patterns of auditory nerve fibers, the great majority of which innervate inner hair cells, respond to these vibratory patterns through nonlinear mechanoelectric transduction mechanisms in the organ of Corti. Everything we perceive in our auditory environment is, thus, derived from information encoded in trains of all-or-none action potentials in ensembles of auditory nerve fibers. Information is transmitted from the cochlea to the cochlear nuclei in the spatial locations of fiber connections along the basilar membrane (cochlear place) and in the rate and timing of the discharges of fiber ensembles.

At low frequencies (less than about 5000 Hz), the timing of single auditory nerve discharges is governed by the unidirectional motion of the cochlear partition (Brugge et al, 1969). When a low-frequency tone is sounded, the fiber discharges are locked to a particular portion of the sine wave stimulus and therefore occur at time intervals that correspond to integral multiples of the period of the stimulating sinusoid (Rose et al, 1967). When complex stimuli are presented, the action potentials occur at times corresponding to the relative times of occurrence of the peaks of the complex waveform (Brugge et al, 1969; Rose et al, 1969). Thus, information regarding low-frequency sounds may be transmitted to the brain as a *time code*. This view of the way low-frequency information is transmitted was originally put forward by Wever (1949) in his volley

theory of hearing.

At higher stimulus frequencies, greater than about 3 to 4 kHz, phase-locked behavior of auditory neurons is not evident. Thus, information regarding high-frequency sounds depends on which fibers are activated and at which point they project in the central nervous system. The tonotopy established on the basilar membrane and the cochleotopic projection of the auditory nerve array provide the mechanical and neuronal substrates for the "place theory" of hearing, which appears to operate throughout the central auditory system (Aitkin, 1976).

Information reaching the cochlear nuclei is also carried in the rate of discharge of a fiber. The discharge rate of auditory nerve fibers is a rising monotonic function of stimulus level, and although a single fiber is not capable of encoding the stimulus level over the entire dynamic range of hearing, such coding may be possible in an ensemble of fibers with differing acoustic thresholds.

Many of the experimental data on the auditory nerve are able to account for peripheral mechanisms involved in auditory perception, including masking, aural combination tones, and speech. In recent years we have come to understand some of the inner ear mechanisms involved in speech analysis (Greenberg, 1988). The cochlea quite faithfully responds to incoming speech waveforms. The temporal discharge patterns of the array of active auditory nerve fibers represents, in turn, the presence and trajectories of stimulus formants. In addition, information about frequencies contained in stimulus peaks is carried in the fibers' discharge rates. Thus, the cochlea and auditory nerve apparently create a representation of the speech waveform in a three-dimensional array of timing, rate, and place (Geisler, 1988; Sachs et al, 1988).

It is of interest to consider what these results may imply for the interpretation of hearing loss that accompanies auditory nerve damage and the success exhibited by cochlear prosthetic devices that stimulate electrically peripheral auditory nerve endings. Dandy (1934) sectioned the eight nerve in human patients to relieve symptoms of Ménière's disease and noted that when only a small portion of the cochlear division of the nerve remained intact the result was usually only a high-frequency loss; in no case was there a selective hearing loss for low frequencies. Neff (1947) later repeated these observations in cats. Johnson and House (1964) and Johnson (1968), in reviewing case histories of more than 200 patients operated on for acoustic neuromas of various sizes, found that the majority of these patients suffered postoperatively from a sloping high-tone loss, again with no selective loss for the lowest frequencies. This may be explained by considering the fact that although damage to the auditory nerve would reduce the number of afferent fibers reaching the brain, it is likely that many of those remaining would still be activated by intense low-frequency stimuli and, thus, would still be able to transmit low-frequency information.

Volleying of afferent discharges also appears to be the basis for neural encoding of sound sensation that is evoked by electrical stimulation of the auditory nerve in humans (Merzenich et al, 1973). Psychoacoustic and physiologic studies in deaf patients with bipolar electrodes permanently implanted in the scala tympani indicate that the low-tone sensations, up to 500 or

600 Hz, arising from such electrical stimulation are similar to sensations of "periodicity pitch" experienced by normal listeners. The fact that many patients are unable to use such a device alone for speech recognition points to the fact that temporal coding by itself may not be adequate to transmit all of the information about such a complex stimulus. Nor does this approach take into account changes in circuitry in the central auditory pathways that may have taken place as a consequence of a long-standing sensorineural hearing loss of cochlear origin.

Discharge Characteristics of Central Auditory Neurons

A central auditory neuron receives inputs from many cells located in lower and higher auditory centers, as well as from neighboring neurons within the same cell group. These afferent inputs may be excitatory or inhibitory, and the net response of a neuron to convergent volleys of impulses is determined by the spatiotemporal interactions of these inputs and from activation of the neuron's intrinsic electrical properties. The fact that both inhibitory and excitatory pathways are activated by acoustic stimulation has been recognized in single-neuron studies at all levels of the auditory system in both anesthetized and unanesthetized animals.

Within the cochlear nuclei, in which the transformation of the auditory nerve input has been studied extensively, a functional heterogeneity is found to match the complex morphologic picture of nerve cells and afferent endings. We already described the categories of spatial patterns of activity of CN neurons as expressed by their response areas (see Fig. 3). Temporal patterns of neuronal discharges, based on a cell's response to short tone bursts at the CF, also fall into only a few classes. Figure 13 illustrates the major ones along with the somewhat quaint, but generally accepted, descriptive names assigned to them. With a limited number of functional classes and a limited number of morphologic classes, it would not be surprising to find a relationship between the two. Using combined intracellular recording and horseradish peroxidase (HRP) labeling in vivo. Rhode and colleagues have been able to correlate the morphologic and physiologic characteristics and add considerably to out knowledge of the circuitry of the cochlear nuclei (Rhode, 1985, 1990). Similar complexity is exhibited, within higher auditory centers, but much less is known about the mechanisms involved in forming these discharge patterns and receptive fields.

Coding of Stimulus Intensity

A question of great interest to auditory physiologists is how intensity is encoded in the spike discharges in a population of neurons. The answer to that question is incomplete, but it is likely to involve the *rates* at which cell discharge along with the *timing* of the discharges, the *number* of neuronal elements activated by the stimulus, and the *relative locations* of the active cells. As a rule, the number of spikes evoked in a primary auditory nerve fiber during a given time is an increasing monotonic function of sound intensity over a range of 20 to 50 dB. It is clear, therefore, that a single eight nerve fiber is incapable of detecting intensity differences over the full 100-dB range of hearing of a normal listener. However, since different auditory nerve fibers have different stimulus thresholds, an ensemble of auditory nerve fibers will, as a whole, have a wider dynamic range than any one of its constituent elements. Hence, raising stimulus

intensity results in fibers of successively higher threshold being recruited into the active neuronal pool. From a psychophysical standpoint, a localized rate code may be sufficient for transmitting information from the cochlea to the brain (Viemeister, 1988).

