

Synaptic Organization and Plasticity in the Auditory System of the Deaf White Cat

Michael A. Muniak, Catherine J. Connelly, Natasha N. Tirko,
Jahn N. O'Neil, and David K. Ryugo

Keywords Auditory nerve • Brain stem • Cochlear degeneration • Cochlear implant • Cochlear nucleus • Congenital deafness • Critical period • Development • Electrical stimulation • Endbulb of Held • Fractal analysis • Spherical bushy cell • Spiral ganglion • Spontaneous discharge rate • Ultrastructure

1 Introduction

The development of a functional auditory sensory system is essential for social communication through spoken language and perception of our external environment. The vertebrate inner ear is a highly specialized structure that transduces airborne sound vibrations into neural signals. The auditory pathway makes use of the physical features of sound encoded by these signals—frequency, intensity, and timing—to construct an auditory scene that includes information about distance, direction, motion, identity, and content. With hearing loss, this information can become severely degraded or absent altogether. The National Institute of Deafness

M.A. Muniak
Garvan Institute of Medical Research, Sydney NSW 2010, Australia

C.J. Connelly • D.K. Ryugo (✉)
Garvan Institute of Medical Research, Sydney NSW 2010, Australia

School of Medical Sciences, University of New South Wales, Sydney NSW 2052, Australia
e-mail: d.ryugo@garvan.org.au

N.N. Tirko
Neuroscience Institute, New York University School of Medicine,
New York, NY 10016, USA

J.N. O'Neil
Johns Hopkins University School of Medicine, Center for Hearing and Balance,
Baltimore MD 21205, USA

and Other Communication Disorders estimates 36 million adults in the United States will be affected by hearing loss by the year 2030 (Gordon-Salant et al., 2010), making it the most common of sensory losses. It has become clear that simply providing peripheral amplification is not the sole solution, as hearing loss can initiate changes in brain organization. Understanding the nature of these changes is essential to the successful implementation of reparative therapies.

Synaptic organization in the auditory system has been shown to be reactive and malleable to experience. In this regard, deafness has important implications for all components in the auditory pathway, from cochlea to cortex. Although the general blueprint for the auditory pathway appears to be established before the onset of hearing, reduced auditory stimulation to the system for a prolonged period after birth has definable pathologic effects on the structural and functional organization of synapses, cells, and pathways. Studying these effects can be accomplished in a number of experimental models, but one of the most reliable is that of the deaf white cat. The deaf white cat is a known model of a cochleosaccular degeneration resembling the Scheibe deformity observed in humans. This defect presents an excellent opportunity for the study of auditory development and structural abnormalities precipitated by congenital deafness. This chapter reviews the current understanding of synaptic organization in the central auditory system in deafness, highlighting observations made in the deaf white cat model. Perhaps most significantly, the restorative effects of electrical stimulation on the auditory system by way of cochlear implantation are presented. The available data demonstrate that synaptic organization in the auditory system is highly plastic to environmental influences.

2 Animal Models of Deafness: Advantages and Limitations

Deafness is a disorder with numerous causes (see the chapter by Brownstein, Shivatzki, and Avraham). Several animal models of deafness have been developed to characterize its consequences under controlled conditions and to reveal the molecular mechanisms that produce these changes. Experimental models include the use of cochlear ablation, chemical deafening, acoustic trauma, and genetic manipulations. Other studies have examined naturally occurring models of deafness such as the congenitally deaf white cat and various other genetic mutations that affect hearing. Animal models of deafness represent the human condition for the study of the effects of profound hearing loss on the central auditory system, consideration of the mechanisms of pathophysiology, and exploration of potential therapies.

The differential consequences of congenital versus acquired deafness often reveal important events involved in development (Parks et al., 2004; Shepherd et al., 2006). Neural activity influences the refinement of the genetic template of brain circuitry, including axonal distribution and synapse formation within the auditory system (Leake et al., 2006; Baker et al., 2010). Depending on the scientific question and goal of the experiment, different methods for inducing deafness are used.

2.1 Surgical Deafening: Cochlear Ablation

Cochlear ablations have been used to study the effects of total auditory deprivation before the onset of hearing (Russell & Moore, 1995; Gabriele et al., 2000). Surgical deafening is accomplished by either drilling away the cochlea to remove the organ of Corti and spiral ganglion (SG; e.g., Illing et al., 1997; Hildebrandt et al., 2011) or transecting the auditory nerve (Koerber et al., 1966). These highly invasive and destructive procedures produce severe changes that extend into the central auditory pathways. The loss and atrophy of neurons and shrinkage of the neuropil are more severe in younger than in older animals (Trune, 1982; Hashisaki & Rubel, 1989). The resultant abnormalities, however, cannot be attributed wholly to the loss of the cochlea because there are other variables that must be considered, including physical trauma to existing blood supply and tissue, inflammation and edema, as well as anterograde degeneration of the auditory nerve fibers that terminate in the cochlear nucleus and retrograde degeneration of auditory efferents originating from the superior olivary complex (Illing et al., 1997). Transsynaptic changes have also been observed following the blockade of auditory nerve activity via tetrodotoxin (Sie & Rubel, 1992), suggesting milder forms of sensory intervention can be used to manipulate brain development.

2.2 Chemical Deafening: Aminoglycoside Ototoxicity

Chemical deafening typically involves the administration of aminoglycosides, causing toxic effects in the kidneys and to auditory and vestibular structures of the inner ear. Aminoglycosides represent a class of more than 130 antibiotics that are used to treat bacterial infections such as tuberculosis, but the prevalence of their use is diminishing (Pakyz et al., 2008). When prescribed at high doses, aminoglycosides damage the auditory receptor cells, resulting in hearing loss, tinnitus, disequilibrium, or a combination of all three. Hearing loss as a result of ototoxicity is gradual, and its extent can be variable due to individual and species differences in susceptibility, efficacy of the particular drug, and mode of administration (Hardie et al., 1998; Leake et al., 1999; McFadden et al., 2004; Hartley et al., 2010).

Mammalian sensory receptor cells do not regenerate when subjected to ototoxic damage, in sharp contrast to those of birds (Tucci & Rubel, 1990). Thus, ototoxic poisoning typically causes irreversible sensorineural hearing loss. The administration of ototoxic drugs in neonatal animals can produce consequences that resemble congenital hereditary deafness because destruction of the organ of Corti occurs before the onset of hearing and causes the obliteration of spontaneous and driven activity in the auditory nerve (Shepherd & Javel, 1997). The effects are not, however, identical to congenital hereditary deafness (Ryugo et al., 2010).

2.3 Noise Deafening: Acoustic Trauma

There are various paradigms for inducing deafness via acoustic trauma, which can cause reorganization within the central auditory system as a result of peripheral deafferentation. Acoustic trauma is produced by exposing animals to a continuous loud sound (typically 100-130 dB SPL) for several minutes to hours in a sound isolation booth (Illing et al., 2005; Mulders et al., 2011). Auditory brain stem response (ABR) recordings to a range of frequencies can determine the approximate degree of impairment after exposure. This trauma can cause temporary and/or permanent hearing loss, making it fundamentally different from the two previously mentioned models.

Acoustic trauma is a complicated phenomenon wherein stereocilia, blood flow, stria vascularis, fibrocytes, and hair cell synapses can be independently damaged. If this damage contributes to receptor cell loss, there can be a subsequent gradual loss of SG cells (Webster & Webster, 1981; Kujawa & Liberman, 2009). After noise exposure, threshold shifts can occur temporarily, whereas after a few weeks postexposure, permanent hearing loss can set in. It has yet to be identified which aspects of inner ear damage are most responsible for which aspects of noise-induced hearing loss. Nevertheless, acoustic trauma is used to study the natural progression of hearing loss and serves as a model for damage prevention using antioxidants and other reagents (Henderson et al., 2006).

2.4 Hereditary Deafness: Genes and Genetic Engineering

There are many naturally occurring models of congenital deafness, such as congenitally deaf white cats, Dalmatian dogs, blue-eyed white alpacas, waltzing guinea pigs, and numerous strains of mice carrying deafness genes. In addition there are knock-in and knock-out mouse models with genetically engineered defects. Among these, the cat and mouse models are the most frequently used in the current literature.

The effects of congenital deafness are not restricted to the auditory nerve and cochlear nucleus (Saada et al., 1996; Shepherd & Hardie, 2001). Transneuronal alterations in cell size and number, receptive field properties, and laminar organization are expressed at higher nuclei of the auditory system, including the superior olivary complex (West & Harrison, 1973; Schwartz & Higa, 1982), inferior colliculus (Snyder et al., 2000), and auditory cortex (Klinke et al., 2001; Kral et al., 2001). Thus, the reactive but pathologic alterations that have been observed in parts of the central auditory system are reflections of a wider range of possible changes throughout the brain initiated by hearing loss and deafness.

3 The Deaf White Cat

The deaf white cat has long held a fascination to humans (Fig. 1). The earliest observations on the association between heritable deafness in the cat and a white coat can be traced back to the 19th century. A brief correspondence from 1829 noted that all deaf offspring of a deaf white female cat were invariably white (Bree, 1829), an anecdote that merited a mention by Darwin in his landmark work (Darwin, 1859). Over the following years, there was ongoing speculation regarding the relationship between feline deafness, white fur, the preponderance of blue eyes, and gender (for instance, see the back and forth between Darwin and Tait: Darwin, 1859, 1875; Tait, 1873, 1883). More rigorous analyses in the 20th century have since identified a single autosomal dominant locus, *White* (*W*), as responsible for the pleiotropic effects, including a white coat, blue eyes, and deafness. All three features can be attributed to an absence or abnormality of melanocytes, although the correlation between white coat color, blue irises, and deafness is imperfect. White cats exhibit white fur of varying length but can be born with a colored spot that fades with age. Moreover, they may be either unilaterally or bilaterally deaf, or simply hard-of-hearing, demonstrating varying degrees of loss, from mild to profound (Bamber, 1933; Wilson & Kane, 1959; Bergsma & Brown, 1971; Mair, 1973).

The deaf white phenotype has been reported in multiple species, including the mouse (Chabot et al., 1988; Ruan et al., 2005), dog (Hudson & Ruben, 1962; Clark et al., 2006), mink (Hilding et al., 1967), horse (Haase et al., 2007, 2009), rat (Tsuji-mura et al., 1991), Syrian hamster (Hodgkinson et al., 1998), alpaca (Gauly et al., 2005), and human (Beighton et al., 1991). Such conditions are distinct from albinism, though the absence of pigment can often pervade the whole body.



Fig. 1 Photograph of a congenitally deaf white cat outfitted with a cochlear implant (Clarion II; donated by Advanced Bionics Corporation). The signal transmitter sits on top of the head and is magnetically coupled to the receiver, which is surgically placed under the skin. A six-channel lead extends from the receiver and is inserted into the cochlea. The external microphone and speech processor are housed in a backpack custom fitted to the cat

Investigations of the genetic basis for distinctive coat color phenotypes represent some of the earliest mapped and characterized genetic mutations (Silvers, 1979). Early in embryogenesis, melanoblasts, also known as pigment precursor cells, migrate from the neural crest to the skin, eye, and inner ear. Mutations affecting any step in this migration pathway—proliferation, survival, or distribution—are often expressed as coat color variation. Genes identified in these early events include *Pax3*, *Mitf*, *Slug*, *Ednrb*, *Edn3*, *Sox10*, and *Kit* (Epstein et al., 1991; Tachibana et al., 1992, 1994; Hodgkinson et al., 1993; Baynash et al., 1994; Attie et al., 1995; Herbarth et al., 1998; Southard-Smith et al., 1998; Syrris et al., 1999; Sanchez-Martin et al., 2002). A well-known example of this phenotype in human literature is that of Waardenburg syndrome (Waardenburg, 1951). This condition alone accounts for up to 5% of cases of congenital deafness worldwide (Nayak & Isaacson, 2003), and shares some clear parallels with the deaf white cat: heterochromia iridum, a white forelock, and congenital deafness. With such phenotypic similarities, studying the central effects of congenital hearing loss in the white cat may contribute to our understanding of the developmental consequences of deafness in humans.

3.1 Abnormal Cochlear Morphology

Degeneration in the inner ear of congenitally deaf white cats was first reported at the turn of the 20th century (Rawitz, 1897; Alexander, 1900; Alexander & Tandler, 1905). Many subsequent observations have described this condition in detail, which is characterized by a collapse of Reissner's membrane onto the undifferentiated organ of Corti, a thinning of the stria vascularis, and a malformation of the tectorial membrane (Fig. 2; Wolff, 1942; Wilson & Kane, 1959; Boshier & Hallpike, 1965;

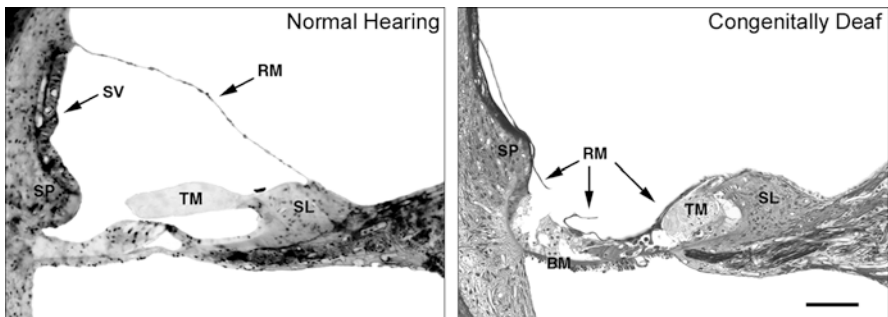


Fig. 2 Light micrographs of mid-modiolar, Nissl-stained cochlear sections showing the organ of Corti from normal hearing (left) and congenitally deaf (right) cats. Note the collapsed Reissner's membrane and absent organ of Corti from the deaf cat. Scale bar = 50 μ m. BM, basilar membrane; RM, Reissner's membrane; SL, spiral limbus; SP, spiral prominence; SV, stria vascularis; TM, tectorial membrane. (Adapted from Ryugo et al., 2003)

Mair, 1973; Rebillard et al., 1981a; Ryugo et al., 2003). This pattern of cochlear deterioration is the predominant pathological finding in these animals (Ryugo et al., 2003). Degradation is also present in the saccular partition (Mair, 1973), and the combined cochleosaccular defects closely mirror that of the Scheibe deformity of deaf-mutism reported in humans (Scheibe, 1892). Early observers of this coincidence advocated for the use of animal models such as the deaf cat in research programs studying congenital deafness (Fraser, 1924).

Several studies have described the early stages of cochlear degeneration (Bosher & Hallpike, 1965; Mair, 1973; Mair & Elverland, 1977; Rebillard et al., 1981a; Ryugo et al., 2003; Baker et al., 2010). At birth, the cochlear morphology of kittens destined to become deaf is similar to that of pigmented kittens, with inner and outer hair cells intact in both groups (Heid et al., 1998; Baker et al., 2010). At postnatal day 3, ultrastructural abnormalities are apparent in stria cells (Mair & Elverland, 1977). Definite pathological signs begin to emerge by postnatal day 5 (Bosher & Hallpike, 1965; Mair, 1973; Baker et al., 2010): the stria vascularis appears abnormally thin and Reissner's membrane begins to elongate, causing it to ruffle irregularly along its length. In addition, the tectorial membrane begins to shrink, curling upon itself and rolling against the spiral ligament. The expansion of Reissner's membrane continues in rapid fashion such that by the end of the second postnatal week it has collapsed completely. At this point, the tectorial membrane is also tightly bound to the spiral ligament. By the start of the third postnatal week the pathology appears complete, with a total absence of the cochlear duct, organ of Corti, and hair cells. The specific genetic and molecular cause(s) of this cochlear degeneration in the white cat remain unknown (Geigy et al., 2007).

The congenital degeneration of the cochlea typically occurs bilaterally, but it is also possible to find instances of unilateral and/or partial malformations accompanied by a hearing impairment rather than a profound loss (Mair, 1973; Rebillard et al., 1981a; Ryugo et al., 1998). Early reports suggested that cochlear degeneration is an all-or-nothing phenomenon (Bosher & Hallpike, 1965; Bergsma & Brown, 1971; Mair, 1973), but later research demonstrated that differing degrees of pathological severity are possible, and that the degenerative process is not necessarily continuous with age (Rebillard et al., 1981a; Ryugo et al., 2003).