Although the rate of response of central auditory neurons to a changing stimulus level may be similar to that of auditory nerve fibers, the number of spikes evoked by sound is a nonmonotonic function of sound intensity (Fig. 14). At all levels of the auditory pathway it is common to find that as stimulus intensity is raised, the number of spikes evoked increases to a maximum and decreases sharply over a range of only 20 to 30 dB. In the monkey auditory cortex, neurons in the same animal differ in terms of the intensity too which they are most sensitive. The range of most-effective intensities covers the full range of hearing so that regardless of at which point the stimulus lies within the dynamic range of the ear, there exists a population of cortical neurons that is firing maximally. This finding that different auditory neurons are most sensitive to different sound intensities implies that intensity may be represented as a "place" in the central auditory system. Suga (1977) has demonstrated in the bat cortex a systematic map of stimulus intensity. It remains for a similar demonstration to made in other species, such as the cat and the monkey.

Coding of Stimulus Frequency

As mentioned previously, each fiber of the auditory nerve is excited within a restricted range of frequencies and intensities, reflecting to a large extent the mechanical tuning around that place on the basilar membrane than the fiber innervates. Thus, the central auditory system receives information about stimulus frequency in terms of which fibers of the auditory nerve are activated in accordance with a *place theory* of pitch perception. The place principle is clearly supported by many kinds of evidence. However, it is not possible to explain pitch perception and discrimination entirely with the simplistic concept that each fiber corresponds to a specific pitch. Response areas of individual neurons are relatively broad at suprathreshold intensities (see Fig. 3), and therefore at sounds of even moderate intensity, a neuron is activated over a relatively wide range of frequencies. Hence, place theorists must postulate that the central nervous system, for purposes of pitch discrimination, ignores all of the evoked activity except at the peak or boundary of the array of active fibers or that this mechanism operates only near the threshold of hearing.

Another mechanism by which frequency information about low-pitched sounds is conveyed to and through the central auditory system is based the phenomenon of phase-locking. The phase-locked activity at low-stimulus frequencies, which, as mentioned earlier, characterizes the discharges of primary afferent fibers and is the basis for the volley theory of pitch discrimination, is recorded in only a few neuronal populations in the central auditory system. Within the cochlear nuclei, it appears that primarily those cells that are innervated as end-bulbs of Held by the ascending branches of the auditory nerve are capable of faithfully transmitting phase-locked information (Lavine, 1971; Goldberg and Brownell, 1973; Rose et al, 1974). The MSO is a major recipient of these precisely timed action potentials that originate in the CN, although phase-locking has been observed for a small number of cells within the NLL, the ICC.

Phase-locked activity has not been reported at the level of the auditory cortex. Thus, if timing to a stimulus cycle is a mechanism involved in pitch discrimination, most of this time information is extracted by a specific pool of neurons within lower brain stem centers. There is no direct evidence that the central nervous system actually uses these temporal rhythms to determine pitch, but it is well established that the relative timing of afferent volleys from the two ears is used to localize a low-frequency sound source in space (Yin and Kuwada, 1984).

Because of the evidence for both place and volley mechanisms, many auditory theorists accept a king of *duplex theory* in which the temporal cadence of neuronal discharges is used for encoding information about low-frequency tones, whereas the place of stimulation in the cochlea and central auditory system encodes high-frequency information. Such a theory applies only to the processing of tonal stimuli. In the case of amplitude-modulated signals for which the carrier frequency is greater than that in which phase-locking occurs, the response of a single auditory nerve fiber or central auditory neuron may be precisely time-locked to the modulation envelope. Likewise, a train of very brief sounds with broad spectral content, such as clicks, which may be perceived by a listener as having tonal qualities, may also entrain the discharges of auditory neurons at all levels of the auditory nerve system.

Coding of Binaural Stimuli - Mechanisms of Sound Localization

Over the past decade, considerable progress has been made in our understanding of the neural mechanisms that underlie a listener's ability to localize the source of a sound in space (Masterton and Imig, 1984; Yin and Kuwada, 1984; Phillips and Brugge, 1985). Listeners use the information arriving at the two ears as a way of localizing a sound source, and it is well established that interaural time and intensity disparities are among the important cues. These two dichotic cues arise because the ears are separated by an interaural distance and because the interaural space is occupied by a head that, at certain frequencies, casts an acoustic shadow. The interaural distance imposes an interaural time delay (ITD) between the signals reached the two ears, and the acoustically opaque head imposes an interaural intensity difference (IID). If one considers the head only as a spherical obstacle to sound waves reaching the two ears for humans a sound originating from a source to one side of the head would reach the farther ear some 600 microsec later than it reaches the nearer ear. The head is also a low-pass filter so that the far ear lies in a sound shadow whose depth depends upon the direction and wavelength of the sound. Interaural intensity differences are negligible at low frequencies but may be as great as 20 dB at high frequencies. The situation is far more complex, of course, since sound waves interact with the head, pinnae, and external ear canals in ways creating spectral and temporal differences not only partially understood (Kuhn, 1987).

Convergence of the outputs of the bilaterally placed cochlear nuclei occurs first in the SOC, and neurons here are excited or inhibited by sound delivered to both ears. Systematic electrophysiologic studies of single neurons in this region of the brain stem and the nuclei to which they project have now provided us with the neural basis by which the nervous system encodes these two important localization cues.

Neurons in the MSO are extremely sensitive to small interaural time differences. For these cells, the discharge rate is a function of the difference in time of arrival of the tones at the two ears (Fig. 15). The MSO receives afferent input from the AVCN of each side, which typically tends to be synchronized with the waveform of the effective low-frequency stimulus. When interaural time delay is adjusted so that the phase-locked spikes from the two AVCN converge on an MSO cell at nearly the same instant, the probability of a discharge from that cell is maximal. When the interaural time difference is shifted, as usually happens when a sound source moves along the azimuth, the converging discharges arrive out of phase, and output of the neuron is consequently reduced. Rose and colleagues (1966) and Yin and coworkers (1984) studied this phenomenon in the inferior colliculus, the nucleus that both receives a direct input from the MSO and preserves its ITD sensitivity. They discovered that for many ICC neurons, the most effective interaural time was not greatly altered by changes in intensity or frequency of the tones (Figs. 15 and 16). They called this time delay the *characteristic delay* of the neuron and argued that it corresponds to a sound coming from a specific region in space that would create the temporal disparity. Neurons that have a characteristic delay are clearly capable of encoding information about the location of a multicomponent low-frequency signal source. The underlying mechanism can be modeled as a cross-correlator (Yin and Kuwada, 1984), and the data support the delay line concept put forward by Jeffress (1948) more than four decades ago. Moreover, the presence of a population of neurons having different characteristic delays implies that a "place" mechanism is acting to encode the location of a low-frequency sound. Although a systematic map of auditory space has been discovered in the midbrain of the owl (Knudsen et al, 1977), no such precise organization has been found in the ICC of a mammal. There is evidence, however, for such an organization in the superior colliculus (Palmer and King, 1985).

Within the LSO there are neurons that are particularly sensitive to small changes in interaural intensity differences. These cells are typically excited by stimulation of one ear and inhibited by stimulation of the other (Tsuchitani and Boudreau, 1966). The LSO is composed almost exclusively of cells with these properties. Most of these neurons have fairly high CFs in which IIDs would be expected to play a major role in high-frequency sound localization. The function that relates spike rate to interaural intensity difference is a steeply decreasing monotonic function with a dynamic range of about 20 dB for most cells (Fig. 17). The curves are positioned so that these neurons tend to be tuned to sounds originating in contralateral acoustic space.

Cells sensitive to ITD and IID are found at all levels of the auditory system, from the SOC to the auditory cortex. Thus, information regarding sound location is preserved within and made widely available to circuits throughout the central nervous system. It is a general rule in sensory systems that the topography of a sensory surface is preserved at each synaptic station along the relevant central pathway. The central representation of auditory space is, conversely, created by temporal and spatial neural interactions of inputs from the two cochleas. As mentioned earlier, within the high-frequency representation of primary auditory cortex, binaurally sensitive neurons are segregated into columns or patches. These form maps that lie roughly orthogonal to isofrequency contours of AI. Middlebrooks and Pettigrew (1981) mapped the auditory cortex using tonal stimuli in a sound field free of acoustic obstructions and reflections. They found that about half of the neurons encountered were selective for the location of the sound, and these

formed two classes. *Hemifield* units responded to sounds presented in the contralateral sound field. They may correspond to IID-sensitive cells isolated under dichotic listening conditions. *Axial* units had small, completely circumscribed spatial receptive fields that coincided with the acoustic axis created by the pinna. There was no indication of a systematic map of sound space in AI, but the segregation of neuronal classes was consistent with the columns and patches described earlier.

Coding of Complex Sounds

Although a great deal is known about the processing of information pertaining to frequency, intensity, and location of a pure tone, much less is understood about the mechanisms that underlie encoding of more complex acoustic stimuli, such as those used in normal communication. We saw previously that complex sounds, such as human speech, are encoded in discharge timing and rate, spatially distributed across the auditory nerve array. A central question now concerns how this information is processed and transmitted to higher centers by neurons in the cochlear nuclei. At the level of the cochlear nuclei, attempts have been made to predict, from tone-response properties of single cells, the responses to more complex stimuli such as noise (Greenwood and Goldberg, 1970; Møller, 1969) and natural vowel sounds (Moore and Cashin, 1974). In the studies by Moore and Cashin, the general level of responsiveness of many cells to any particular vowel could be inferred from the relative amounts of sound energy that fell within a neuron's excitatory and inhibitory response areas. There were some curious exceptions to these observations, however, and the temporal pattern of spikes evoked by given vowel sounds depends to some extent on the type of cell under study. At higher levels in the auditory system, such as the auditory cortex, there appears to be no simple one-to-one mapping of a species-specific vocalization to a discharge of a single cortical neuron (Newman and Symmes, 1979; Glass and Wollberg, 1983). Neither the specific spectra content nor the communicative significance serves as a feature sufficient to evoke a unique neural response. Instead, a cortical cell's response appears to depend in a complex way on specific patterns of acoustic transients embedded in time varying and spectrally diverse stimuli.

The Central Vestibular System

The vestibular system in humans, and in many other animal species, serves three main functions: (1) the control of spinal reflexes that elicit adjustments of muscle activity and body position for the maintenance of upright posture; (2) the control of eye movements that help stabilize gaze during head motion, thereby reducing movement of an image on the retina; and (3) the perception of motion and spatial orientation. This is accomplished by complex interactions of the output of the five paired labyrinthine receptors and activity in other systems involved in vision and proprioception (Precht, 1979).

The Vestibular Nuclear Complex

The vestibular nuclear complex occupies the dorsolateral region of the rostral medulla and caudal pons. Four major nuclei have long been recognized in a number of mammalian species.

They are the *superior vestibular nucleus* (nucleus of Bekhterev), *lateral vestibular nucleus* (LVN or nucleus of Deiters), *medial vestibular nucleus* (MVN), and *descending vestibular nucleus* (inferior or spinal nucleus). As many as seven smaller cell groups are distinguishable from the main nuclei on cytoarchitectural and connectional grounds. Using the nomenclature of Brodal (1974), these groups include the *interstitial nucleus* of the vestibular nerve, *group f, group l, group x, group y, group z,* and the *supravestibular nucleus.*

Primary Afferent Projections to the Vestibular Nuclei

The primary vestibular nuclei have their bipolar cell bodies in the vestibular (Scarpa's) ganglion, which is located within the internal auditory meatus. Peripheral branches of these neurons make synaptic contact with receptor cells within the maculae and cristae, whereas the central branches project to the central nervous system. The vestibular nerve enters the caudal pons at the cerebellopontine angle medial to the cochlear nerve. On entering the brain stem, the majority of primary vestibular afferents bifurcate into multibranched short ascending and long descending axons (Fig. 18). These axons distribute to the various cell groups of the vestibular nuclear complex in some topographic order (Koelliker, 1891; Held, 1892; Cajal, 1909; Lorente de No, 1933a; Hauglie-Hanssen, 1968; Carleton and Carpenter, 1984). Ascending fibers project throughout the superior and medial vestibular nuclei and the ventral part of the LVN, whereas descending branches reach the descending nucleus and caudal part of the LVN. Some fibers give off collaterals to the interstitial nucleus of the vestibular nerve, whereas others continue onward to end in the accessory cuneate nucleus, subtrigeminal lateral reticular nucleus, and circumscribed areas of the reticular formation. A heavy projection, in the juxtarestiform body, reaches the ipsilateral nodulus and ventral uvula of the cerebellum; a lesser projection reaches the flocculus, lobules V and VI, and lingula. Although most vestibular fibers terminate within the four principal vestibular nuclei, not all regions of these nuclear groups receive primary vestibular input (Walberg et al, 1958). Thus, impulses from the labyrinthine receptors cannot activate all parts of the vestibular complex monosynaptically. These histologic findings are in agreement with results from electrophysiologic experiments in which monosynaptic, disynaptic, and polysynaptic excitatory postsynaptic potentials (EPSPs) have been recorded in neurons located within various subdivisions of the vestibular complex (Rubin et al, 1977).