A second, less common type of cochlear pathology has also been identified in congenitally deaf white cats (Ryugo et al., 2003). This pattern takes the form of excessive growth of epithelial cells on Reissner's membrane and within the membranous labyrinth. This hypertrophic growth effectively smothers the organ of Corti and stria vascularis, causing Reissner's membrane to completely fill the space of the cochlear duct. Unlike the degenerative collapse described previously, this abnormal growth may manifest at or before birth (Baker et al., 2010). Less frequently, a combination of both exuberant growth at the apex and collapse of Reissner's membrane at the base of the cochlea has been observed (Ryugo et al., 2003). All aforementioned types of cochlear pathologies, however, result in sensorineural deafness.

3.2 *Physiological Determination of Hearing Status*

The hearing status of deaf cats can be evaluated using various physiological measures such as evoked potentials (i.e., ABRs) or cochlear microphonics. Behavioral audiometry can also be used to test hearing (Bergsma & Brown, 1971; West & Harrison, 1973), but such metrics are indirect indicators of brain activity. When undertaking measurements, one must remain aware that the cochlea is functionally immature at birth (Pujol & Marty, 1970) and continues to develop over the initial postnatal days regardless of final hearing status (Mair, 1973). Further, the ear canals of kittens are not fully open until the third or fourth postnatal week (Olmstead & Villablanca, 1980; Ryugo et al., 2003). Behavioral responses elicited by sound have been shown to take 4 weeks to fully develop in normal hearing kittens (Olmstead & Villablanca, 1980).

The first physiological test for the presence of sound-evoked activity in the cochleae of congenitally deaf cats was the cochlear microphonic, which was measured by placing an electrode lead near the round window (Howe, 1935a; Suga & Hattler, 1970). Immediately after birth, a small cochlear microphonic may be observed (Mair & Elverland, 1977). Subsequent testing of white cats, however, shows a complete absence of sound-evoked activity in some, suggesting a nonfunctioning cochlea. Indeed, subsequent histological investigations showed significant atrophy in the cochleae of all physiologically silent subjects. Accordingly, measurements of the endocochlear potential failed to find a positive resting potential in what remains of the cochlear duct in these subjects (Suga & Hattler, 1970). Similar findings have been shown when measuring evoked potentials of the brain (Suga & Hattler, 1970; Elverland et al., 1975; Rebillard et al., 1981a,b; Heid et al., 1998; Ryugo et al., 2003). ABR measures also indicate that some cats are not completely deaf, but rather have elevated response thresholds. The cochlear ducts of these cats appear relatively normal in histological sections, but sometimes display an outward bulging of Reissner's membrane and a thin tectorial membrane, suggestive of a partial expression of the typical cochlear defect (Ryugo et al., 2003).

Studies of multiple age groups have demonstrated that hearing status does not change appreciably with age (Rebillard et al., 1981b; Ryugo et al., 2003), echoing histological evidence (Rebillard et al., 1981a; Ryugo et al., 2003). Repeated ABR measures of cats from birth to adulthood showed that if an animal exhibits normal hearing, there was virtually no change in threshold sensitivity over time (Ryugo et al., 2003). The animals that were profoundly deaf failed to hear from the outset. Lastly, animals that showed partial deafness had elevated ABR response thresholds that did not change over the course of development. This observation suggests that the overall hearing status of these cats does not change significantly after the initial 3 weeks of cochlear degeneration, and kittens that are profoundly deaf never experience normal hearing.

The spontaneous activity of auditory nerve fibers can also be used to evaluate the status of the cochlea. In normal hearing cats, spontaneous firing rates reflect response thresholds of individual fibers, and single-unit recordings can be grouped

into at least two classes: fibers with high spontaneous discharge rates (e.g., >18 spikes/s) have low thresholds to pure tones, whereas fibers with low spontaneous discharge rates (e.g., <18 spikes/s) have high thresholds for evoked responses (Kiang et al., 1965; Liberman & Kiang, 1978; Evans & Palmer, 1980; Fekete et al., 1984). In cats with hair cell damage due to acoustic trauma, only a small percentage of nerve fibers originating from the damaged region of the cochlea show low spontaneous firing rates, with the remainder showing no spontaneous or evoked activity whatsoever (Liberman & Kiang, 1978; Liberman & Dodds, 1984). Similarly, in profoundly deaf cats little to no spontaneous activity has been recorded and accordingly no evoked activity observed (Ryugo et al., 1998). Partially deaf cats, however, sometimes exhibit elevated spontaneous discharge rates, occasionally exceeding 100 spikes/s, despite evoked response thresholds of greater than 60 dB SPL (Ryugo et al., 1998). These cats exhibited structural abnormalities in the cochlea, as described previously, but retained a full complement of inner and outer hair cells. These results indicate that all electrical activity entering the central auditory system is significantly altered in congenitally deaf cats.

3.3 Reintroduction of Neural Activity via Cochlear Implants

Neural activity has been found to be extremely important for normal postnatal development and maintenance of sensory systems (Wiesel & Hubel, 1963; Van der Loos & Woolsey, 1973). Indeed, the process of hearing is necessary for refinement of the genetic blueprint for auditory circuitry, including axonal distribution, pruning, and synapse formation (Parks et al., 2004; Shepherd et al., 2006; Walmsley et al., 2006; Ryugo & Limb, 2009; Sanes & Bao, 2009). Deprivation of auditory experience can introduce a series of pathologic and atrophic changes that include more widespread distributions of axonal projections (Leake et al., 2006), abnormal projections (Nordeen et al., 1983a,b; Moore & Kitzes, 1985), delayed maturation (Sanes, 1993; Kandler, 2004), and language impairments (Robbins, 2006).

When experiential deprivation can be traced to the malfunction of a sensory end organ, it may be possible to reintroduce sensation via direct stimulation of the remaining neural circuits, bypassing the impaired receptors. The cochlear implant works on this principle by directly stimulating SG cells, thus restoring activity to the auditory pathway (Rauschecker & Shannon, 2002). Not long after serious development began on electrical auditory prostheses for human use, the potential of the congenitally deaf cat was recognized as a model for examining the central effects of cochlear implantation (Elverland et al., 1975). Various methods have been used to reintroduce sound-evoked activity to genetically and neonatally deafened cats (Matsushima et al., 1991; Lustig et al., 1994; Klinke et al., 1999), including a miniaturized six-channel cochlear implant that utilizes a speech processor identical to that used with human patients (Kretzmer et al., 2004). With such devices, cats have been trained with food rewards to respond to specific sounds,

indicating that behaviorally relevant signals are being processed (Klinke et al., 1999; Kretzmer et al., 2004; Ryugo et al., 2005; O'Neil et al., 2010). For instance, animals were trained to approach their food bowls in response to a specific bugle call, but not other bugle calls. Importantly, the bugle call required specific spectral content, as monotonic calls with the same rhythmic structure failed to elicit a behavioral response.

4 Synaptic Development and Organization: Effects of Deafness and Electrical Stimulation

In the auditory system, structure and function have exhibited a mutually interactive role in brain development and organization. The relatively homogeneous sound-evoked activity of auditory nerve fibers (Kiang et al., 1965) is transformed into a variety of response patterns by the different cell types found in the cochlear nucleus (Young & Oertel, 2003). These reshaped signals are then conveyed to higher auditory centers, each with their own resident cell types. The spectrum of responses depends not only on the synaptic organization of axonal terminations, but also on intrinsic neurons, descending influences, receptor distributions, types of ion channels, and second messenger systems. Together, these features determine the signaling capabilities for each cell class. To understand how sound is processed, researchers must discern distinct cell populations, analyze their synaptic profiles, and identify features of their signal processing capabilities.

To represent sound accurately, it is essential that neural activity be time locked to acoustic events. Sound conveys meaning through the temporal fluctuations of frequency and amplitude. As such, neural activity pertaining to sound must be synchronized to specific features of the physical stimulus. Different sounds are distinguished by the distinctive characteristics of their time-varying features (e.g., the howl of a wolf vs. a train whistle). It is broadly accepted that different physical features of sound are parsed and encoded along separate pathways in the brain. Eventually, these separate streams of information must reconvene with precise timing to produce an accurate conscious percept of the stimulus. Temporal fidelity is clearly an important feature of the auditory system, and synapses play a crucial role in maintaining this accuracy.

Synapses are defined by both presynaptic and postsynaptic characteristics. Presynaptic factors of neural transmission include vesicle size, shape, and number; types of neurotransmitters present; available neuromodulators; and transport molecules. Postsynaptic influences include the type and distribution of transmitter receptors, subunit composition of these receptors, shape and curvature of the postsynaptic density (PSD), and associated second-messenger and retrograde signaling systems. Moreover, the size and distribution of synaptic terminals, target compartment (e.g., cell body, dendritic shaft, or spine), and origin of the projection must also be considered. Proper transmission of acoustic signals thus depends on

the precise composition and spatial arrangement of release sites on their cellular targets. Abnormalities of synaptic structure or distribution, such as those resulting from congenital deafness, will alter signal transmission, corrupting the neural representation of the acoustic stimulus.

4.1 *Spiral Ganglion Cells*

SG cells are located within Rosenthal's canal in the cochlea. Each ganglion cell emits a peripheral process that contacts hair cells in the organ of Corti and a central process that bundles together with other auditory nerve fibers to form the auditory nerve. The auditory nerve conveys all known auditory information from the cochlea to the brain (Nayagam et al., 2011). Some of the earliest histological investigations of congenitally deaf white cats have observed SG cell loss in these subjects (Alexander & Tandler, 1905; Howe, 1935b; Mair, 1973; West & Harrison, 1973; Pujol et al., 1977). Ganglion cell survival was thought to depend on the health of the organ of Corti, with losses occurring secondary to hair cell degeneration (Webster & Webster, 1981; Spoendlin, 1984; Leake & Hradek, 1988; Hardie & Shepherd, 1999), but recent data suggest that the supporting cells are more crucial to ganglion cell survival than hair cells (Zilberstein et al., 2012). Cell reductions are greatest in the middle regions of the cochlea (Fig. 3; Elverland & Mair, 1980; Heid et al., 1998; Chen et al., 2010), and the magnitude of loss increases with age (Mair, 1973; Heid et al., 1998; Chen et al., 2010). Even before this effect becomes statistically significant, there is a slow increase in unmyelinated cells, suggesting the degradation of the myelin sheath may be a harbinger of cell loss (Elverland & Mair, 1980). However, any remaining SG cells, even after prolonged periods of deafness, retain myelination of their central processes (Ylikoski & Savolainen, 1984; Shepherd & Javel, 1997).

The presence of SG cells is obviously crucial to the success of cochlear implants, as they directly stimulate ganglion neurons. Curiously, studies of human temporal bones of deceased implant recipients show no correlation between SG cell loss and performance on speech recognition tasks (Nadol et al., 1989, 2001; Khan et al., 2005a,b; Fayad & Linthicum, 2006). The implication is that although there may be a minimum threshold for ganglion cell survival and cochlear implant benefit, the "heavy lifting" is performed by the brain.

Electrical stimulation has been postulated to have a positive effect on SG cell survival, slowing the rate of degeneration (see the chapter by Leake, Stakhovskaya, and Rebscher). Most studies on this topic have used ototoxically deafened cats, and results have been mixed. Some report that electrical stimulation increases ganglion cell density (Leake et al., 1991, 1999; Mitchell et al., 1997), whereas others find no effect (Araki et al., 2000; Coco et al., 2007; Chen et al., 2010). Of note, a change in cell density does not necessarily mean that there is a change in cell number because tissue shrinkage can lead to an increase in density.

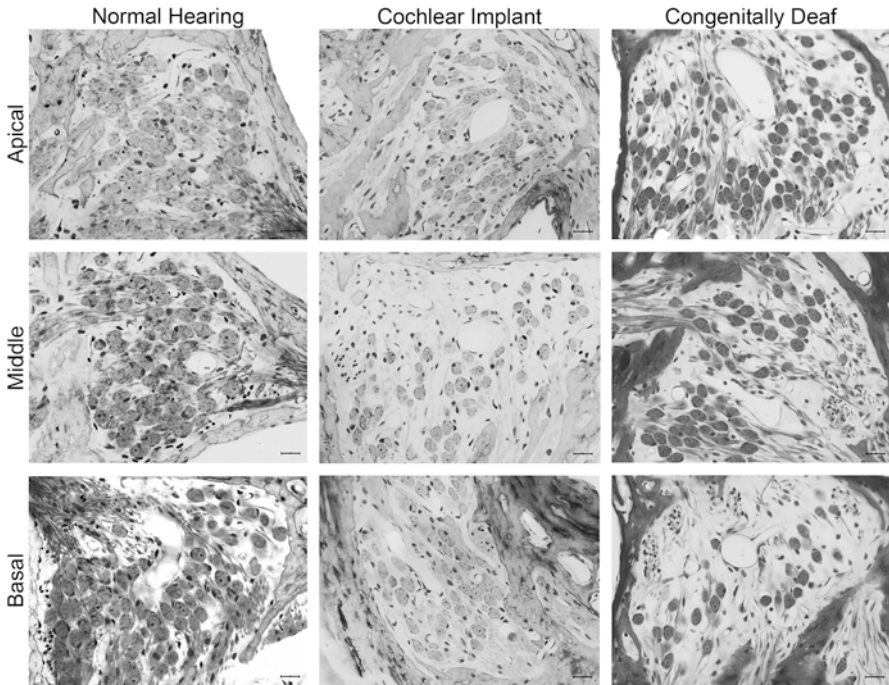


Fig. 3 Photomicrographs of the Nissl-stained spiral ganglia of 6-month-old cats through the middle of each cochlear turn illustrating cell size, density, and the effects of congenital deafness and cochlear implantation. In general, deafness with or without electrical stimulation—via a cochlear implant—results in a loss of size and number of primary neurons. There was no significant difference between the implanted and un-implanted deaf cats, but there were significant reductions of ganglion cell density when compared to normal hearing cats. Scale bars = 20 μm . (Adapted from Chen et al., 2010)

Only one report to date has investigated the effects of implantation on SG cell survival in congenitally deaf white cats (Chen et al., 2010). Quantitative analyses showed no marked improvement in terms of SG cell counts, cell density, or cell size when compared to deaf, unstimulated cats. Cell sizes from both groups were smaller than that of normal-hearing cats. Under the conditions of hereditary deafness, chronic electrical stimulation provides no clear benefits to SG cells despite unambiguous evidence of significant effects on synapses in the central auditory system.

4.2 Cochlear Nucleus

The cochlear nucleus serves as the gateway to the central auditory system, receiving all sensory input and giving rise to all ascending pathways (Lorente de N6, 1981).

The manner in which this nucleus distributes information to the rest of the brain is presumed to contain clues about stimulus coding, feature detection, and functional circuits. Sound stimulation during early development is critical for the normal organization of auditory structures (Rubel et al., 1984). Sensory deafferentation results in severe alterations in the development of the cochlear nucleus (Trune, 1982; Lustig et al., 1994), most certainly impairing its processing capacity.

In congenitally deaf cats, cochlear nucleus volume is reduced by approximately 50%, accompanied by increases in cell density (Saada et al., 1996). In the anteroventral cochlear nucleus, cell density increased by 40%, whereas a 10% increase was observed in the dorsal cochlear nucleus. Similar changes were observed with astrocyte density. These observations reveal a differential impact on cells in the cochlear nucleus to congenital deafness, suggesting selective processing impairments at this level. Such changes may impose significant limits on the restorative potential of auditory prostheses.

4.2.1 Spherical Bushy Cells and the Endbulb of Held

Auditory nerve fibers are the primary source of excitation to cells of the ventral cochlear nucleus (Koerber et al., 1966). In the anteroventral cochlear nucleus, myelinated auditory nerve fibers give rise to large, axosomatic synaptic terminals known as endbulbs of Held (Held, 1893; Ramón y Cajal, 1909; Lorente de Nó, 1981). The structure of this giant synaptic terminal has been extensively studied as a model for synapse formation, transmission, and reaction to deafness (Limb & Ryugo, 2000; Oleskevich et al., 2004; Baker et al., 2010).

During postnatal development, the endbulb begins as a solid, spoon-shaped growth cone having many filopodia and transforms into an intricate axosomatic structure (Fig. 4, top; Ryugo & Fekete, 1982). The calyx-like appearance of the mature endbulb is marked by the emergence of several thick, gnarled branches that divide repeatedly to form an elaborate arborization of *en passant* and terminal swellings that clasp the postsynaptic spherical bushy cell (SBC). The endbulb is one of the largest synaptic endings in the brain (Lenn & Reese, 1966), and one to three endbulbs selectively contact a single SBC (Brawer & Morest, 1975; Cant & Morest, 1979; Ryugo & Sento, 1991). They can contain up to 2000 release sites (Ryugo et al., 1996), transmitting activity with high fidelity to the postsynaptic SBC (Pfeiffer, 1966; Manis & Marx, 1991; Babalian et al., 2003). The size and evolutionary conservation of endbulbs among terrestrial vertebrates emphasize its crucial role in vertebrate hearing, ensuring that spike activity is temporally coupled to acoustic events (Ryugo & Parks, 2003).