The central projections of ganglion cells innervating individual semicircular canals or otolithic organs have been traced in cat and monkey (Stein and Carpenter, 1967; Gacek, 1969; Carleton and Carpenter, 1983). Portions of the vestibular ganglion innervating the cristae project primarily upon the superior vestibular nucleus and rostral parts of the medial nucleus. Portions of the vestibular ganglion innervating the cristae project primarily upon the superior vestibular nucleus and rostral parts of the medial nucleus. Portions of the vestibular ganglion innervating the macula of the utricle reach parts of the medial, lateral, and descending nuclei, whereas the central projection of the saccule reaches parts of the descending vestibular nucleus. Although there is a high degree of segregation of inputs from the cristae and maculae, there are regions within the vestibular complex in which overlapping of afferent terminals from the three semicircular canals and the utricle occurs. These observations are consistent with the findings from single-neuron studies that neurons of the vestibular nuclei are influenced by both angular

acceleration and head tilt and that a significant fraction of cells may be activated by angular acceleration in the planes of more than one canal (Duensing and Schaefer, 1959; Duensing, 1968a and b; Markham and Curthoys, 1972; Kubo et al, 1977). All these findings are in agreement with observations made in a variety of other experiments that the otolith system can influence quite strongly the effects produced by stimulation of the semicircular canals (Bergstedt, 1961a and b; Owada and Okubo, 1963; Crampton, 1966; Milojevic and Voots, 1966; Siegborn, 1976).

Each subdivision of the vestibular nerve associated with a specific end-organ contains two classes of axons that can be differentiated on functional and structural grounds (Goldberg and Fernandez, 1975). Both classes project to the major nuclei of the vestibular complex in which the majority of them make monosynaptic excitatory contacts (Goldberg et al, 1985, 1987). Disynaptic inhibitory postsynaptic potentials (IPSPs) are commonly seen as well. IPSPs and EPSPs are also evoked by stimulation of the opposite vestibular nerve, and the latencies suggest a direct commissural connection from the contralateral vestibular complex (Shimazu, 1972; Rubin et al, 1977). This kind of bilateral interaction, mediated via second-order commissural neurons, may ensure the highly sensitive response of vestibular neurons and provide the basis for precisely controlled oculomotor and spinal activity. Secondary neurons in the vestibular nuclei projecting to targets in the cerebellum, spinal cord, and oculomotor (III) nuclei also differ in the proportions of the two classes of primary and commissural afferents that impinge upon them (Highstein et al, 1987).

The lateral vestibular nucleus is an important target of utricular output (Stein and Carpenter, 1967; Peterson, 1970). Cells in the LVN project, in turn, to the spinal cord via the ipsilateral lateral vestibulospinal tract. Electrophysiologic studies show that Deiters' neurons that are activated monosynaptically by vestibular nerve stimulation are located mainly in the ventral half of the nucleus (Wilson et al, 1967a; Peterson, 1970; Sans et al, 1972). Thus, considering the somatotropic arrangements in Deiters' nucleus, it is not surprising to find a higher percentage of cells representing cervical rather than lumbar levels firing monosynaptically to labyrinthine stimulation (Wilson et al, 1967a). Saccular afferents also end in some regions of the LVN (Hwang and Poon, 1975; Wilson et al, 1968b), as do afferents from all three semicircular canals to some degree (Sans et al, 1972). In the rat LVN, Sotelo and Palay (1970) frequently found two morphologically distinct junctional complexes occurring on the same perikaryon or dendrite, suggesting convergent input from more than one source.

The medial nucleus appears less precisely organized than the lateral nucleus in terms of its afferent and efferent connections. It receives strong mono- and polysynaptic input from semicircular canals but is also influenced by otolithic receptors (Shimazu and Precht, 1965; Stein and Carpenter, 1967; Gacek, 1969; Sans et al, 1972; Peterson, 1970). Second-order neurons receiving canal input are concentrated in the rostral part of the nucleus, the region that projects to the spinal cord via the medial vestibulospinal tract, the extraocular motor nuclei, the vestibulocerebellum, and the contralateral vestibular nuclei. Cells responding to head tilt are located more caudally in the nucleus.

Cells in the superior nucleus are excited by labyrinthine stimulation, which is in agreement with anatomic findings of inputs mainly from the semicircular canals (Stein and Carpenter, 1967; Gacek, 1969). Its cells respond mainly to vertical canal angular acceleration, with some input from the horizontal canal receptors (Abend, 1977). The superior nucleus, along with the medial nucleus, is responsible for the projections from vestibular nuclei to the extraocular motor nuclei (Tarlov, 1970) and, thus, together form major relay centers for ocular reflexes mediated by the semicircular canals.

Less is known about the function of the descending nucleus. Afferent inputs from the labyrinth originate in the three semicircular canals and the utricle and saccule (Stein and Carpenter, 1967; Gacek, 1969). The rostral part of the nucleus receives a heavy input from the gravitational receptors, which agrees with the finding that there is an exceptionally strong response recorded here when the head is tilted. The descending nucleus projects to both cerebellum and spinal cord.

Schwarz and colleagues (1977) described the ultrastructure of cells and endings in both the descending and medial vestibular nuclei. Cell types are similar in both nuclei, and within each nucleus there are two cells classes that differ from one another in both size and synaptic morphologic findings. Vestibular nerve section results in degeneration of only one kind of nerve terminal, leaving others - presumably of cerebellar, spinal, or intranuclear origin - intact on the same neuron.

There are, in addition to labyrinthine and central nervous system connections, local circuits within the vestibular complex that could subserve interactions that take place between vestibulospinal and vestibulo-ocular reflexes. One such circuit provides excitatory and inhibitory input from the MVN and LVN neurons that are monosynaptically activated from the vestibular nerve (Matsuoka et al, 1981).

In summary, the vestibular system is not one-dimensional, and the vestibular nuclei are not just simply relay stations for transmitting afferent activity. Considering all degrees of freedom for stimulating the vestibular system, one observes very complex phenomena in terms of eye movements and postural reflexes. Central vestibular circuits are capable of reconstructing actual head motion in three-dimensional space. Experimental tools now available to study the vestibular system in three dimensions include not only modern neuroanatomic, neurophysiologic, and psychophysical methods but space-lab technology as well.

Vestibulocerebellar Relationships

Primary vestibular afferents project mainly to the vestibulocerebellum (nodulus, flocculus, uvula, and ventral paraflocculus) of the same side, at which point they terminate as mossy fibers (Broadl and Høvik, 1964; Precht and Llinás, 1969; Shinoda and Yoshia, 1975; Carleton and Carpenter, 1984). The secondary fibers known to project to these areas have a widespread origin, including the four main vestibular nuclei and group x of both sides of the brain stem (Kotchabkakdi and Walberg, 1978). Physiologic experiments have now shown that these second-

order neurons relay to the cerebellum both labyrinthine and spinal information. In addition, activity originating in the labyrinth reaches the cerebellar cortex via neurons in the reticular formation sensitive to vestibular stimulation. This activity arising in the labyrinth and reaching the cerebellum is integrated with activity from other sources, principally those involved with visual and neck receptors. Purkinje cells in the flocculus project back upon neurons in the vestibular nuclei, forming an important component of a control system regulating the vestibulo-ocular reflexes.

Direct and secondary vestibular projections are found to the vestibular cerebellum and also to the anterior and posterior lobes, which are also referred to as the "spinal cerebellum" (Kotchabkakdi and Walberg, 1978). These areas project, in turn, to vestibular nuclei. A fourth route to the cerebellum is via the reticular formation. Neurons in the reticular formation known to project to the cerebellum have been found to be sensitive to head tilt. Anatomic and physiologic evidence points to primary and secondary vestibular input to the fastigial and dentate nuclei, although the primary projection to the dentate may be weak. Input is from both the maculae and cristae.

Input to the Vestibular Nuclei from the Cerebellum

The large contingent of afferent fibers to the vestibular nuclei comes from the cerebellum. Cerebello-vestibular projections may be divided into three groups. They include the projections from the vestibulocerebellum, the vermis of the anterior and posterior lobes, and the fastigial nuclei.

The flocculus projects to all four main vestibular nuclei and group f, in which afferent fibers terminate in rather circumscribed regions (Fig. 19). The vestibular projections of the nodulus and uvula differ from those of the flocculus. The projections of the nodulus and uvula to the vestibular nuclei are ipsilateral only, an observation that correlates with the asymmetric effects of unilateral lesions or electrical stimulation of these cerebellar areas. Both the nodulus and uvula send fibers to the superior and descending nuclei, whereas the nodulus alone reaches the medial nucleus. Despite the fact that there is considerable overlap in the projection from these cerebellar lobes, the afferent terminals are, in general, distributed to different areas within the respective nuclei. The predominantly inhibitory nature of cerebellar Purkinje cells is well known. Several laboratories have demonstrated that stimulation of the flocculus monosynaptically inhibits some vestibular neurons, which project to ocular motoneurons (Precht et al, 1971; Baker et al, 1972; Fukuda et al, 1972; Ito et al, 1973). These findings may explain the observation that vestibular nystagmus is inhibited by stimulation of the vestibulocerebellum but is enhanced by lesions of this area. Ablation of the nodulus and adjoining paleocerebellum results in disturbances in equilibrium as well as in eye movements. Experimental evidence so far would indicate that these effects of ablations are due to release of vestibular nuclei from paleocerebellar inhibition.

A direct projection from the cerebellar vermis to the vestibular nuclei has been known for many years. The sites of termination of this pathway are restricted to the dorsomedial part of the descending nucleus and the dorsal part of the lateral nucleus on the ipsilateral side of the

brain stem. Furthermore, fibers from different regions of the vermis end in the same territory within each of these nuclei. There may be a few fibers to the superior nucleus. The projection onto the lateral nucleus has been studied most thoroughly (Fig. 20). The target of cerebellar cortical axons is restricted to the dorsal half of only the lateral nucleus and hence covers only a portion of the forelimb and hindlimb regions. In addition, the projection from the anterior lobe vermis is somatotopically organized. In an electron microscopic study, Mugnaini and Walberg (1967) discovered that within the lateral nucleus, synaptic contacts of vermis Purkinje cells occurred on neurons of all sizes. The major effect of anterior lobe Purkinje cell activation is monosynaptic inhibition, although the fact that Purkinje cell axons establish various kinds of contacts on all parts of the vestibular neuron raises questions of whether Purkinje cells are entirely inhibitory. Following cerebellar stimulation, neurons of the lateral nucleus show not only an IPSP but also a distinct disinhibition phenomenon due to depression of tonic discharges from Purkinje cells by the action of interneurons within the cerebellar cortex (Eccles et al, 1967; Ito et al, 1968). Thus, Purkinje cells can modulate activity in both excitatory and inhibitory directions. A most dramatic demonstration of the net inhibitory influence on vestibular nuclei is the disappearance of decerebrate rigidity during electrical stimulation of the anterior lobe vermis.

Various parts of the cerebellar cortex have differential connections with functional cell groups of vestibular neurons and, hence, cerebellar influences interact with vestibular afferent activity. For example, neurons of the lateral nucleus that respond to tilt are inhibited by stimulation of the anterior vermis (Shimazu and Smith, 1971) but are not influenced by stimulation of the vestibulocerebellu.

Input to the Vestibular Nuclei From Deep Cerebellar Nuclei

A third pathway over which the cerebellar cortex can exert influence on vestibular nuclei is a complex and indirect one (Fig. 21). The pathway consists of two links, Purkinje cells of the cerebellar cortex project to the fastigial nucleus, and the fastigial nucleus, in turn, projects to the vestibular nuclei. Brodal and associates (1962) concluded from extensive studies in the rabbit, cat, and monkey that only the vermis proper of the cerebellar cortex projects onto the fastigial nucleus. They postulated that anterior parts of the vermis send fibers to the anterior regions of the fastigial nucleus and the posterior parts to posterior regions. Later experiments confirmed these general principles of organization. The fastigio-vestibular link in the projection is more complex than this. It has crossed and uncrossed components. Crossed fastigiovestibular fibers project to the peripheral zone of the superior vestibular nucleus, the most ventral part of the medial nucleus, the ventral half of the lateral nucleus, and the ventrolateral part of the descending nucleus, group f and group x. The uncrossed projection supplies most of the medial vestibular nucleus, except the most ventral tip, peripheral regions of the superior vestibular nucleus, dorsal half of the lateral nucleus, the dorsomedial parts of the descending nucleus, and the media nucleus, except its most ventral region.

In summary, the crossed and uncrossed fastigiovestibular fibers supply different regions within the lateral, medial, and descending vestibular nuclei. Only in the superior nucleus do they share common territory. Likewise, the vermis projects in a topographic fashion on the vestibular

nuclei. These areas receive, in turn, input from secondary vestibular neurons, as well as from neurons in the spinal cord and reticular formation. Thus, there exists here a complex, tightly woven vestibuloreticulospinocerebellar system that operates for the control of movement and the maintenance of upright posture.

Experiments that involve destructive lesions or electrical stimulation indicate that the lateral vestibular nucleus exerts a strong facilitatory influence on the myostatic reflexes of extensor muscles essential for postural tonus. Because of this, there is considerable interest in the differential distribution of fastigial and cerebellar cortical afferents to this nucleus. The ventral half of the LVN receives from the contralateral fastigial nucleus, whereas the dorsal part receives the uncrossed fastiovestibular projection. Recall that the caudal half of the lateral nucleus also receives a direct projection of the anterior lobe of the vermis. Hence, the dorsal part of the forelimb region of Deiters' nucleus is acted on directly from the forelimb region of the vermis and indirectly via the fastigial nucleus. The ventral part of Deiters' nucleus receives input from the posterior lobe via corresponding pathways. The same principle pertains for hindlimb regions. It can be generally concluded that the fastigial nucleus has an excitatory influence on the vestibular nuclei as demonstrated with intracellular recording from cells in the LVN. On both anatomic and electrophysiologic grounds it appears likely that much of the verbal inhibition of decerebrate rigidity and inhibition of Deiters' neurons is mediated over direct cerebellocorticovestibular pathways. Another possible mechanism is that Purkinje cell inhibition of neurons of the fastigial nucleus reduces tonic fastigial excitatory bombardment on vestibular neurons.