Auditory perception is sensitive to time differences in the range of 10–20 μ s, making it clear that precision in synaptic transmission is the norm (Grothe, 2000). The endbulb of Held is important for processing timing cues used for sound localization, as well as time-varying cues in speech such as voice onset, stressed syllables, gaps, and amplitude modulation. Even minor perturbations in synaptic

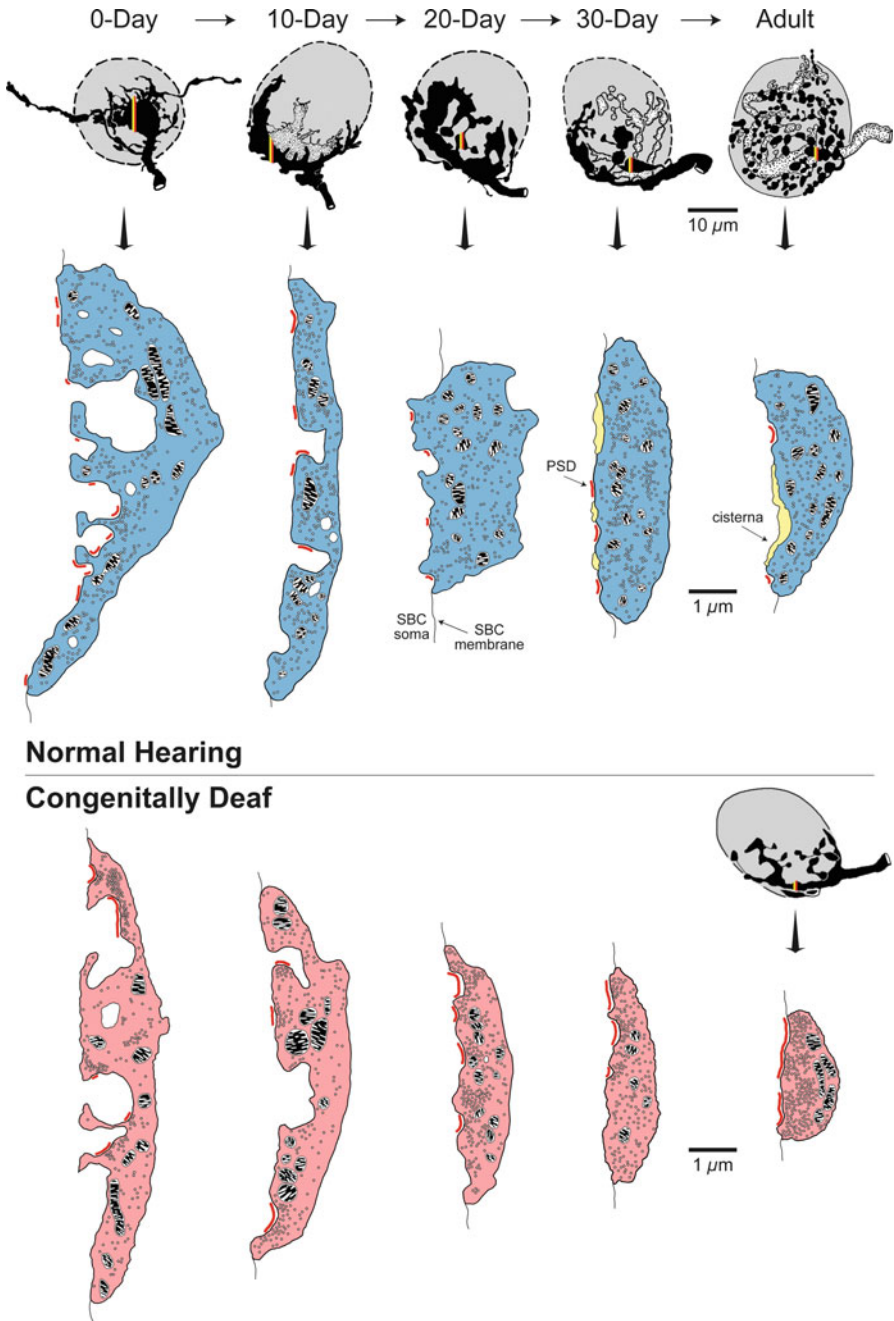


Fig. 4 Development of the endbulb of Held in normal hearing (top) and congenitally deaf (bottom) cats from birth to adulthood. At birth, the postnatal endbulb (black) in normal hearing cats begins as a club-shaped ending with many filopodia and appendages. With maturation, the

transmission at the endbulb, such as jitter, delay, or failure, are predicted to disrupt the accurate processing of time-varying features.

In normal hearing cats, individual endbulb arborizations have been shown to systematically vary with respect to their average spike rates (Fig. 5; Sento & Ryugo, 1989). Endbulbs from auditory nerve fibers having high levels of spontaneous discharge rates exhibit modest levels of branching with relatively large *en passant* and terminal swellings. In contrast, endbulbs from fibers having relatively low spontaneous rates exhibit highly elaborate branching with relatively small *en passant* and many terminal swellings. These differences in branching complexity were confirmed by statistically significant differences in fractal values. Moreover, the larger swellings on highly active endbulbs resembled the swollen endings of overactive terminals observed in other systems, likely caused by the cumulative fusion of synaptic vesicles (Heuser & Reese, 1973; Boyne et al., 1975; Burwen & Satir, 1977). An analogous relationship between spontaneous rate and endbulb morphology has also been observed in guinea pigs (Tsuji & Liberman, 1997), suggesting this trend reflects a fundamental organizational principle in mammals.

Electron microscopy was used to study the fine structure of endbulb terminals on SBCs. At birth, terminals show a convoluted membrane abutment to SBCs, but over the course of development this profile becomes less complex (Fig. 4, top; Baker et al., 2010). Numerous PSDs are evident within each terminal, showing a characteristic dome-shaped curvature. In addition, cisternae appear between endbulb terminals and SBCs in more mature animals. It was observed that endbulbs arising from fibers with relatively low levels of spike discharges were associated with larger PSDs, whereas those from fibers with relatively high spike discharge rates had smaller but more curved PSDs, larger mitochondria, and greater numbers of associated synaptic vesicles (Fig. 5; Ryugo et al., 1996). These data are consistent with observations from rats exposed to repetitive tones or silence (i.e., high vs. low activity); stimulated animals possessed endbulbs with smaller PSDs compared to animals exposed to silence (Rees et al., 1985). The interpretation of this phenomenon is that small synapses facilitate the diffusion of transmitter away from the

←

Fig. 4 (continued) club fenestrates and primary branches emerge. These primary branches continue to grow and branch, forming an elaborate nest around the postsynaptic SBC (gray). The endbulb is composed of a network of fine branches that interconnect numerous swellings that house synapses. Profiles of endbulb swellings (approximated on endbulb as a yellow/red stripe) also show developmental trends (blue, hearing; pink, deaf). Endbulbs at birth have a convoluted surface abutting the SBC, which becomes less complex into adulthood. Endbulbs of deaf animals are generally smaller than normal. The number of PSDs (red) at birth in deaf animals is less than half that of normal. Although mature endbulbs of both deaf and normal animals have the same number of PSDs, the PSDs of deaf animals are longer and flatter than the normal convex PSDs. Deaf endbulbs exhibit an increase in synaptic vesicle density near the PSDs. No remarkable differences are seen with respect to mitochondria size or volume fraction between the two groups. Endbulbs of normal cats begin to develop cisternae (yellow) around postnatal day 10, whereas deaf endbulbs never develop them to any noticeable degree. (Adapted from Ryugo & Fekete, 1982; Ryugo & Spirou, 2009; Baker et al., 2010)

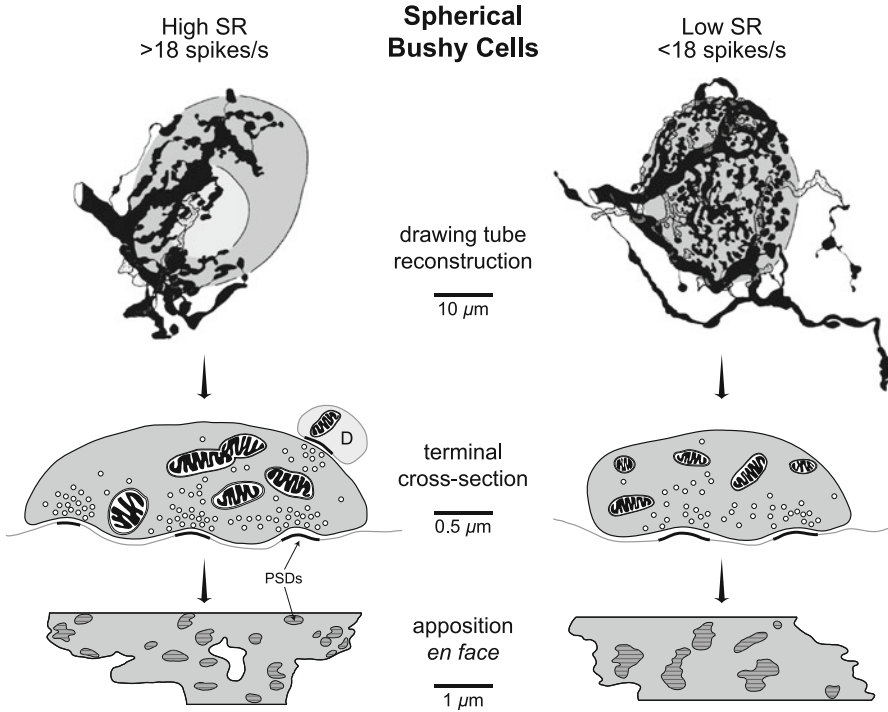


Fig. 5 Summary diagram illustrating endbulbs of Held and activity-related morphology. Endbulbs arising from low spontaneous rate (SR), high-threshold auditory nerve fibers are more highly branched and elaborate compared to those of high-SR, low-threshold auditory nerve fibers. Such differences are observed even when endbulbs are from the same animal and matched in frequency sensitivity, implying the differences are due to activity differences. Cross-sections through endbulb terminals (middle) show intracellular features; lower figures are *en face* views of terminal appositions (bold outline) reconstructed from ultrathin sections (horizontal lines), showing synaptic area (dark-gray regions). Low-SR fibers produce larger but fewer synapses and have smaller mitochondria. In contrast, endings of high-SR fibers express smaller but more numerous synapses, exhibit greater curvature of their postsynaptic densities, contain more synaptic vesicles, have larger mitochondria, and form more axodendritic (D) synapses. (Adapted from Sento & Ryugo, 1989; Ryugo et al., 1996)

active zone, and so are more efficient for rapid and repetitive discharges. These results demonstrate that the synapse structure of endbulbs is clearly plastic and subject to activity-related influences.

Neural activity in SG cells and synaptic transmission at their terminal endings, such as the endbulb, appear to be essential for the normal development of both endings and target neurons (Rubel & Fritzsch, 2002). Given the transneuronal degeneration of SG cells after hair cell loss, it is not surprising that cochlear nucleus cells share a similar fate when ganglion cells degenerate; they either die or shrink in size (Trune, 1982). As expected, in congenitally deaf white cats, numerous studies

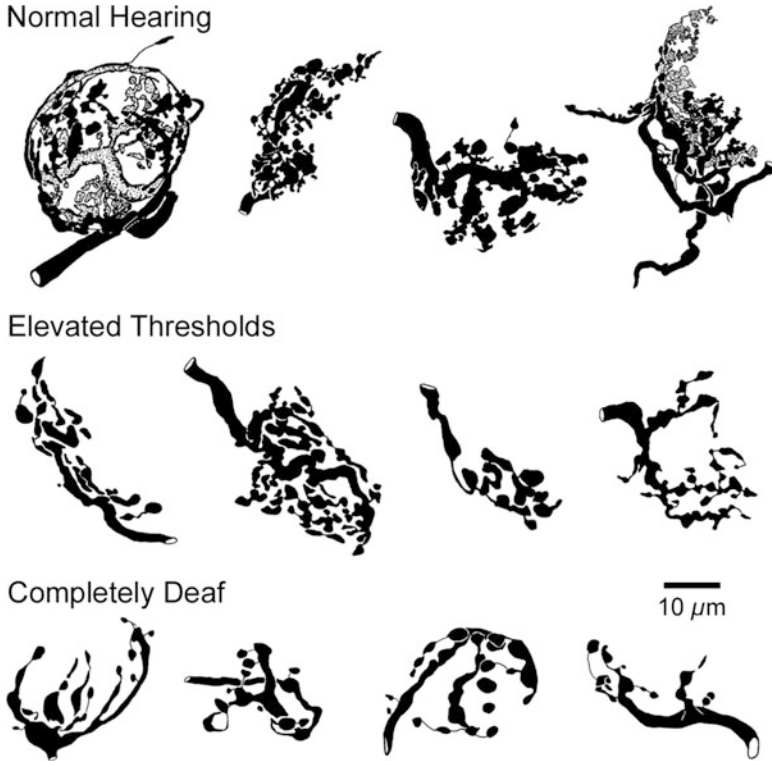


Fig. 6 Reconstructions of horseradish peroxidase-labeled endbulbs of Held for normal hearing cats, hard-of-hearing cats, and congenitally deaf white cats. Note the branching complexity is generally diminished as hearing sensitivity worsens. Normal cats have the most elaborate branching, hard-of-hearing cats were less elaborate, and congenitally deaf cats had the least complicated arborization. The complexity correlates inversely to hearing status, and not length of deafness. (Adapted from Ryugo et al., 1997, 1998)

have reported atrophic changes in the size of SBCs with reductions ranging from 30% - 50% (West & Harrison, 1973; Larsen & Kirchhoff, 1992; Saada et al., 1996; O’Neil et al., 2010). Such decreases were not found in neurons of nonauditory nuclei in the brain stem, implying changes were specific to the auditory pathway (Saada et al., 1996).

Given the distinctive form of the endbulb, and the influence of synaptic activity on its morphology, it was predicted that congenital deafness—an extreme form of auditory nerve inactivity—should result in obvious and definable abnormalities. Indeed, the degree of complexity in the arborization of the endbulb appears to be graded with respect to hearing threshold, as quantified by fractal analysis (Ryugo et al., 1997, 1998). In profoundly deaf cats, the extent and complexity of endbulb branching was significantly atrophic compared to normal hearing cats, with thin branches and reduced numbers of associated swellings (Fig. 6, bottom).