Vestibulospinal Relations

Projections to Spinal Cord

There are three separate pathways over which the vestibular nuclei may influence the spinal cord: the *lateral vestibulospinal tract* (LVST), the descending fibers of the medial longitudinal fasciculus or *medial vestibulospinal tract* (MVST), and the *reticulospinal tract* (Fig. 22). The first two pathways derive from neurons in the vestibular nuclei, whereas the third arises from cells of the reticular formation affected by vestibular stimulation. Each of these projections interacts in the spinal cord with input from still other sources.

The lateral vestibulospinal tract arises from the lateral vestibular nucleus and terminates throughout the cord on the ipsilateral side. Deiters' nucleus is the intermediate link between the cerebellar vermis and motoneurons that innervate extensor muscles. The projection is somatotopically organized. Cells of all sizes contribute to the pathway, and the fiber bundle contains axons of different caliber having conduction velocities that range from 24 to 140 m/sec (Ito et al, 1964; Wilson et al, 1965). The great majority of these fibers reach laminae VII and VIII (Nyberg-Hansen and Mascitti, 1964), at which point they exert an excitatory influence directly on both gamma and alpha motoneurons innervating extensor muscles. Stimulation of the lateral nucleus produces monosynaptic EPSPs in extensor motoneurons of upper cervical (Wilson and Yoshia, 1969), thoracic (Wilson et al, 1970), and lumbosacral cord (Lund and Pompeiano,

1968; Grillner et al, 1970). The monosynaptic effect, which is conveyed by the rapidly conducting lateral vestibulospinal fibers (Grillner et al, 1971), is most pronounced in neck motoneurons (Wilson and Yoshida, 1969), emphasizing the close functional relationship among the labyrinth, the vestibular nuclei, and the neck muscles. The polysynaptic effects on extensor or flexor motoneurons are likely to be due to interneurons located in laminae VII and VIII.

The medial vestibulospinal tract is considerably smaller quantitatively than is the LVST. Anatomic (Nyberg-Hansen, 1964) and electrophysiologic (Wilson et al, 1968a) results indicated that the MVST originates in the medial vestibular nucleus, probably from cells located chiefly in the rostral half of the nucleus. Fibers of this tract descend in the ventral funiculus on both sides of the spinal cord as far as midthoracic levels, at which point they terminate mainly in laminae VII and VIII. Many of the cells of origin of this tract are activated by labyrinthine stimulation, some monosynaptically (Wilson et al, 1967a, 1968b). A single vestibulospinal neuron may receive its input from more than one labyrinthine receptor and send an axon that diverges considerably, its multiple collaterals projecting to different segments of cervical cord (Shinoda et al, 1988). Thus, the labyrinthine control of head movement at the level of the spinal cord involves a complex interaction of convergent and divergent activity from multiple receptor organs.

The pontomedullary reticular formation receives its major vestibular input via the four main vestibular nuclei. The reticulospinal tract carrying secondary vestibular information originates in the bulbar reticular formation and descends to all levels of the spinal cord bilaterally (Peterson, 1984). Both gamma and alpha motoneurons receive polysynaptic input via this tract.

Spinal Input to Vestibular Nuclei

Based on the results of axonal degeneration following spinal cord section, Brodal and Angaut (1967) showed that a direct spinovestibular projection in the cat was modest, entirely ipsilateral, and distributed only to parts of the vestibular complex that do not receive primary vestibular afferent fibers. They found some degeneration within the most caudal parts of the descending and medial nuclei, with slight degeneration in the dorsal and caudal parts of the lateral nucleus. This is in accord with electrophysiologic results indicating that cervico-ocular reflexes are mediated principally via these two vestibular nuclei (Hikosaka and Maeda, 1973; Rubin et al, 1975). Groups x and z also show signs of outstanding terminal degeneration following spinal cord lesions. Bowsher (1962) found that spinal afferent fibers in humans reach the dorsal part of the lateral nucleus and a region that appears to be the human homologue of group x. A large proportion of direct spinovestibular fibers originate at low levels of the spinal cord, below the caudal end of Clarke's column, indicating that at least some of the fibers reaching the vestibular nuclei from the spinal cord are not collaterals of the dorsal spinocerebellar tract.

In addition to a direct spinovestibular pathway, there are spinoreticulovestibular connections over which spinal activity can reach vestibular nuclei indirectly (Brodal et al, 1962). Also, axon collaterals of fibers of the olivocerebellar tract may convey spinal impulses to the vestibular nuclei (Ito and Yoshida, 1966; Allen et al, 1971). Electrophysiologic studies in the cat

have convincingly demonstrated that the direct short latency spinal input to the vestibular nuclei is mainly excitatory, although later inhibitory effects are seen as well (Wilson et al, 1965, 1966; Precht et al, 1967). Allen and co-workers (1971) showed that some neurons of the lateral nucleus receive convergent input composed of an early EPSP through olivovestibular fibers and a late IPSP via an olivocerebellovestibular path.

Many cells within the vestibular complex that are excited by spinal stimulation also respond to horizontal rotations (Precht et al, 1967). Thus, facilitatory input arising from the spinal cord may contribute to a tonic resting discharge of vestibular neurons, which can be modified by labyrinthine input. These neuronal interactions appear to form part of the basis for the interplay between the vestibular and proprioceptive systems in the regulation of upright posture and in the interactions between input from neck muscles and labyrinthine receptors in oculomotor integration.

Vestibulo-Ocular Relationships

Under normal conditions, eye movements induced by natural stimulation of the vestibular labyrinth are compensatory in nature - that is, when the head moves, the eyes counter-rotate to maintain a stable retinal image. The close correlation between the direction of nystagmus and the planes of movement of the head indicates that connections between vestibular receptors and extraocular motoneurons are precisely organized. The movements that are under labyrinthine control are affected by impulses arriving over a bisynaptic pathway as well as over polysynaptic circuits in the brain stem and cerebellum that provide various feedback circuits.

The basic structure of the short latency, direct vestibulo-ocular reflex arc is relatively simple, in the sense that the pathway consists of only three neurons in series: the primary afferent neuron from a labyrinthine receptor, the vestibular nucleus neuron, and the motor neurons of the oculomotor complex (Fig. 23). Electrical stimulation of the vestibular nerve produces either EPSPs or IPSPs within oculomotor neurons (Sasaki, 1963; Baker et al, 1969; Highstein et al, 1971; Precht and Baker, 1972). Thus, each receptor organ is capable of simultaneously exciting agonists and inhibiting antagonists to product a reflex turning of the eyes.