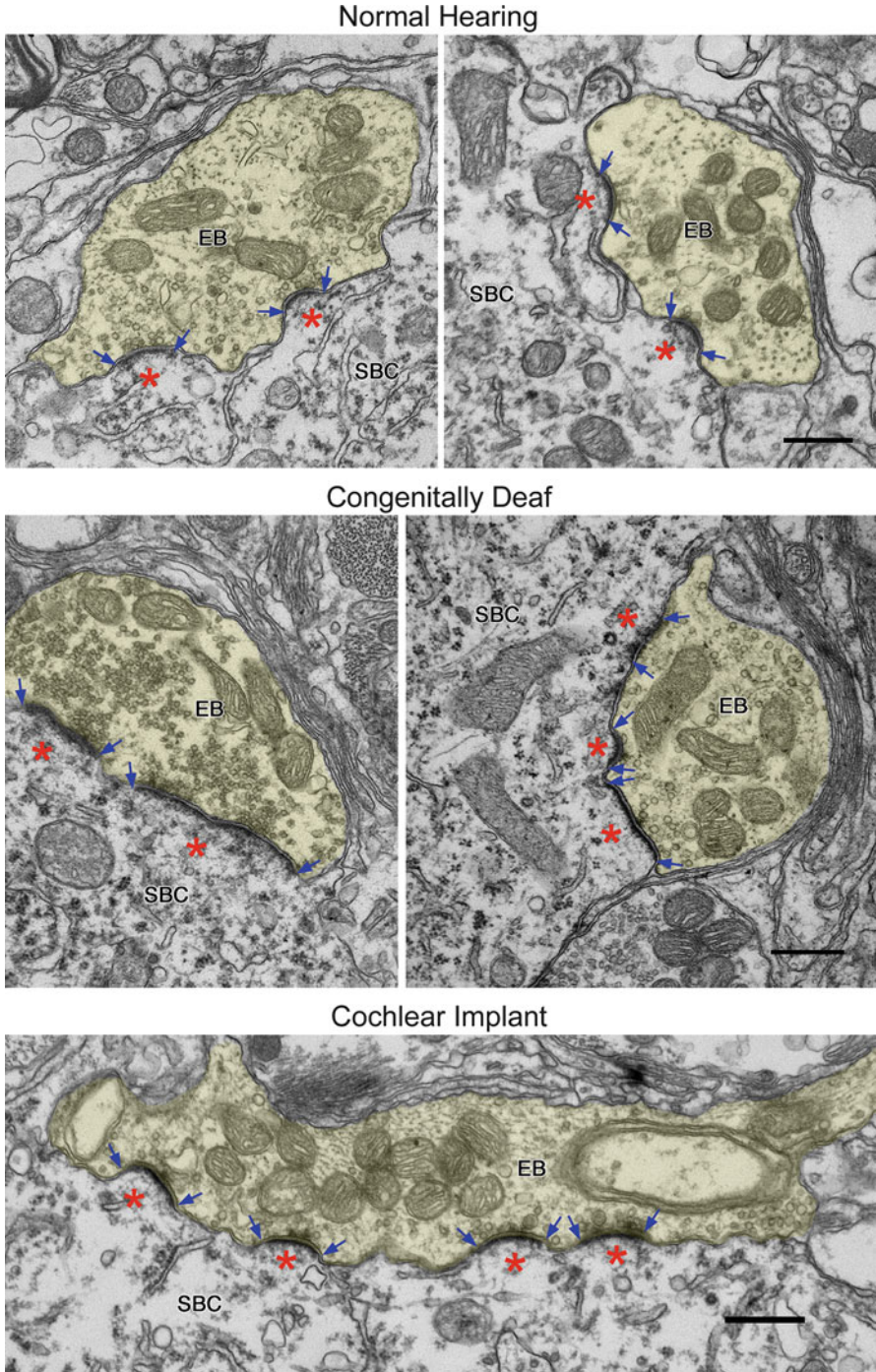


Fig. 7 Electron micrographs showing endbulbs of Held (yellow shading) in normal, congenitally deaf, and implanted cats. PSDs (asterisks, delimited by arrows) are indicative of synaptic release

Hard-of-hearing cats displayed endbulbs with intermediate levels of arbor complexity; fractal values for these cats were statistically different from both completely deaf and normal-hearing cats (Fig. 6, middle). Normal-hearing cats possessed the most elaborate and complex endbulb arborizations (Fig. 6, top).

When endbulbs from each cohort were examined at greater resolution with an electron microscope, additional abnormalities were found as a result from hearing loss (Ryugo et al., 1997, 1998). In normal hearing cats, endbulbs gave rise to numerous punctate, dome-shaped PSDs (Fig. 7, top). In sharp contrast, endbulbs of congenitally deaf cats exhibited flattened and hypertrophied PSDs (Fig. 7, middle). In addition, there was an increase in synaptic vesicle density in proximity to the release site and a loss of intermembraneous cisternae (Baker et al., 2010). Interestingly, other synaptic abnormalities, such as reduced number and size of PSDs, could be observed at birth in some white kittens, well before pathological symptoms are evident in the cochlea (Fig. 4, bottom; Baker et al., 2010). Endbulb synapses from cats with a hearing loss, but that were not deaf, showed intermediate PSD size and curvature between those of normal hearing and completely deaf cats (Ryugo et al., 1998). These observations emphasize that neural activity has an influence on structural properties down to the synaptic level. Further, the silencing of neural activity may be perinatal in congenitally deaf animals, involving a loss of spontaneous bursting activity from the cochlea before its destruction (Jones et al., 2007; Tritsch et al., 2007).

In hard-of-hearing cats, synaptic abnormalities are also evident. Transmission irregularities have been reported in the DBA/2J mouse, a strain that exhibits adolescent-onset hearing loss (Wang & Manis, 2005, 2006). The presence of these irregularities introduced jitter to, and even caused failure of, signal transmission from the presynaptic endbulb to the postsynaptic SBC, normally an extremely secure synapse (Pfeiffer, 1966). Such anomalies are predicted to corrupt the processing of timing information, such that even moderate hearing loss might produce perceptual difficulties in addition to problems involving elevated thresholds.

The synaptic changes observed in congenitally deaf white cats are likely due to the loss of neural activity in the auditory nerve rather than a genetic syndrome unrelated to spike activity. First, ototoxic deafening of normal cats produces a similar flattening and hypertrophy of PSDs (Ryugo et al., 2010). Second, similar pathologic changes in endbulb morphology have been observed in congenitally deaf guinea pigs (Gulley et al., 1978) and congenitally deaf (*shaker-2*) mice (Limb & Ryugo, 2000; Lee et al., 2003). Because these other animals are deaf by completely independent hereditary processes, yet show similar synaptic anomalies,

←
Fig. 7 (continued) sites and lie along the surface of the postsynaptic SBC, evident by their dense, fuzzy appearance facing the synaptic cleft. Normal hearing cats show distinct dome-shaped PSDs. In congenitally deaf cats, PSDs are abnormal, becoming flat and elongated. The endbulb of a congenitally deaf cat that received electrical stimulation from a cochlear implant at a young age exhibits synapses with normal morphology. Scale bars = 0.5 μm . (Adapted from Ryugo et al., 2005; O'Neil et al., 2010)

Spherical Bushy Cells

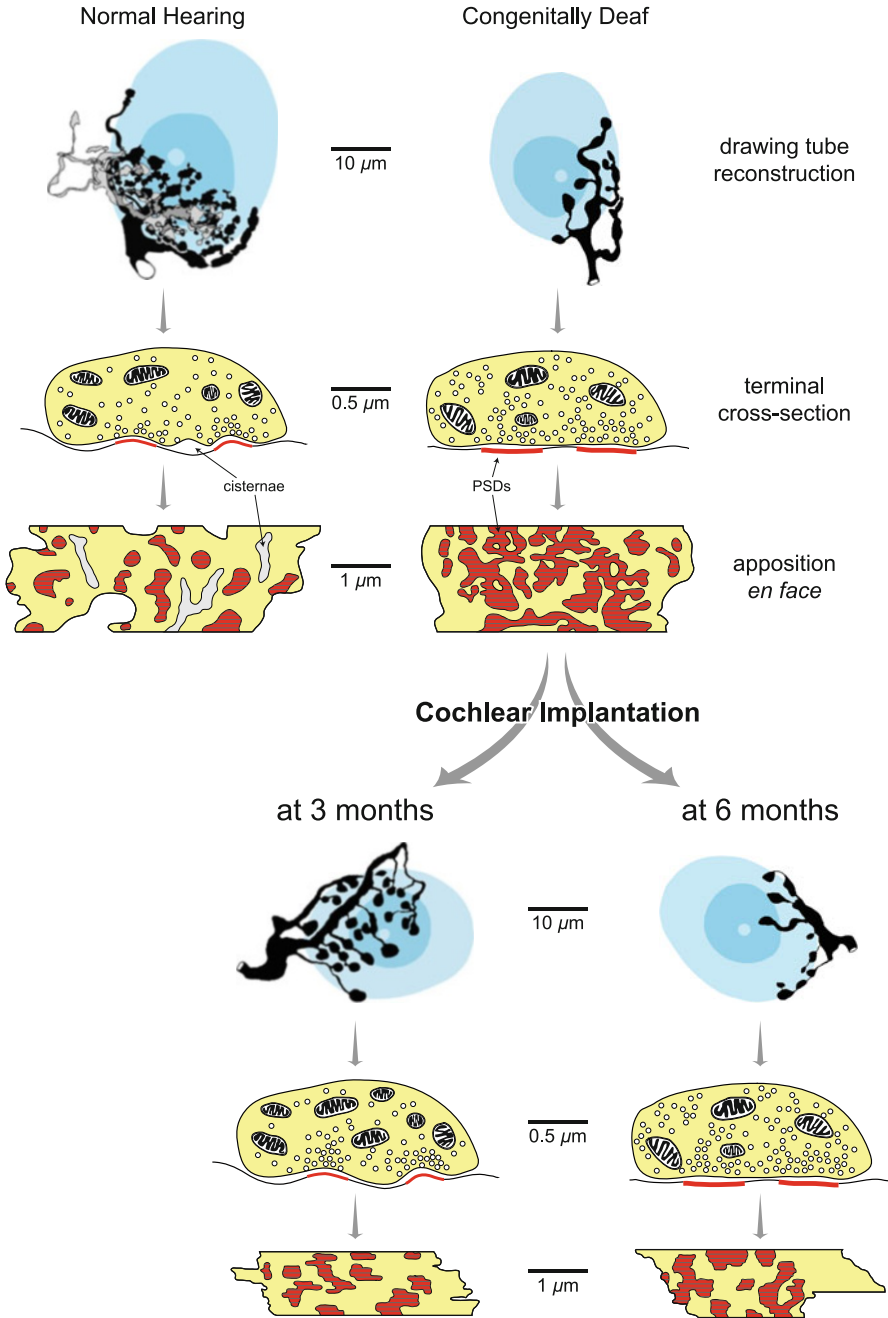


Fig. 8 Summary diagram illustrating endbulb of Held plasticity under conditions of normal hearing, congenital deafness, and congenital deafness with cochlear implantation. Deafness results in a reduction of terminal arborization and complexity. Endbulb synapses of deaf animals

one can attribute the synaptic pathology to the lack of auditory nerve activity caused by deafness. Third, the return of neural activity in the auditory nerve by way of electrical stimulation restores synaptic morphology in the endbulb (Ryugo et al., 2005).

Endbulbs were studied in congenitally deaf cats that were given implants at 3 and 6 months of age (Fig. 1; Ryugo et al., 2005; O'Neil et al., 2010). In young-implanted animals, synapse restoration was evident in endbulbs ipsilateral to stimulation (Fig. 7, bottom; Ryugo et al., 2005; O'Neil et al., 2010). PSDs returned to their smaller size and were statistically identical to those of normal hearing cats. The PSDs also regained their normal dome-shaped curvature. The endbulb itself appears to regain some degree of its complexity; normal numbers of boutons are observed, but they remain larger than those of normal cats (Fig. 8; O'Neil et al., 2011). Modest improvements were also observed at synapses of the contralateral auditory nerve, though the exact mechanism for this benefit remains unknown (O'Neil et al., 2010). Synaptic recovery, however, was not observed in the late-implanted, 6-month-old group (O'Neil et al., 2010). This result suggests that the rescue of synapses may be possible only during the "critical" developmental period preceding puberty, occurring around 6 months of age (Fig. 8), an observation with clear clinical implications for implantation in children. The restoration of endbulb synapses is hypothesized to represent the first link for the proper delivery of afferent signals to the central auditory system in a timely, coherent, and synchronized way.

Curiously, electrical stimulation of auditory nerve fibers did not promote the recovery of SBC soma size in deaf cats (O'Neil et al., 2010). This failure of restoration by electrical stimulation mirrors observations made in the SG (Chen et al., 2010). This has also been examined in ototoxic models of deafness (see chapter by Leake, Stakhovskaya, and Rebscher), and as with observations on peripheral benefits, the effects of electrical stimulation produced mixed results on SBC size; some authors report small but positive benefits (Lustig et al., 1994; Stakhovskaya et al., 2008), whereas others show no effect (Hultcrantz et al., 1991; Ni et al., 1993; Ryugo et al., 2010). In addition, electrical stimulation appears to largely restore the size of endbulb PSDs in ototoxically deafened cats, while synaptic vesicle numbers remained reduced (Ryugo et al., 2010). Because SG neurons die at a faster rate with ototoxic treatments compared to hereditary deafness (Anniko, 1985; Chen et al., 2010), it may be that ototoxic treatments not only damage auditory receptors, but also SG neurons and central neurons, confounding the benefits of stimulation. Hereditary deafness obviously represents a different model than that of ototoxic deafness, so although the two models may provide

←
Fig. 8 (continued) hypertrophy and lose their characteristic dome shape. Synaptic vesicle density also increases. Electrical stimulation through a cochlear implant in young but not older cats restores synaptic morphology. Synapses regain their dome shape and punctate distribution, and synaptic vesicle density around the release site returns to normal. The endbulb itself partially regains its highly branched arborization, but swellings do not return to the small size typical of those in hearing cats. (Adapted from Redd et al., 2000; O'Neil et al., 2010, 2011)

congruent data in many instances, it is not surprising that the separate animal models sometimes yield different effects (Ryugo et al., 2010).

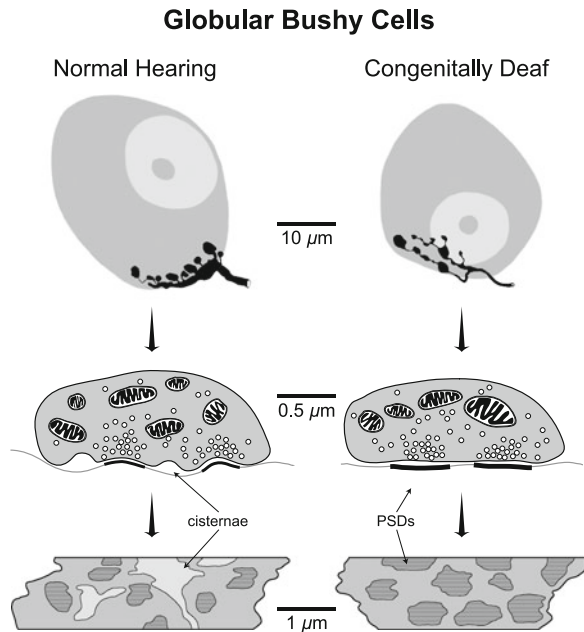
4.2.2 Other Cell Types

Though not as extensively studied as the endbulb, effects of congenital deafness have also been observed in other cells of the cochlear nucleus. Pyramidal cells, one of the principal cell types of the dorsal cochlear nucleus that gives rise to ascending projections, were found to shrink by about 30% in silhouette area with deafness, echoing observations with SBCs (Saada et al., 1996). This similarity comes despite differences in sensory input: SBCs receive somatic endbulbs that cover up to 80% of their surface (Lorente de Nó, 1981), and spontaneous activity all but ceases with deafness (Ryugo et al., 1998); pyramidal cells receive small endings from the auditory nerve upon their basal dendrites (Ryugo & May, 1993), and spontaneous activity continues unabated after nerve section (Koerber et al., 1966), likely due to persistent input from other sources via granule cells (Mugnaini et al., 1980; Itoh et al., 1987; Wright & Ryugo, 1996).

To explore whether other cell types that receive auditory nerve input are affected by deafness the way that SBCs are affected by endbulb input, terminations on globular bushy cells (GBCs) were examined (Fig. 9; Redd et al., 2000). GBCs are the recipients of axosomatic terminals that are distributed in the vicinity of the auditory nerve root. These complex but distinctly smaller endbulbs earned them the nickname of “modified” endbulbs (Harrison & Irving, 1966; Lorente de Nó, 1981; Rouiller et al., 1986). Modified endbulbs of congenitally deaf cats were 50% smaller than those in normal hearing cats, but unchanged in structural complexity, as measured by fractal analysis (Redd et al., 2000). GBC silhouette area was also reduced by 13%. Electron microscopic analysis revealed synaptic changes similar to observations in the endbulb of Held and spherical bushy cells: PSDs of modified endbulbs were both hypertrophied and flattened and showed a complete loss of their extracellular cisternae. Thus, similar yet distinct abnormalities are evident at two primary axosomatic synapses of the auditory nerve in congenitally deaf white cats.

Primary bouton endings of the auditory nerve that synapse on type I and type II multipolar cells of the cochlear nucleus were also examined for deafness-related changes (Fig. 10; Redd et al., 2002). As these endings were not as morphologically distinct as endbulbs, it was necessary to classify them largely on the basis of the upstream projections of their target neurons. Type I multipolar cells project to the contralateral inferior colliculus and receive relatively few axosomatic terminals (~15; Cant, 1982; Redd et al., 2002), whereas type II multipolar cells project to the contralateral cochlear nucleus and receive more axosomatic terminals (~30; Alibardi, 1998; Redd et al., 2002). Curiously, although multipolar cell bodies were found to be smaller in congenitally deaf animals, no significant changes were observed in obvious synaptic features (e.g., PSD size, synaptic vesicle density; Redd et al., 2002). This observation is in stark contrast to the changes observed at SBC and GBC synapses (Ryugo et al., 1997, 1998; Redd et al., 2000), indicating

Fig. 9 Summary diagram illustrating the effects of deafness on globular bushy cells in the cochlear nucleus. Compared to hearing cats, modified endbulbs of deaf cats are equally complex, synapsing on shrunken GBCs, and exhibit hypertrophy and flattening of PSDs and complete loss of extracellular cisternae. (Adapted from Redd et al., 2000)

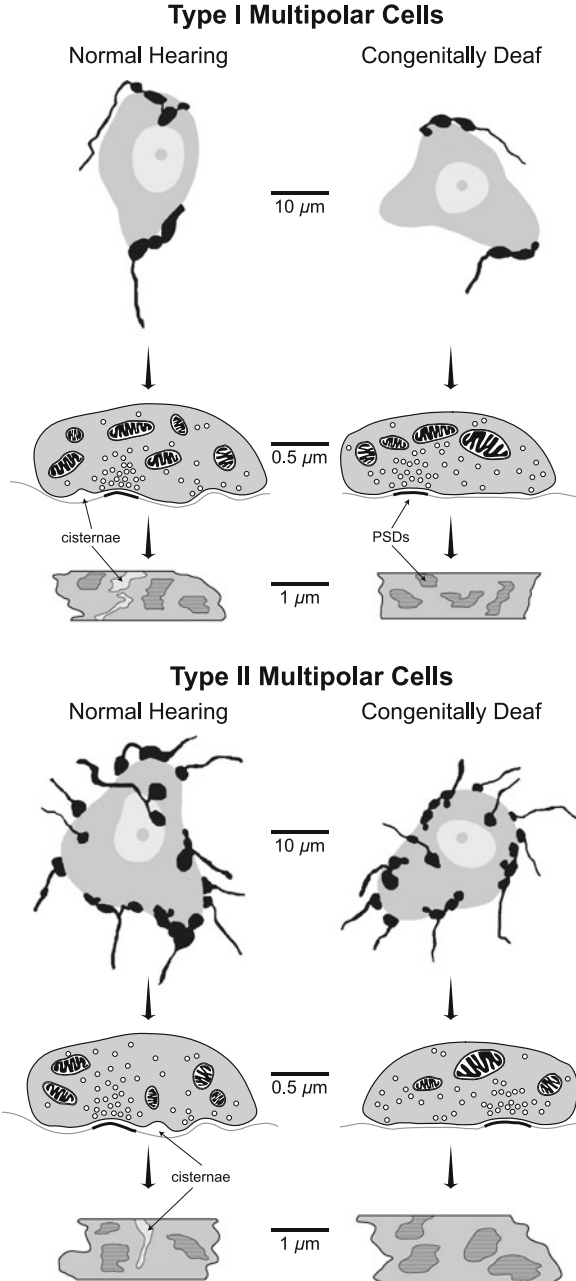


that different endings and target neurons show differential sensitivities to congenital deafness. The effects of electrical stimulation on non-SBC synapses of the cochlear nucleus have yet to be fully examined.

4.3 Superior Olivary Complex

The superior olivary complex is home to a group of interrelated nuclei, including the medial superior olive (MSO), lateral superior olive (LSO), and medial and lateral nuclei of the trapezoid body (MNTB, LNTB), that are located on each side of the ventral brain stem, medial to the cochlear nuclei (Schwartz, 1992). Neurons in these structures are the first to receive and integrate information arising from both ears. Binaural auditory pathways are important for processing sound location, enhancing sound quality, and fostering better speech understanding. The brain circuits that mediate these binaural functions for azimuthal localization are initiated by two classes of auditory nerve endings, including the endbulb of Held, that, in turn, establish two separate pathways in the brain stem. One circuit mediates localization of lower frequency sounds by extracting interaural time differences (ITDs) in the arrival of sound to each ear, whereas the other pathway is specialized for higher frequency sounds using interaural level differences (ILDs). The basic anatomical substrate for this duplex theory is elegant in its simplicity but generally incorrect. Additional details have emerged regarding the fine structure of synaptic connections and a prominent role for inhibition in this processing.

Fig. 10 Summary diagram illustrating the effects of deafness on type I and type II multipolar cells in the cochlear nucleus. Compared to hearing cats, multipolar cells are reduced in size and there is a loss of cisternae. No statistically significant differences were found between synapses of hearing and deaf cats. (Adapted from Redd et al., 2002)



Although both pathways appear to be wired before hearing onset (Kandler & Friauf, 1993; Kil et al., 1995), studies of these circuits after unilateral cochlear ablations in neonates also suggest a critical role of auditory experience for establishing mature circuits (Kitzes et al., 1995; Russell & Moore, 1995; Kapfer et al., 2002).

4.3.1 Medial Superior Olive

The linkage of endbulbs and SBCs in the anteroventral cochlear nucleus has been implicated in the ITD pathway. SBCs, in turn, send projections to the superior olivary complex (Cant & Casseday, 1986), terminating on neurons of the ipsilateral LSO and bilaterally on neurons of the MSO. In the MSO, the cell bodies of principal neurons are arrayed as a vertical sheet with dendrites extending horizontally to each side. Inputs from the ipsilateral cochlear nucleus terminate on lateral dendrites, whereas inputs from the contralateral cochlear nucleus terminate on the medial dendrites. This arrangement allows the principal cells of the MSO to process time-locked synaptic input from both ears, with ipsilateral axonal delay lines systematically compensating for the extra travel time of the contralateral projection (Smith et al., 1993). In this model, individual MSO cells serve as coincidence detectors for different ITDs (Jeffress, 1948; Joris et al., 1998), creating a representation of the azimuthal space.

It is becoming clear that glycinergic inhibition is also required for fine-tuning the sensitivity of MSO cells (Grothe & Sanes, 1993; Magnusson et al., 2005; Zhou et al., 2005; Chirila et al., 2007; Pecka et al., 2008). Inhibition arrives via projections from the LNTB and MNTB that are driven by sounds arriving to the ipsilateral and contralateral ears, respectively (Cant & Hyson, 1992; Kuwabara & Zook, 1992). Sensitivity to ITDs is refined during early auditory experience (Seidl & Grothe, 2005), as is the projection pattern of inhibitory inputs, which are initially distributed on the somata and dendrites, but become largely confined to the somata after experience and maturation (Kapfer et al., 2002). This pattern mirrors the developmental change in the control of synaptic transmission of MSO inputs by γ -aminobutyric acid B (GABA_B) receptors (Hassfurth et al., 2010). Before hearing onset, GABA_B receptors have their largest effect on excitatory transmission, but in mature animals these receptors control inhibition of MSO cells. As with inhibitory inputs, the location of this control shifts from dendrites to the soma with auditory experience (Hassfurth et al., 2010). Significantly, animals raised in an altered sound environment that obfuscates ITD cues, as well as species that do not utilize ITDs for sound localization, fail to exhibit these refinements (Kapfer et al., 2002; Seidl & Grothe, 2005; Werthat et al., 2008), highlighting the importance of normal sensory experience for the proper maturation of circuits.

Studies on experience-dependent plasticity and development of the MSO have largely utilized rodent models with cochlear ablations, although some observations have also been made in congenitally deaf white cats. Early reports have identified a reduction in the size of MSO cells in deaf animals (West & Harrison, 1973; Schwartz & Higa, 1982), consistent with findings in the cochlear nucleus. Electron microscopy has also been used to identify differences in synaptic excitation and/or inhibition on MSO cells. As with rodents, MSO cells of the normal hearing cat exhibit roughly equal proportions of excitatory and inhibitory terminals on the soma, but receive mostly excitatory with few inhibitory terminals on the dendrites (Fig. 11, top; Clark, 1969; Tirko & Ryugo, 2012). One study has suggested that in

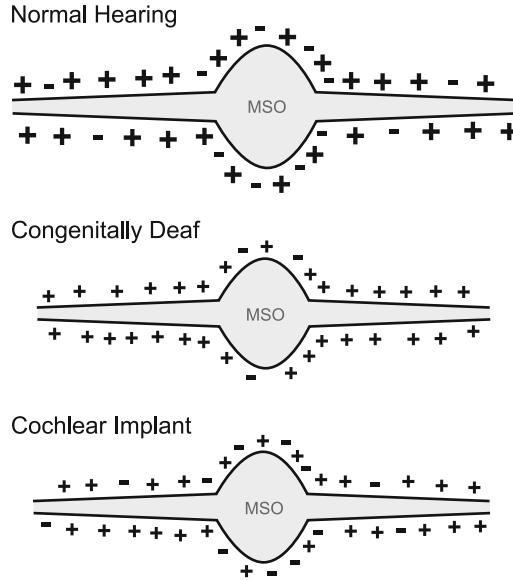


Fig. 11 Schematic summary of the distribution and size of input terminals to the principal cells of the MSO. In normal hearing cats, there is an approximately even split of excitatory (+) and inhibitory (-) terminals on the cell body, with mostly excitatory inputs to the dendrites. With congenital deafness, the size of the MSO cell body and input terminals shrink. The relative number of inhibitory terminals is reduced on the cell body and vanishes on the dendrites. The introduction of activity to the auditory system via cochlear implants restores the distribution of inhibitory terminals to the neurons and partially restores terminal size. (Adapted from Tirko & Ryugo, 2012)

congenitally deaf cats there is a decrease in the number and size of axosomatic terminals on MSO cells (Schwartz & Higa, 1982), though the excitatory and/or inhibitory nature of these projections was not examined.

More recently, observations were made on principal MSO cells of congenitally deaf and electrically stimulated white cats (Tirko & Ryugo, 2012). Deafness results in a stark disruption of inhibitory terminals on MSO cells (Fig. 11, middle); the proportion of inhibitory axosomatic terminals was reduced to around 25%, and virtually no inhibitory axodendritic terminals were observed. In addition, excitatory axodendritic boutons were significantly reduced in size. Three months of electrical stimulation of the auditory nerve, via cochlear implantation, rescued all of these parameters (Fig. 11, bottom); inhibitory terminals were restored to their former proportions, and excitatory boutons were statistically identical to those of normal cats. Importantly, pathological symptoms in the MSO were already present in deaf kittens at 3 months of age, the time at which implantation was performed. These results demonstrate that deafness has a definite impact on the balance of excitation and inhibition in the MSO, a finding with implications for processing of ITD cues. Moreover, electrical stimulation through cochlear implants exerts a powerful effect on the restoration of this balance.

4.3.2 Lateral Superior Olive

The LSO is involved in processing ILDs (Tollin, 2003). This circuit compares the difference in sound intensity between the two ears, exploiting the “shadow” cast by the head upon the sound arriving at the ear farther from the sound source. ILDs are encoded by integrating both excitatory input from ipsilateral SBCs of the cochlear nucleus and inhibitory glycinergic input from the MNTB. The MNTB receives excitatory input from contralateral GBCs of the cochlear nucleus driven, in turn, by modified endbulbs of the auditory nerve. These complementary inputs to LSO neurons are tonotopically organized, allowing for bilateral intensity comparisons to be made on a frequency-specific basis (Kandler et al., 2009).

As with the MSO, response properties of LSO neurons appear to mature after the onset of hearing (Sanes & Rubel, 1988). During this developmental period there is significant pruning of both the dendritic arborization of LSO cells (Sanes et al., 1992a; Rietzel & Friauf, 1998), as well as the terminal fields of excitatory and inhibitory inputs (Sanes & Siverls, 1991; Sanes, 1993; Kim & Kandler, 2003). This refinement appears to take place along the tonotopic axis of the LSO, creating a precise tonotopic representation of ILDs. Changes in synaptic response profiles might contribute to this rearrangement, as glycinergic inputs to the LSO are initially depolarizing in neonates before hearing onset (Kandler & Friauf, 1995). Unilateral cochlear ablations have been shown to limit the refinement of both input arbors and target dendrites in the LSO, further emphasizing the activity dependence of development (Sanes et al., 1992b; Sanes & Takacs, 1993).

The effects of congenital deafness on LSO neurons of deaf white cats are generally unknown other than an observation that cell sizes are reduced (West & Harrison, 1973). A recent report, however, has investigated the LSO of the congenitally deaf (*dn/dn*) mouse (Couchman et al., 2011). In these mice, there is a lack of the tonotopic refinement of single- vs. multiple-firing neurons found in normal animals, but other response properties appear to be unchanged. Curiously, it appears that inhibitory glycinergic synapses develop normally in these mice—inferred by the distribution and morphology of gephyrin clusters—despite the lack of sound-driven activity. This result is unexpected, given changes in inhibition associated with deafness in the MSO (Tirko & Ryugo, 2012). This disparity may reflect differences in the way circuits are initially formed in the LSO and MSO after auditory experience. A potential confound in this comparison is the finding of spontaneous activity in the ventral cochlear nucleus of these deaf mice (Youssoufian et al., 2008), an unexpected finding given the classic view on the effects of silencing the auditory nerve (Koerber et al., 1966). This spontaneous activity could suggest that some hair cells might survive and that afferent circuits are not absolutely silent. The latent spontaneous activity, even if abnormal, could initiate some normal synaptic development. Further investigations are needed to explain these variations in the ILD circuit of these different species.

4.3.3 Medial Nucleus of the Trapezoid Body

The MNTB plays an important role in sound localization pathways by providing temporally precise inhibition to neurons of the MSO and LSO. This nucleus is home to the calyx of Held (Held, 1893), a giant presynaptic terminal that arises from GBCs of the contralateral cochlear nucleus. The calyx is considered to be the fastest and most secure synapse in the brain (Forsythe & Barnes-Davies, 1993), activating principal cells of the MNTB and facilitating the delivery of well-timed inhibition to binaural nuclei for sound localization. The development and morphology of the calyx (Kandler & Friauf, 1993) is remarkably similar to that of the endbulb of Held in the cochlear nucleus (Ryugo & Fekete, 1982), although the developmental fenestration of the calyx seems to occur sequentially along the tonotopic axis of the MNTB (Ford et al., 2009).

With two separate synapses in the auditory pathway sharing morphological similarities, it is tempting to speculate that the consequences of congenital deafness on endbulbs are propagated to the calyx as well. In the gerbil, sensory deafferentation via cochlear ablation or ototoxic drugs appears to slightly alter calyx development (Ford et al., 2009). Animals examined shortly after the age of hearing onset reveal calyces with varying degrees of complexity or fenestration, similar to normal hearing controls. However, the degree of fenestration is no longer graded over the tonotopic axis, but is instead uniformly distributed throughout the MNTB. Although suggestive, this finding does not exclude the possibility that each calyx will continue to mature with age, despite the lack of sensory input. Indeed, this situation occurs with congenitally deaf (*dn/dn*) mice (Youssoufian et al., 2008). Immature mice, as with gerbils, show varying degrees of complexity in calyx morphology. Slightly older but still immature deaf animals, however, exhibit calyx fenestrations and volumes indistinguishable from those of normal hearing mice, and also maintain a normal capacity for synaptic transmission (Oleskevich et al., 2004). For comparison, it is worth noting that endbulb volume in the cochlear nucleus decreases with deafness in these animals (Youssoufian et al., 2008), echoing results in the cat (Ryugo et al., 1997). Interestingly, despite the apparent preservation of the calyx, the effects of deafness on the MNTB are evident by the elimination of tonotopic gradients of voltage-dependent channels, potentially interrupting intrinsic neuronal mechanisms for generating time-delay gradients (Leao et al., 2006). As with findings in the LSO of these congenitally deaf mice, a potential confound is the appearance of some spontaneous activity in the ventral cochlear nucleus, which suggests the survival of some sensory receptor cells may contribute to the maturation of this circuit (Youssoufian et al., 2008).

These results from other animal models imply that, despite many similarities, the consequences of deafness may differ at different synapses in the brain. The fate of the calyx of Held in congenitally deaf white cats remains unknown, and synaptic changes at the ultrastructural level have yet to be examined.

4.4 *Inferior Colliculus*

The inferior colliculus is a large midbrain structure with three principal subdivisions and a complex organization (Winer & Schreiner, 2005). The dorsal and lateral cortices form a “rind” around a core central nucleus (Morest & Oliver, 1984; Winer, 2006). The central nucleus is tonotopically organized and receives ascending auditory input from the cochlear nucleus, superior olivary complex, and nuclei of the lateral lemniscus, as well as descending inputs from the auditory cortex and superior colliculus (Roth et al., 1978; Adams, 1979; Andersen et al., 1980). It is the synaptic station for nearly all auditory information ascending to or descending from the forebrain.