The major excitatory and inhibitory pathways of this reflex arc have been worked out by selective stimulation of individual canal receptors and recording in oculomotor neurons. Excitatory activity is carried via the contralateral MLF, whereas inhibitory activity is transmitted over the MLF ipsilaterally (Ohgaki et al, 1988). There is not a simple one-to-one relationship between a canal receptor and a specific set of eye muscles. Also, disynaptic excitatory and inhibitory pathways from the otolithic organs to the oculomotor nuclei exist to allow for both divergence and convergence of activity between the vestibular labyrinth and the oculomotor neuron pool.

The circuitry that subserves conjugate reflex eye movements under normal conditions is far more complex than this; it involves labyrinthine signals from five receptor organs on each side of the head, impulses relayed through four pairs of vestibular nuclei, and final output from

six pairs of oculomotor neurons located in the third, fourth, and sixth cranial nerve nuclei. Anatomic results in the cat (Tarlov, 1970) are in agreement with electrophysiologic findings (Ito et al, 1976) that the vestibulo-ocular reflex is mediated over several routes. By using microstimulation techniques, it has been determined that the superior vestibular nucleus contains those cells that have an inhibitory action on oculomotor neurons in all nuclei on the same side and in the motor nucleus of the medial rectus muscle of the opposite side. In addition, inhibitory neurons for neurons in the sixth nucleus may be found in the rostral pole of the medial vestibular nucleus (Baker et al, 1969; Highstein, 1973). The rostral two thirds of the medial nucleus contains neurons that make excitatory synaptic connections with all contralateral subnuclei except the medial rectus nucleus, which is excited ipsilaterally. Group y cells appear to produce monosynaptic excitation in the nucleus of the third nerve through the brachium conjunctivum (Highstein, 1973). Although Tarlov (1970) and Rubin and associates (1978) found in the cat that the contribution to the ascending contralateral and ipsilateral MLF comes almost exclusively from the medial and superior vestibular nuclei, McMasters and co-workers (1966) traced fibers in the monkey from all four nuclei.

Three systems related to vision act in concert to stabilize gaze: a saccadic system, a smooth pursuit system, and an optokinetic system. Rapid eye movements (saccads) bring an object quickly to the fovea, maintaining gaze on a moving target is the job of the smooth pursuit system, and the optokinetic system is thought to do the same using the entire retina. Important sites at which visual and vestibular input come together are in the vestibular nuclei themselves (Waespe and Henn, 1979). In nonfoveate animals, the pathway includes the accessory optic system, inferior olive, cerebellar cortex, and vestibular nuclei. In foveate animals, visual input reaches vestibular nuclei over a complex set of pathways that includes the retinogeniculocortical system, visual associate areas, pontine nuclei, cerebellum, pretectal nuclei, and other brain stem nuclei (Baloh and Honrubia, 1989). In all cases, the final common path is the oculomotor neuron. A linear model for the interactions of the visual and vestibular oculomotor systems is given by Raphen and Cohen (1986).

Vestibulo-ocular reactions also appear to be mediated over more complex pathways involving ipsilateral and commissural interneurons and the brain stem reticular formation (Lorente de No, 1933b; Szentágothai, 1950). The four main vestibular nuclei differ in their projections to the reticular formation (Ladpli and Brodal, 1968). Studies using the Golgi method have revealed that ascending fibers from the reticular formation give off collaterals to the oculomotor, trochlear, and abducens nucleus (Scheibel and Scheibel, 1958). Szentágothai (1964) found in his Golgi studies that afferent fibers entering the oculomotor complex are of two types. One type (type A) has large presynaptic terminals, which are distributed within a well-circumscribed area of the nucleus and appear to contact somata and proximal dendrites of a few nearby motor neurons. From a functional standpoint, type A fibers appears well suited to carry out the powerful and precisely localized activation of extraocular motor nuclei by vestibular neurons. Type B fibers, in contrast, are small, with terminal branches distributed over a wide area. These fibers may arise from cells in the reticular formation.

Stability of an image on the retina also involves input from the neck muscle receptors. This can be readily observed in an experimental animal. When the body is rotated while the head is held stationary, the eyes deviate so that the normal relationship between head and torso is maintained. Like the vestibulo-ocular reflex pathways, the neck-ocular reflex involves synergistic excitatory and inhibitory input to oculomotor neurons via the medial and descending vestibular nuclei primarily. The interactions of these two reflex pathways are the consequence of convergence of semicircular canal and neck-muscle afferents onto secondary vestibular neurons.

Other Input to the Vestibular Nuclei

There is a modest projection to the vestibular nuclei from the interstitial nucleus of Cajal in the mesencephalon (Pompeiano and Walberg, 1957). The fibers travel in the MLF and terminate in the dorsal and caudal parts of the ipsilateral medial vestibular nucleus. The electrophysiologic results of Markham and colleagues (1966) show that stimulation of the interstitial nucleus leads to excitation or inhibition of vestibular neurons that are also driven from the canals. Wilson and co-workers (1968b) localized most of the cells that respond to MLF stimulation to the ventral part of the medial nucleus. There are also inputs to the vestibular nuclei that have been traced from several other sources, including the perihypoglossal nuclei, the nucleus prepositus, the nucleus intercalatus, the nucleus of Roller, the inferior olive, the mandibular nerve, the glossopharyngeal nerve, and the nucleus gracilis and the nuclei reticularis gigantocellularis and reticularis pontis caudalis of the brain stem reticular formation (Carleton and Carpenter, 1983).

Clinical and experimental physiologic evidence points to an interaction between vestibular nuclei on the two sides of the brain stem. Using modern neuroanatomic tracing methods, Carleton and Carpenter (1983) described contralaterally projecting neurons in the medial, descending, and superior vestibular nuclei. Commissural neurons may connect homologous or different vestibular nuclei. The MVN gives rise to the largest contingent for commissural axons. These findings are more or less in harmony with earlier work (Gacek, 1978; Ladpli and Brodal, 1968). Commissural neurons may mediate excitation or inhibition. Stimulation of the opposite vestibular nerve also may give IPSPs and EPSPs in second-order vestibular neurons with latencies consistent with a direct commissural afferent projection (Goldberg et al, 1987). The interactions of these bilateral excitatory and inhibitory inputs provides a neural substrate for the integrative action of the various muscle groups involved in vestibular reflexes.