The inferior colliculus retains a rudimentary cochleotopic organization in long-term deafened animals (Snyder et al., 1990; Shepherd et al., 1999). The preservation of this organization may be due in part to the general retention of normal ascending projections to the midbrain, despite the absence of auditory experience, such as in deafened ferrets (Moore, 1990) or congenitally deaf cats (Heid et al., 1997). The development and maintenance of projections to the midbrain in deafness hint at the power of the genetic blueprint (Young & Rubel, 1986; Friauf & Kandler, 1990). Some circuits, however, fail to differentiate fully without sensory input, such as inputs from the dorsal nucleus of the lateral lemniscus that no longer exhibit their typical banded projection pattern in deafferented rats (Franklin et al., 2008).

Synaptic abnormalities are suggested by the functional deficits in neurons in the central nucleus of inferior colliculus. Electrical stimulation of the auditory nerve in cats that were ototoxically deafened from birth showed impaired temporal responses such as longer latencies, increased jitter, and a poorer ability to follow rapidly repeating stimuli (Snyder et al., 1995; Shepherd et al., 1999; Vollmer et al., 2005). These results were clearly due to long-term deafness, rather than a consequence of artificial electrical stimulation, as control subjects were deafened just before experimentation and failed to show the same deficits. Given these results, it is of little surprise that congenitally deaf white cats show a reduced sensitivity to ITDs (Hancock et al., 2010). To simulate ITDs in these animals, temporally precise current pulses were delivered to each ear using bilateral implants. Single-unit data in the inferior colliculus of congenitally deaf cats showed that only 48% of units were sensitive to ITDs compared to 84% of units from acutely deafened animals. For neurons that did show ITD sensitivity, ITD tuning was less sharp and best ITDs were variable, resulting in deficient coding within the natural range of ITDs for a cat.

Can the processing deficits of the inferior colliculus be attributed to altered synapse morphology? Do abnormalities occur in the inferior colliculus, or are they manifestations of deafness-induced changes known to occur in lower structures? Cochlear ablations in rats can cause changes in the gene expression of proteins related to neurotransmission in the midbrain (Holt et al., 2005), and cell size and synaptic density are found to be significantly reduced in the midbrain of ototoxically deafened cats (Hardie et al., 1998; Nishiyama et al., 2000). Further

morphological and functional details regarding any pathology in these midbrain synapses, however, remain unknown. Additional studies are needed to understand fully the consequences of deafness on the circuitry of the inferior colliculus.

4.5 Auditory Cortex

The auditory cortex marks the end of the ascending auditory pathway, though the myriad of intracortical circuits make it difficult to distinguish exactly where the ascending pathways stop and the descending pathways begin. Auditory cortex is assumed to contribute heavily to the rise of sound perception and comprises many subregions with various processing functions (Winer & Schreiner, 2011). Ascending auditory information arrives to the cortex by way of thalamocortical projections (Winer, 2011), and many cortical areas exhibit some degree of tonotopic organization (Schreiner & Winer, 2007). Cortical neurons exhibit extensive forebrain connectivity (Winer, 2011), and also send descending projections of varying number to many subcortical auditory nuclei, as well as some non-auditory structures (Malmierca & Ryugo, 2011). With the arguable exception of the cochlear nuclei, no other central auditory structure has been as extensively studied in the congenitally deaf white cat as the cortex (e.g., Hartmann et al., 1997; Klinke et al., 1999; Kral et al., 2005). Reports have largely focused on cortical response properties, and therefore synaptic consequences can only be inferred (Kral et al., 2001). Much of this work is covered in the chapter by Kral, Baumhoff, and Shepherd and is briefly summarized here.

Auditory cortex of the congenitally deaf cat retains aspects of ascending input circuitry. Electrical stimulation of the auditory nerve produces clear cortical activations, and has been used to reveal a rudimentary cochleotopic organization (Hartmann et al., 1997) as well as a latent, albeit diminished, sensitivity to ITDs (Tillein et al., 2010). Deafness also affects cortical spatiotemporal response dynamics and contralateral dominance (Kral et al., 2009). Current source density analysis of evoked local field potentials shows significant deficiencies in the layer-specific activation patterns of deaf adults, especially in deeper layers (Kral et al., 2000), and this activation pattern develops in an abnormal fashion over the first few postnatal months (Kral et al., 2005). Cochlear implantation of young (Klinke et al., 1999), but not older (Kral et al., 2001), cats results in cortical recruitment indicative of more normal processing, including sound-evoked behaviors, and the amount of recruitment correlates with age (Kral et al., 2002).

What are the relative contributions of synaptic aberrations in the forebrain and subcortical structures that together manifest as altered cortical functionality in congenitally deaf cats? Are some of the observed effects the result of the propagation of poorly encoded signals, beginning with the cochlear nucleus? This question remains unanswered, and efforts are underway to investigate synaptic changes in the cortex of experimentally deafened rodents (see the chapter by Sanes; Sanes & Kotak, 2011). As with brain stem nuclei (Takesian et al., 2009), sensorineural hearing loss results in

significant alterations of inhibitory cortical circuitry (Kotak et al., 2008; Sarro et al., 2008). This circumstance can have severe consequences from the outset, as the balance of excitation and inhibition is crucial during development for the formation of normal cortical receptive fields and other response properties (Froemke & Jones, 2011). As with preceding structures in the auditory pathway, it is clear that the establishment of normal cortical processing capabilities is experience dependent, and the use of electrical stimulation in congenitally deaf subjects must be introduced at an early age for maximum benefit.

5 Functional Outcomes

The concept of the critical period describes biological phenomena that occur or are most severely affected within a limited time window of development. This has been elegantly demonstrated by the imprinting experiments of Lorenz (1935) and applied to observations such as cortical barrel plasticity (Van der Loos & Woolsey, 1973; Weller & Johnson, 1975), the surgical repair of monocular amblyopia (Raviola & Wiesel, 1985), birdsong acquisition (Konishi, 1985), and the functional maturation of auditory cortex (Chang & Merzenich, 2003; de Villers-Sidani et al., 2007). Clinical reports indicate that young children receiving cochlear implants gain superior benefits when compared to older children and adults, drawing support for the idea of a critical period for the proper maturation of hearing (Gantz et al., 1994; Waltzman et al., 1994; Tyler & Summerfield, 1996; reviewed by Francis & Niparko, 2003). Decades of research from animal models of deafness clearly demonstrate a need for auditory experience from an early age for the initial formation of precise synaptic structure, functional organization, and proper distribution of terminals all along the ascending auditory pathways.

Timing cues are critical for recognizing speech in conditions where spectral content is severely degraded (Shannon et al., 1995). In congenitally deaf cats, temporal information is corrupted at the first synapse by malformations of the endbulb (Ryugo et al., 1997, 1998) and presumably exacerbated further by the inappropriate balance of excitation and inhibition in the MSO (Tirko & Ryugo, 2012). Electrical stimulation has revealed some of the consequences of these, and likely other, synaptic deficits: impaired processing of ITD cues in the inferior colliculus (Hancock et al., 2010) and reduced and smeared responses in the auditory cortex (Kral et al., 2000). Implant-induced synaptic plasticity can restore some of these morphological and physiological impairments, but, at least in deaf white cats, only if performed within the developmental period preceding puberty (Kral et al., 2001; O'Neil et al., 2010), echoing clinical observations with children (Francis & Niparko, 2003; Kral & Sharma, 2012).

Implantation, however, does not yet restore all functionality in hearing. In implanted cats, electrically evoked ABR waveforms are somewhat delayed and flattened relative to normal hearing cats (Kretzmer et al., 2004). This pathologic waveform suggests diminished synchrony in the evoked responses, perhaps caused

by an increase in transmission jitter failure. It is possible, however, that stimulation for a longer period would have resulted in more normal responses. Clinical evidence shows that patients with bilateral implants regain some benefits of binaural hearing, such as sound localization and improved speech perception in noisy environments, but are still largely unable to use ITD cues, instead relying disproportionately on ILD signals (van Hoesel, 2004; Seeber & Fastl, 2008). Further, this inability is graded with the age at onset of deafness: Patients who lost their hearing later in life showed some sensitivity to ITDs, whereas those who became deaf early were largely insensitive to ITDs (Litovsky et al., 2010). Measures of ABR responses in young children also show prolonged latencies in the responses between the two ears when the second implant is received more than two years after the first (Gordon et al., 2008). These results support the idea that the proper maturation of binaural pathways is dependent on auditory experience from both ears.

6 Summary

Decades of research have uncovered remarkable reorganization and synaptic plasticity in the auditory system. From the high-fidelity synapses of the endbulbs of Held, to the coincidence detecting neurons of the medial superior olive, the auditory pathway has developed uniquely specialized neural connections that allow organisms to efficiently understand the auditory landscape. These synaptic connections are exceptionally receptive to auditory deprivation and stimulation. The congenitally deaf white cat has proven to be an excellent model for studying the consequences of sensorineural deafness from birth, particularly given the vast amount of literature available for comparison dedicated to the normal hearing cat. Hearing loss results not only in peripheral damage, but also in abnormal development throughout the auditory system, beginning with the first synapse in the brain stem. This aberrant circuitry produces substantial functional deficits, such as impairments in temporal processing in the midbrain and cortex. The cat is also amenable to cochlear implantation, facilitating investigations into the restorative effects of reintroducing electrical activity to the auditory system. Electrical stimulation shows benefits in synaptic plasticity, leading to more normal synaptic morphology in key structures such as the endbulb of Held and improvements in cortical responses. Most importantly, implantation has positive effects on sound-evoked behavior. These benefits, however, are susceptible to age-dependent plasticity. Implantation after a critical period of development leads to limited benefits, as the abnormal circuitry has largely matured. Experimental results in congenitally deaf white cats both inform and reflect observations in the clinic, demonstrating a link from bench to bedside. Many questions, however, remain to be answered: What are the morphological consequences of deafness throughout the central auditory system? What are the effects of implantation on other synapses of the cochlear nucleus? The LSO? The midbrain and forebrain? Does deafness alter descending circuitry in the auditory system? Is a complete restoration of auditory function even

possible, given that some aspects of degeneration appear to begin in the womb? To what degree are the benefits of implantation observed at higher auditory centers due solely to the restoration of brain stem synapses? Can revised stimulation and/or training protocols improve the benefits of implantation? How might we address current limitations with cochlear implant devices, such as speech comprehension in noise and the ability to enjoy music? The fact that we can even pose these questions reveals how far we have come in addressing deafness and its rehabilitation. At the same time, it exposes how much further we have yet to go. Young researchers entering the field should be encouraged by the wide-open nature of the research that lies waiting. Anatomy and physiology must be melded with investigations utilizing molecular biology, bioinformatics, and genetics. No single discipline can expect to solve the myriad of issues involved in communication and its disorders.

Acknowledgments The authors gratefully acknowledge the support from NIH grants DC000232, DC004395, NIMH Grant No. 1009482, and grants from the NSW Office of Science and Medical Research, The Garnett Passe and Rodney Williams Memorial Foundation, and The Fairfax Foundation.

References

- Adams, J. C. (1979). Ascending projections to the inferior colliculus. *Journal of Comparative Neurology*, 183(3), 519–538.
- Alexander, G. (1900). Zur vergleichenden, pathologischen Anatomien des Gehörorganes. 1. Gehörorgan und Gehirn einer unvollkommen albinotischen, weissen Katze. *Archiv für Ohrenheilkunde*, 50, 159–181.
- Alexander, G., & Tandler, J. (1905). Untersuchungen an kongenital tauben Hunden, Katzen und an Jungen kongenital tauber Katzen. *Archiv für Ohrenheilkunde*, 66, 183–219.
- Alibardi, L. (1998). Ultrastructural and immunocytochemical characterization of commissural neurons in the ventral cochlear nucleus of the rat. *Annals of Anatomy – Anatomischer Anzeiger*, 180(5), 427–438.
- Andersen, R. A., Snyder, R. L., & Merzenich, M. M. (1980). The topographic organization of corticocollicular projections from physiologically identified loci in the AI, AII, and anterior auditory cortical fields of the cat. *Journal of Comparative Neurology*, 191(3), 479–494.
- Anniko, M. (1985). Principles in cochlear toxicity. *Archives of Toxicology. Supplement*, 8, 221–239.
- Araki, S., Kawano, A., Seldon, H. L., Shepherd, R. K., Funasaka, S., & Clark, G. M. (2000). Effects of intracochlear factors on spiral ganglion cells and auditory brain stem response after long-term electrical stimulation in deafened kittens. *Otolaryngology-Head and Neck Surgery*, 122(3), 425–433.
- Attie, T., Till, M., Pelet, A., Amiel, J., Edery, P., Boutrand, L., Munnich, A., & Lyonnet, S. (1995). Mutation of the endothelin-receptor B gene in Waardenburg-Hirschsprung disease. *Human Molecular Genetics*, 4(12), 2407–2409.
- Babalian, A. L., Ryugo, D. K., & Rouiller, E. M. (2003). Discharge properties of identified cochlear nucleus neurons and auditory nerve fibers in response to repetitive electrical stimulation of the auditory nerve. *Experimental Brain Research*, 153(4), 452–460.
- Baker, C. A., Montey, K. L., Pongstaporn, T., & Ryugo, D. K. (2010). Postnatal development of the endbulb of held in congenitally deaf cats. *Frontiers in Neuroanatomy*, 4, 19.

- Bamber, R. C. (1933). Correlation between white coat colour, blue eyes and deafness in cats. *Journal of Genetics*, 27(3), 407–413.
- Baynash, A. G., Hosoda, K., Giaid, A., Richardson, J. A., Emoto, N., Hammer, R. E., & Yanagisawa, M. (1994). Interaction of endothelin-3 with endothelin-B receptor is essential for development of epidermal melanocytes and enteric neurons. *Cell*, 79(7), 1277–1285.
- Beighton, P., Ramesar, R., Winship, I., Viljoen, D., Greenberg, J., Young, K., Curtis, D., & Sellars, S. (1991). Hearing impairment and pigmentary disturbance. *Annals of the New York Academy of Sciences*, 630, 152–166.
- Bergsma, D. R., & Brown, K. S. (1971). White fur, blue eyes, and deafness in the domestic cat. *Journal of Heredity*, 62(3), 171–185.
- Bosher, S. K., & Hallpike, C. S. (1965). Observations on the histological features, development and pathogenesis of the inner ear degeneration of the deaf white cat. *Proceedings of the Royal Society of London B: Biological Sciences*, 162(987), 147–170.
- Boyne, A. F., Bohan, T. P., & Williams, T. H. (1975). Changes in cholinergic synaptic vesicle populations and the ultrastructure of the nerve terminal membranes of *Narcine brasiliensis* electron organ stimulated to fatigue in vivo. *Journal of Cell Biology*, 67(3), 814–825.
- Brawer, J. R., & Morest, D. K. (1975). Relations between auditory nerve endings and cell types in the cat's anteroventral cochlear nucleus seen with the Golgi method and Nomarski optics. *Journal of Comparative Neurology*, 160(4), 491–506.
- Bree, W. T. (1829). White cats with blue eyes are always deaf. *The Magazine of Natural History*, 1, 178.
- Burwen, S. J., & Satir, B. H. (1977). Plasma membrane folds on the mast cell surface and their relationship to secretory activity. *Journal of Cell Biology*, 74(3), 690–697.
- Cant, N. B. (1982). Identification of cell-types in the anteroventral cochlear nucleus that project to the inferior colliculus. *Neuroscience Letters*, 32(3), 241–246.
- Cant, N. B., & Morest, D. K. (1979). The bushy cells in the anteroventral cochlear nucleus of the cat: A study with the electron microscope. *Neuroscience*, 4(12), 1925–1945.
- Cant, N. B., & Casseday, J. H. (1986). Projections from the anteroventral cochlear nucleus to the lateral and medial superior olivary nuclei. *Journal of Comparative Neurology*, 247(4), 457–476.
- Cant, N. B., & Hyson, R. L. (1992). Projections from the lateral nucleus of the trapezoid body to the medial superior olivary nucleus in the gerbil. *Hearing Research*, 58(1), 26–34.
- Chabot, B., Stephenson, D. A., Chapman, V. M., Besmer, P., & Bernstein, A. (1988). The proto-oncogene c-kit encoding a transmembrane tyrosine kinase receptor maps to the mouse W locus. *Nature*, 335(6185), 88–89.
- Chang, E. F., & Merzenich, M. M. (2003). Environmental noise retards auditory cortical development. *Science*, 300(5618), 498–502.
- Chen, I., Limb, C. J., & Ryugo, D. K. (2010). The effect of cochlear-implant-mediated electrical stimulation on spiral ganglion cells in congenitally deaf white cats. *Journal of the Association for Research in Otolaryngology*, 11(4), 587–603.
- Chirila, F. V., Rowland, K. C., Thompson, J. M., & Spirou, G. A. (2007). Development of gerbil medial superior olive: Integration of temporally delayed excitation and inhibition at physiological temperature. *Journal of Physiology*, 584(1), 167–190.
- Clark, G. M. (1969). The ultrastructure of nerve endings in the medial superior olive of the cat. *Brain Research*, 14(2), 293–305.
- Clark, L. A., Wahl, J. M., Rees, C. A., & Murphy, K. E. (2006). Retrotransposon insertion in SILV is responsible for merle patterning of the domestic dog. *Proceedings of the National Academy of Sciences of the USA*, 103(5), 1376–1381.
- Coco, A., Epp, S. B., Fallon, J. B., Xu, J., Millard, R. E., & Shepherd, R. K. (2007). Does cochlear implantation and electrical stimulation affect residual hair cells and spiral ganglion neurons? *Hearing Research*, 225(1–2), 60–70.

- Couchman, K., Garrett, A., Deardorff, A. S., Rattay, F., Resatz, S., Fyffe, R., Walmsley, B., & Leao, R. N. (2011). Lateral superior olive function in congenital deafness. *Hearing Research*, 277(1–2), 163–175.
- Darwin, C. (1859). *On the origin of species*. London: John Murray.
- Darwin, C. (1875). *The variation of animals and plants under domestication* (2nd ed. Vol. 2). London: John Murray.
- de Villers-Sidani, E., Chang, E. F., Bao, S., & Merzenich, M. M. (2007). Critical period window for spectral tuning defined in the primary auditory cortex (A1) in the rat. *Journal of Neuroscience*, 27(1), 180–189.
- Elverland, H. H., & Mair, I. W. (1980). Hereditary deafness in the cat: An electron microscopic study of the spiral ganglion. *Acta Oto-Laryngologica*, 90(5–6), 360–369.
- Elverland, H. H., Godtlielsen, O. B., Kayed, K., & Mair, I. W. (1975). Non-surgical recording of auditory pathway function in cats. *Archives of Oto-Rhino-Laryngology*, 211(4), 249–257.
- Epstein, D. J., Vekemans, M., & Gros, P. (1991). Spotch (Sp2H), a mutation affecting development of the mouse neural tube, shows a deletion within the paired homeodomain of Pax-3. *Cell*, 67(4), 767–774.
- Evans, E. F., & Palmer, A. R. (1980). Relationship between the dynamic-range of cochlear nerve-fibers and their spontaneous activity. *Experimental Brain Research*, 40(1), 115–118.
- Fayad, J. N., & Linthicum, F. H., Jr. (2006). Multichannel cochlear implants: Relation of histopathology to performance. *Laryngoscope*, 116(8), 1310–1320.
- Fekete, D. M., Rouiller, E. M., Liberman, M. C., & Ryugo, D. K. (1984). The central projections of intracellularly labeled auditory nerve fibers in cats. *Journal of Comparative Neurology*, 229(3), 432–450.
- Ford, M. C., Grothe, B., & Klug, A. (2009). Fenestration of the calyx of Held occurs sequentially along the tonotopic axis, is influenced by afferent activity, and facilitates glutamate clearance. *Journal of Comparative Neurology*, 514(1), 92–106.
- Forsythe, I. D., & Barnes-Davies, M. (1993). The binaural auditory pathway: Membrane currents limiting multiple action potential generation in the rat medial nucleus of the trapezoid body. *Proceedings of the Royal Society of London B: Biological Sciences*, 251(1331), 143–150.
- Francis, H. W., & Niparko, J. K. (2003). Cochlear implantation update. *Pediatric Clinics of North America*, 50(2), 341–361.
- Franklin, S. R., Brunso-Bechtold, J. K., & Henkel, C. K. (2008). Bilateral cochlear ablation in postnatal rat disrupts development of banded pattern of projections from the dorsal nucleus of the lateral lemniscus to the inferior colliculus. *Neuroscience*, 154(1), 346–354.
- Fraser, J. S. (1924). Congenital deafness in a dog. *Proceedings of the Royal Society of Medicine*, 17(Otol Sect), 29–31.
- Friauf, E., & Kandler, K. (1990). Auditory projections to the inferior colliculus of the rat are present by birth. *Neuroscience Letters*, 120(1), 58–61.
- Froemke, R. C., & Jones, B. J. (2011). Development of auditory cortical synaptic receptive fields. *Neuroscience and Biobehavioral Reviews*, 35(10), 2105–2113.
- Gabriele, M. L., Brunso-Bechtold, J. K., & Henkel, C. K. (2000). Plasticity in the development of afferent patterns in the inferior colliculus of the rat after unilateral cochlear ablation. *Journal of Neuroscience*, 20(18), 6939–6949.
- Gantz, B. J., Tyler, R. S., Woodworth, G. G., Tye-Murray, N., & Fryauf-Bertschy, H. (1994). Results of multichannel cochlear implants in congenital and acquired prelingual deafness in children: Five-year follow-up. *American Journal of Otolaryngology*, 15(Supplement 2), 1–7.
- Gauly, M., Vaughan, J., Hogleve, S. K., & Erhardt, G. (2005). Brainstem auditory-evoked potential assessment of auditory function and congenital deafness in llamas (*Lama glama*) and alpacas (*L. pacos*). *Journal of Veterinary Internal Medicine*, 19(5), 756–760.
- Geigy, C. A., Heid, S., Steffen, F., Danielson, K., Jaggy, A., & Gaillard, C. (2007). Does a pleiotropic gene explain deafness and blue irises in white cats? *Veterinary Journal*, 173(3), 548–553.

- Gordon, K. A., Valero, J., van Hoesel, R., & Papsin, B. C. (2008). Abnormal timing delays in auditory brainstem responses evoked by bilateral cochlear implant use in children. *Otology & Neurotology*, 29(2), 193–198.
- Gordon-Salant, S., Frisina, R. D., Popper, A. N., & Fay, R. R. (2010). *The aging auditory system*. New York: Springer.
- Grothe, B. (2000). The evolution of temporal processing in the medial superior olive, an auditory brainstem structure. *Progress in Neurobiology*, 61(6), 581–610.
- Grothe, B., & Sanes, D. H. (1993). Bilateral inhibition by glycinergic afferents in the medial superior olive. *Journal of Neurophysiology*, 69(4), 1192–1196.
- Gulley, R. L., Wenthold, R. J., & Neises, G. R. (1978). Changes in the synapses of spiral ganglion cells in the rostral anteroventral cochlear nucleus of the waltzing guinea pig following hair cell loss. *Brain Research*, 158(2), 279–294.
- Haase, B., Brooks, S. A., Schlumbaum, A., Azor, P. J., Bailey, E., Alaeddine, F., Mevissen, M., Burger, D., Poncet, P. A., Rieder, S., & Leeb, T. (2007). Allelic heterogeneity at the equine KIT locus in dominant white (W) horses. *Public Library of Science Genetics*, 3(11), e195.
- Haase, B., Brooks, S. A., Tozaki, T., Burger, D., Poncet, P. A., Rieder, S., Hasegawa, T., Penedo, C., & Leeb, T. (2009). Seven novel KIT mutations in horses with white coat colour phenotypes. *Animal Genetics*, 40(5), 623–629.
- Hancock, K. E., Noel, V., Ryugo, D. K., & Delgutte, B. (2010). Neural coding of interaural time differences with bilateral cochlear implants: Effects of congenital deafness. *Journal of Neuroscience*, 30(42), 14068–14079.
- Hardie, N. A., & Shepherd, R. K. (1999). Sensorineural hearing loss during development: Morphological and physiological response of the cochlea and auditory brainstem. *Hearing Research*, 128(1–2), 147–165.
- Hardie, N. A., Martsi-McClintock, A., Aitkin, L. M., & Shepherd, R. K. (1998). Neonatal sensorineural hearing loss affects synaptic density in the auditory midbrain. *NeuroReport*, 9(9), 2019–2022.
- Harrison, J. M., & Irving, R. (1966). The organization of the posterior ventral cochlear nucleus in the rat. *Journal of Comparative Neurology*, 126(3), 391–401.
- Hartley, D. E., Vongpaisal, T., Xu, J., Shepherd, R. K., King, A. J., & Isaiiah, A. (2010). Bilateral cochlear implantation in the ferret: A novel animal model for behavioral studies. *Journal of Neuroscience Methods*, 190(2), 214–228.
- Hartmann, R., Shepherd, R. K., Heid, S., & Klinke, R. (1997). Response of the primary auditory cortex to electrical stimulation of the auditory nerve in the congenitally deaf white cat. *Hearing Research*, 112(1–2), 115–133.
- Hashisaki, G. T., & Rubel, E. W. (1989). Effects of unilateral cochlea removal on anteroventral cochlear nucleus neurons in developing gerbils. *Journal of Comparative Neurology*, 283(4), 5–73.
- Hassfurth, B., Grothe, B., & Koch, U. (2010). The mammalian interaural time difference detection circuit is differentially controlled by GABAB receptors during development. *Journal of Neuroscience*, 30(29), 9715–9727.
- Heid, S., Jähn-Siebert, T. K., Klinke, R., Hartmann, R., & Langner, G. (1997). Afferent projection patterns in the auditory brainstem in normal and congenitally deaf white cats. *Hearing Research*, 110(1–2), 191–199.
- Heid, S., Hartmann, R., & Klinke, R. (1998). A model for prelingual deafness, the congenitally deaf white cat—population statistics and degenerative changes. *Hearing Research*, 115(1–2), 101–112.
- Held, H. (1893). Die centrale Gehörleitung. *Archiv für Anatomie und Physiologie, Anatomische Abteilung*, 201–248.
- Henderson, D., Bielefeld, E. C., Harris, K. C., & Hu, B. H. (2006). The role of oxidative stress in noise-induced hearing loss. *Ear and Hearing*, 27(1), 1–19.
- Herbarth, B., Pingault, V., Bondurand, N., Kuhlbrodt, K., Hermans-Borgmeyer, I., Puliti, A., Lemort, N., Goossens, M., & Wegner, M. (1998). Mutation of the Sry-related Sox10 gene in

- Dominant megacolon, a mouse model for human Hirschsprung disease. *Proceedings of the National Academy of Sciences of the USA*, 95(9), 5161–5165.
- Heuser, J. E., & Reese, T. S. (1973). Evidence for recycling of synaptic vesicle membrane during transmitter release at the frog neuromuscular junction. *Journal of Cell Biology*, 57(2), 315–344.
- Hildebrandt, H., Hoffmann, N. A., & Illing, R. B. (2011). Synaptic reorganization in the adult rat's ventral cochlear nucleus following its total sensory deafferentation. *Public Library of Science One*, 6(8), e23686.
- Hilding, D. A., Sugiura, A., & Nakai, Y. (1967). Deaf white mink: Electron microscopic study of the inner ear. *Annals of Otolaryngology, Rhinology and Laryngology*, 76(3), 647–663.
- Hodgkinson, C. A., Moore, K. J., Nakayama, A., Steingrimsson, E., Copeland, N. G., Jenkins, N. A., & Arnheiter, H. (1993). Mutations at the mouse microphthalmia locus are associated with defects in a gene encoding a novel basic-helix-loop-helix-zipper protein. *Cell*, 74(2), 395–404.
- Hodgkinson, C. A., Nakayama, A., Li, H., Swenson, L. B., Opdecamp, K., Asher, J. H., Jr., Arnheiter, H., & Glaser, T. (1998). Mutation at the anophthalmic white locus in Syrian hamsters: Haploinsufficiency in the *Mitf* gene mimics human Waardenburg syndrome type 2. *Human Molecular Genetics*, 7(4), 703–708.
- Holt, A. G., Asako, M., Lomax, C. A., MacDonald, J. W., Tong, L., Lomax, M. I., & Altschuler, R. A. (2005). Deafness-related plasticity in the inferior colliculus: Gene expression profiling following removal of peripheral activity. *Journal of Neurochemistry*, 93(5), 1069–1086.
- Howe, H. A. (1935a). The relation of the organ of corti to audioelectric phenomena in deaf albino cats. *American Journal of Physiology*, 111(1), 187–191.
- Howe, H. A. (1935b). The reaction of the cochlear nerve to destruction of its end organs: A study on deaf albino cats. *Journal of Comparative Neurology*, 62(1), 73–79.
- Hudson, W. R., & Ruben, R. J. (1962). Hereditary deafness in the Dalmatian dog. *Archives of Otolaryngology*, 75, 213–219.
- Hulcrantz, M., Snyder, R., Rebscher, S., & Leake, P. (1991). Effects of neonatal deafening and chronic intracochlear electrical stimulation on the cochlear nucleus in cats. *Hearing Research*, 54(2), 272–280.
- Illing, R. B., Horváth, M., & Laszig, R. (1997). Plasticity of the auditory brainstem: Effects of cochlear ablation on GAP-43 immunoreactivity in the rat. *Journal of Comparative Neurology*, 382(1), 116–138.
- Illing, R. B., Kraus, K. S., & Meidinger, M. A. (2005). Reconnecting neuronal networks in the auditory brainstem following unilateral deafening. *Hearing Research*, 206(1–2), 185–199.
- Itoh, K., Kamiya, H., Mitani, A., Yasui, Y., Takada, M., & Mizuno, N. (1987). Direct projections from the dorsal column nuclei and the spinal trigeminal nuclei to the cochlear nuclei in the cat. *Brain Research*, 400(1), 145–150.
- Jeffress, L. A. (1948). A place theory of sound localization. *Journal of Comparative and Physiological Psychology*, 41(1), 35–39.
- Jones, T. A., Leake, P. A., Snyder, R. L., Stakhovskaya, O., & Bonham, B. (2007). Spontaneous discharge patterns in cochlear spiral ganglion cells before the onset of hearing in cats. *Journal of Neurophysiology*, 98(4), 1898–1908.
- Joris, P. X., Smith, P. H., & Yin, T. C. (1998). Coincidence detection in the auditory system: 50 years after Jeffress. *Neuron*, 21(6), 1235–1238.
- Kandler, K. (2004). Activity-dependent organization of inhibitory circuits: Lessons from the auditory system. *Current Opinion in Neurobiology*, 14(1), 96–104.
- Kandler, K., & Friauf, E. (1993). Pre- and postnatal development of efferent connections of the cochlear nucleus in the rat. *Journal of Comparative Neurology*, 328(2), 161–184.
- Kandler, K., & Friauf, E. (1995). Development of glycinergic and glutamatergic synaptic transmission in the auditory brainstem of perinatal rats. *Journal of Neuroscience*, 15(10), 6890–6904.