Vestibulothalamocortical Projections

The involvement of a special sense organ for the perception of motion and body position was appreciated by Mach more than a century ago. There seems to be little doubt that these perceptions also require processing of vestibular information at the level of the cerebral cortex. Auras that accompany seizures originating from foci within the intraparietal sulcus may include vestibular sensations (Foerster, 1936). Electrical stimulation of the depth of this sulcus in humans produces sensations of dizziness that may be accompanied by eye movements or pupillary responses (Penfield, 1957), and this area has been shown to exhibit an increase in blood flow

during caloric labyrinthine stimulation (Friberg et al, 1985).

By stimulating the vestibular nerve electrically and recording the evoked cortical potential, Walzl and Mountcastle (1949) were the first to identify in the cat a cortical vestibular area localized within the anterior suprasylvian sulcus. This area is bordered by the face area of SI, the auditory area, and area SII. Later work identified a second field in the cat (Sans et al, 1970) as well as vestibular projection areas in other animals, including guinea pig (Ödkvist et al, 1973a), rabbit (Ödkvist et al, 1973b), and monkey (Fredrickson et al, 1974).

In the monkey, three cortical vestibular fields have been identified (Fig. 24). Cells in area 2v in the postcentral gyrus at the lower end of the intraparietal sulcus of the monkey respond to both caloric and electrical stimulation of the labyrinth. Latencies to electrical stimulation may be as short as 4 msec, indicating a rapidly conducting vestibulothalamic pathway with few synaptic interruptions. Vestibular activity has been localized within cytoarchitectonic field 3a of the monkey, bordering the motor cortex. Cells in the 3a vestibular field have, in general, longer latencies than those in area 2v. Neurons in both fields respond to deep somatic stimulation. Within area 2v, the somatic input is largely from joint receptors. Area 3v receives a high degree of convergence of vestibular and peripheral somatosensory input, including group I (muscle spindle) afferent fibers and cutaneous modalities (Ödkvist et al, 1975). Thus, information from labyrinthine receptors converges with information pertaining to body position and motion.

The specific roles played by the two vestibular areas are not fully understood. Area 2v may receive input from neighboring fields 5 and 7 and, hence, act to integrate information it receives about spatial sensation. In the monkey, neurons in area 2v are sensitive indicators of head motion or visual field motion (Büttner and Buettner, 1978). It is well known that lesions of the parietal lobe result in bizarre disturbance of spatial conceptualization that may have a vestibular component (Schwarz and Fredrickson, 1974). Area 3a, in contrast, has direct fiber connections with area 4 or the motor cortex (Jones and Powell, 1968, 1969). Kornhuber and Aschoff (1964) showed, in fact, that neurons in the cat motor cortex respond to somatic and vestibular stimulation. It would thus appear that this area plays a role in postural adjustments that relate to conscious limb movement.

More recently, a larger cortical region containing vestibular neurons was found in the temporal operculum of the lateral sulcus and the retroinsular area of the monkey (Akbarian et al, 1988). This field, referred to as the parietoinsular vestibular cortex (PIVC), is also a multisensory integrating center. Its neurons are activated by vestibular stimulation, as well as by visual stimulation and stimulation of neck muscles and mechanoreceptors of the skin. From the neural response properties, PIVC may be thought of as a cortical region whose organization is based on optimal stimulus planes for head rotation in space.

The sources within the vestibular complex of axons that ascend to the cortex via the thalamus are still only partially understood. Despite ardent attempts to find specific vestibular thalamic nuclei, it appears that vestibular input to the thalamus is widespread and overlaps the representations of other sensory modalities (Mergner et al, 1981). Liedgren and co-workers

(1976b), in a study of single neurons in the thalamus of squirrel monkeys, found that in addition to a high incidence of short latency responses to vestibular stimulation in the nucleus ventroposterior lateralis (VPL) and the posterior nuclear group (PO), thalamic cells sensitive to vestibular input were scattered throughout the thalamic nuclei that receive somatosensory afferent inputs, including the pulvinar, nucleus centrum medianum, nucleus centralis lateralis, zona incerta, nucleus lateralis posterior (LP), and nucleus ventralis inferior (VPI). The majority of vestibular thalamic neurons also received a somatosensory convergent input. Only 5 per cent of cells recorded throughout the vestibular complex by Liedgren and Rubin (1976) were activated by antidromic discharge from the thalamus. Of these, 76 per cent were found in the LVN. The vestibular neurons that project to the thalamus lacked monosynaptic labyrinthine input but received convergent polysynaptic vestibular and somatosensory volleys, the prominent somatosensory effect being excitation by pressure to subcutaneous tissue and joint manipulation. The presence of vestibulothalamic pathways has been confirmed anatomically using modern tracer methods (Raymond et al, 1976; Condé and Condé, 1978; Büttner and Lang, 1979). In the monkey there appear to be at least two parallel vestibulothalamocortical pathways. One projects from the vestibular nuclei to the nucleus ventroposterior lateralis pars oralis (VPLo), and the other to the region in and around the medial geniculate body and posterior thalamic group (PO). In addition, Magnin and Putkonen (1978) described modulation of single neuron discharges in the thalamic reticular nucleus (RT) and ventral lateral geniculate nucleus (LGV) of the cat under sinusoidal vestibular stimulation in the horizontal plane. These neurons had many of the physiologic properties of cells in the vestibular complex and, in addition, many of them could be driven by optokinetic stimulation. Saccadic responses of these neurons contrast with the lack of oculomotor responses reported for vestibular neurons of VPPL and VPI of monkeys (Büttner and Henn, 1976; Magnin and Fuchs, 1977).

The parallel vestibulothalamic pathways continue as separate projections to the vestibular cortical areas 2v and 3a. After injection of horseradish peroxidase into the anterior ectosylvian vestibular area of the cat, Liedgren and co-workers (1976a) found retrogradely labeled cells in the medial (magnocellular) division of the medial geniculate body. These observations are in accord with earlier anatomic findings and with electrophysiologic results. Neurons with HRP reaction product were occasionally found in LP and at the border between the medial division of MGB and the suprageniculate nucleus. In the monkey, Liedgren and Schwarz (1976) showed short latency vestibular-evoked potentials in this area of the thalamus. Liedgren and associates (1976a) also found in the cat that HRP injections into area 3a resulted in retrogradely labeled cells appearing mainly in the VPLo. Short latency field potentials in response to electrical stimulation of the vestibular nerve were also recorded close to VPL and VPM (located between the lower parts of VPL and VPM). Hawrylyshyn and colleagues (1978) found that electrical stimulation of two specific areas of the thalamus evoked vestibular sensations in human patients. They included the nucleus ventrointermedius (Vim), which corresponds in monkey to the VPLo, the region of the brachium of the inferior colliculus, and the MGB. In addition to receiving input from the vestibular thalamic areas, cortical field PIVC receives input from the frontal eye fields, prefrontal cortex, parietal cortex (area 7), cingulate cortex, somatosensory cortex, area 2v, and oral pulvinar (Akbarian et al, 1988).