- Kandler, K., Clause, A., & Noh, J. (2009). Tonotopic reorganization of developing auditory brainstem circuits. *Nature Neuroscience*, 12(6), 711–717.
- Kapfer, C., Seidl, A. H., Schweizer, H., & Grothe, B. (2002). Experience-dependent refinement of inhibitory inputs to auditory coincidence-detector neurons. *Nature Neuroscience*, 5(3), 247–253.
- Khan, A. M., Whiten, D. M., Nadol, J. B., Jr., & Eddington, D. K. (2005a). Histopathology of human cochlear implants: Correlation of psychophysical and anatomical measures. *Hearing Research*, 205(1–2), 83–93.
- Khan, A. M., Handzel, O., Burgess, B. J., Damian, D., Eddington, D. K., & Nadol, J. B., Jr. (2005b). Is word recognition correlated with the number of surviving spiral ganglion cells and electrode insertion depth in human subjects with cochlear implants? *Laryngoscope*, 115(4), 672–677.
- Kiang, N. Y.-S., Watanabe, T., Thomas, E. C., & Clark, L. F. (1965). *Discharge patterns of single fibers in the cat's auditory nerve*. Cambridge, MA: MIT Press.
- Kil, J., Kageyama, G. H., Semple, M. N., & Kitzes, L. M. (1995). Development of ventral cochlear nucleus projections to the superior olivary complex in gerbil. *Journal of Comparative Neurology*, 353(3), 317–340.
- Kim, G., & Kandler, K. (2003). Elimination and strengthening of glycinergic/GABAergic connections during tonotopic map formation. *Nature Neuroscience*, 6(3), 282–290.
- Kitzes, L. M., Kageyama, G. H., Semple, M. N., & Kil, J. (1995). Development of ectopic projections from the ventral cochlear nucleus to the superior olivary complex induced by neonatal ablation of the contralateral cochlea. *Journal of Comparative Neurology*, 353(3), 341–363.
- Klinke, R., Kral, A., Heid, S., Tillein, J., & Hartmann, R. (1999). Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation. *Science*, 285(5434), 1729–1733.
- Klinke, R., Hartmann, R., Heid, S., Tillein, J., & Kral, A. (2001). Plastic changes in the auditory cortex of congenitally deaf cats following cochlear implantation. *Audiology and Neuro-Otology*, 6(4), 203–206.
- Koerber, K. C., Pfeiffer, R. R., Warr, W. B., & Kiang, N. Y. (1966). Spontaneous spike discharges from single units in the cochlear nucleus after destruction of the cochlea. *Experimental Neurology*, 16(2), 119–130.
- Konishi, M. (1985). Birdsong: From behavior to neuron. *Annual Review of Neuroscience*, 8, 125–170.
- Kotak, V. C., Takesian, A. E., & Sanes, D. H. (2008). Hearing loss prevents the maturation of GABAergic transmission in the auditory cortex. *Cerebral Cortex*, 18(9), 2098–2108.
- Kral, A., & Sharma, A. (2012). Developmental neuroplasticity after cochlear implantation. *Trends in Neurosciences*, 35(2), 111–122.
- Kral, A., Hartmann, R., Tillein, J., Heid, S., & Klinke, R. (2000). Congenital auditory deprivation reduces synaptic activity within the auditory cortex in a layer-specific manner. *Cerebral Cortex*, 10(7), 714–726.
- Kral, A., Hartmann, R., Tillein, J., Heid, S., & Klinke, R. (2001). Delayed maturation and sensitive periods in the auditory cortex. *Audiology and Neuro-Otology*, 6(6), 346–362.
- Kral, A., Hartmann, R., Tillein, J., Heid, S., & Klinke, R. (2002). Hearing after congenital deafness: Central auditory plasticity and sensory deprivation. *Cerebral Cortex*, 12(8), 797–807.
- Kral, A., Tillein, J., Heid, S., Hartmann, R., & Klinke, R. (2005). Postnatal cortical development in congenital auditory deprivation. *Cerebral Cortex*, 15(5), 552–562.
- Kral, A., Tillein, J., Hubka, P., Schiemann, D., Heid, S., Hartmann, R., & Engel, A. K. (2009). Spatiotemporal patterns of cortical activity with bilateral cochlear implants in congenital deafness. *Journal of Neuroscience*, 29(3), 811–827.
- Kretzmer, E. A., Meltzer, N. E., Haeggeli, C. A., & Ryugo, D. K. (2004). An animal model for cochlear implants. *Archives of Otolaryngology – Head and Neck Surgery*, 130(5), 499–508.

- Kujawa, S. G., & Liberman, M. C. (2009). Adding insult to injury: Cochlear nerve degeneration after “temporary” noise-induced hearing loss. *Journal of Neuroscience*, 29(45), 14077–14085.
- Kuwabara, N., & Zook, J. M. (1992). Projections to the medial superior olive from the medial and lateral nuclei of the trapezoid body in rodents and bats. *Journal of Comparative Neurology*, 324(4), 522–538.
- Larsen, S. A., & Kirchoff, T. M. (1992). Anatomical evidence of synaptic plasticity in the cochlear nuclei of white-deaf cats. *Experimental Neurology*, 115(1), 151–157.
- Leake, P. A., & Hradek, G. T. (1988). Cochlear pathology of long term neomycin induced deafness in cats. *Hearing Research*, 33(1), 11–33.
- Leake, P. A., Hradek, G. T., Rebscher, S. J., & Snyder, R. L. (1991). Chronic intracochlear electrical stimulation induces selective survival of spiral ganglion neurons in neonatally deafened cats. *Hearing Research*, 54(2), 251–271.
- Leake, P. A., Hradek, G. T., & Snyder, R. L. (1999). Chronic electrical stimulation by a cochlear implant promotes survival of spiral ganglion neurons after neonatal deafness. *Journal of Comparative Neurology*, 412(4), 543–562.
- Leake, P. A., Hradek, G. T., Chair, L., & Snyder, R. L. (2006). Neonatal deafness results in degraded topographic specificity of auditory nerve projections to the cochlear nucleus in cats. *Journal of Comparative Neurology*, 497(1), 13–31.
- Leao, R. N., Sun, H., Svahn, K., Berntson, A., Yousoufian, M., Paolini, A. G., Fyffe, R. E., & Walmsley, B. (2006). Topographic organization in the auditory brainstem of juvenile mice is disrupted in congenital deafness. *Journal of Physiology*, 571(3), 563–578.
- Lee, D. J., Cahill, H. B., & Ryugo, D. K. (2003). Effects of congenital deafness in the cochlear nuclei of Shaker-2 mice: An ultrastructural analysis of synapse morphology in the endbulbs of Held. *Journal of Neurocytology*, 32(3), 229–243.
- Lenn, N. J., & Reese, T. S. (1966). The fine structure of nerve endings in the nucleus of the trapezoid body and the ventral cochlear nucleus. *American Journal of Anatomy*, 118(2), 375–389.
- Liberman, M. C., & Kiang, N. Y. (1978). Acoustic trauma in cats: Cochlear pathology and auditory-nerve activity. *Acta Oto-Laryngologica*, 86(S358), 1–63.
- Liberman, M. C., & Dodds, L. W. (1984). Single-neuron labeling and chronic cochlear pathology. II. Stereocilia damage and alterations of spontaneous discharge rates. *Hearing Research*, 16(1), 43–53.
- Limb, C. J., & Ryugo, D. K. (2000). Development of primary axosomatic endings in the anteroventral cochlear nucleus of mice. *Journal of the Association for Research in Otolaryngology*, 1(2), 103–119.
- Litovsky, R. Y., Jones, G. L., Agrawal, S., & van Hoesel, R. (2010). Effect of age at onset of deafness on binaural sensitivity in electric hearing in humans. *Journal of the Acoustical Society of America*, 127(1), 400–414.
- Lorente de Nó, R. (1981). *The primary acoustic nuclei*. New York: Raven Press.
- Lorenz, K. (1935). Der Kumpan in der Umwelt des Vogels. Der Artgenosse als auslösendes Moment sozialer Verhaltensweisen. *Journal für Ornithologie*, 83(2), 137–213.
- Lustig, L. R., Leake, P. A., Snyder, R. L., & Rebscher, S. J. (1994). Changes in the cat cochlear nucleus following neonatal deafening and chronic intracochlear electrical stimulation. *Hearing Research*, 74(1–2), 29–37.
- Magnusson, A. K., Kapfer, C., Grothe, B., & Koch, U. (2005). Maturation of glycinergic inhibition in the gerbil medial superior olive after hearing onset. *Journal of Physiology*, 568(2), 497–512.
- Mair, I. W. (1973). Hereditary deafness in the white cat. *Acta Oto-Laryngologica*, 76(S314), 1–48.
- Mair, I. W., & Elverland, H. H. (1977). Hereditary deafness in the cat: An electron microscopic study of the stria vascularis and Reissner’s membrane. *Archives of Oto-Rhino-Laryngology*, 217(2), 199–217.

- Malmierca, M. S., & Ryugo, D. K. (2011). Descending connections of auditory cortex to the midbrain and brain stem. In J. A. Winer & C. E. Schreiner (Eds.), *The auditory cortex* (pp. 189–208). New York: Springer.
- Manis, P. B., & Marx, S. O. (1991). Outward currents in isolated ventral cochlear nucleus neurons. *Journal of Neuroscience*, 11(9), 2865–2880.
- Matsushima, J. I., Shepherd, R. K., Seldon, H. L., Xu, S. A., & Clark, G. M. (1991). Electrical stimulation of the auditory nerve in deaf kittens: Effects on cochlear nucleus morphology. *Hearing Research*, 56(1–2), 133–142.
- McFadden, S. L., Ding, D., Jiang, H., & Salvi, R. J. (2004). Time course of efferent fiber and spiral ganglion cell degeneration following complete hair cell loss in the chinchilla. *Brain Research*, 997(1), 40–51.
- Mitchell, A., Miller, J. M., Finger, P. A., Heller, J. W., Raphael, Y., & Altschuler, R. A. (1997). Effects of chronic high-rate electrical stimulation on the cochlea and eighth nerve in the deafened guinea pig. *Hearing Research*, 105(1–2), 30–43.
- Moore, D. R. (1990). Auditory brainstem of the ferret: bilateral cochlear lesions in infancy do not affect the number of neurons projecting from the cochlear nucleus to the inferior colliculus. *Developmental Brain Research*, 54(1), 125–130.
- Moore, D. R., & Kitzes, L. M. (1985). Projections from the cochlear nucleus to the inferior colliculus in normal and neonatally cochlea-ablated gerbils. *Journal of Comparative Neurology*, 240(2), 180–195.
- Morest, D. K., & Oliver, D. L. (1984). The neuronal architecture of the inferior colliculus in the cat: Defining the functional anatomy of the auditory midbrain. *Journal of Comparative Neurology*, 222(2), 209–236.
- Mugnaini, E., Osen, K. K., Dahl, A. L., Friedrich, V. L., Jr., & Korte, G. (1980). Fine structure of granule cells and related interneurons (termed Golgi cells) in the cochlear nuclear complex of cat, rat and mouse. *Journal of Neurocytology*, 9(4), 537–570.
- Mulders, W. H., Ding, D., Salvi, R., & Robertson, D. (2011). Relationship between auditory thresholds, central spontaneous activity, and hair cell loss after acoustic trauma. *Journal of Comparative Neurology*, 519(13), 2637–2647.
- Nadol, J. B., Jr., Young, Y. S., & Glynn, R. J. (1989). Survival of spiral ganglion cells in profound sensorineural hearing loss: Implications for cochlear implantation. *Annals of Otolaryngology and Rhinology*, 98(6), 411–416.
- Nadol, J. B., Jr., Shiao, J. Y., Burgess, B. J., Ketten, D. R., Eddington, D. K., Gantz, B. J., Kos, I., Montandon, P., Coker, N. J., Roland, J. T., Jr., & Shallop, J. K. (2001). Histopathology of cochlear implants in humans. *Annals of Otolaryngology, Rhinology and Laryngology*, 110(9), 883–891.
- Nayagam, B. A., Muniak, M. A., & Ryugo, D. K. (2011). The spiral ganglion: Connecting the peripheral and central auditory systems. *Hearing Research*, 278(1–2), 2–20.
- Nayak, C. S., & Isaacson, G. (2003). Worldwide distribution of Waardenburg syndrome. *Annals of Otolaryngology, Rhinology and Laryngology*, 112(9 Pt 1), 817–820.
- Ni, D., Seldon, H. L., Shepherd, R. K., & Clark, G. M. (1993). Effect of chronic electrical stimulation on cochlear nucleus neuron size in normal hearing kittens. *Acta Oto-Laryngologica*, 113(4), 489–497.
- Nishiyama, N., Hardie, N. A., & Shepherd, R. K. (2000). Neonatal sensorineural hearing loss affects neurone size in cat auditory midbrain. *Hearing Research*, 140(1–2), 18–22.
- Nordeen, K. W., Killackey, H. P., & Kitzes, L. M. (1983a). Ascending auditory projections to the inferior colliculus in the adult gerbil, *Meriones unguiculatus*. *Journal of Comparative Neurology*, 214(2), 131–143.
- Nordeen, K. W., Killackey, H. P., & Kitzes, L. M. (1983b). Ascending projections to the inferior colliculus following unilateral cochlear ablation in the neonatal gerbil, *Meriones unguiculatus*. *Journal of Comparative Neurology*, 214(2), 144–153.
- Oleskevich, S., Youssoufian, M., & Walmsley, B. (2004). Presynaptic plasticity at two giant auditory synapses in normal and deaf mice. *Journal of Physiology*, 560(3), 709–719.

- Olmstead, C. E., & Villablanca, J. R. (1980). Development of behavioral audition in the kitten. *Physiology and Behavior*, 24(4), 705–712.
- O’Neil, J. N., Limb, C. J., Baker, C. A., & Ryugo, D. K. (2010). Bilateral effects of unilateral cochlear implantation in congenitally deaf cats. *Journal of Comparative Neurology*, 518(12), 2382–2404.
- O’Neil, J. N., Connelly, C. J., Limb, C. J., & Ryugo, D. K. (2011). Synaptic morphology and the influence of auditory experience. *Hearing Research*, 279(1–2), 118–130.
- Pakyz, A. L., MacDougall, C., Oinonen, M., & Polk, R. E. (2008). Trends in antibacterial use in US academic health centers: 2002 to 2006. *Archives of Internal Medicine*, 168(20), 2254–2260.
- Parks, T. N., Rubel, E. W., Fay, R. R., & Popper, A. N., Eds. (2004). *Plasticity of the auditory system*. New York: Springer.
- Pecka, M., Brand, A., Behrend, O., & Grothe, B. (2008). Interaural time difference processing in the mammalian medial superior olive: The role of glycinergic inhibition. *Journal of Neuroscience*, 28(27), 6914–6925.
- Pfeiffer, R. R. (1966). Anteroventral cochlear nucleus: Wave forms of extracellularly recorded spike potentials. *Science*, 154(3749), 667–668.
- Pujol, R., & Marty, R. (1970). Postnatal maturation in the cochlea of the cat. *Journal of Comparative Neurology*, 139(1), 115–118.
- Pujol, R., Rebillard, M., & Rebillard, G. (1977). Primary neural disorders in the deaf white cat cochlea. *Acta Oto-Laryngologica*, 83(1–2), 59–64.
- Ramón y Cajal, R. (1909). *Histologie du système nerveux de l’homme et des vertébrés*, Vol. 1. Madrid: Instituto Ramón y Cajal.
- Rauschecker, J. P., & Shannon, R. V. (2002). Sending sound to the brain. *Science*, 295(5557), 1025–1029.
- Raviola, E., & Wiesel, T. N. (1985). An animal model of myopia. *New England Journal of Medicine*, 312(25), 1609–1615.
- Rawitz, B. (1897). Über die Beziehungen zwischen unvollkommen Albinismus und Taubheit. *Archiv für Anatomie und Physiologie, Physiologische Abteilung*, 21, 402–405.
- Rebillard, M., Pujol, R., & Rebillard, G. (1981a). Variability of the hereditary deafness in the white cat. II. Histology. *Hearing Research*, 5(2–3), 189–200.
- Rebillard, M., Rebillard, G., & Pujol, R. (1981b). Variability of the hereditary deafness in the white cat. I. Physiology. *Hearing Research*, 5(2–3), 179–187.
- Redd, E. E., Pongstaporn, T., & Ryugo, D. K. (2000). The effects of congenital deafness on auditory nerve synapses and globular bushy cells in cats. *Hearing Research*, 147(1–2), 160–174.
- Redd, E. E., Cahill, H. B., Pongstaporn, T., & Ryugo, D. K. (2002). The effects of congenital deafness on auditory nerve synapses: Type I and type II multipolar cells in the anteroventral cochlear nucleus of cats. *Journal of the Association for Research in Otolaryngology*, 3(4), 403–417.
- Rees, S., Guldner, F. H., & Aitkin, L. (1985). Activity dependent plasticity of postsynaptic density structure in the ventral cochlear nucleus of the rat. *Brain Research*, 325(1–2), 370–374.
- Rietzel, H. J., & Friauf, E. (1998). Neuron types in the rat lateral superior olive and developmental changes in the complexity of their dendritic arbors. *Journal of Comparative Neurology*, 390(1), 20–40.
- Robbins, A. M. (2006). Language development in children with cochlear implants. In S. B. Waltzman & J. T. Roland, Jr. (Eds.), *Cochlear implants* (2nd ed., pp. 153–166). New York: Thieme.
- Roth, G. L., Aitkin, L. M., Andersen, R. A., & Merzenich, M. M. (1978). Some features of the spatial organization of the central nucleus of the inferior colliculus of the cat. *Journal of Comparative Neurology*, 182(4), 661–680.

- Rouiller, E. M., Cronin-Schreiber, R., Fekete, D. M., & Ryugo, D. K. (1986). The central projections of intracellularly labeled auditory nerve fibers in cats: An analysis of terminal morphology. *Journal of Comparative Neurology*, 249(2), 261–278.
- Ruan, H. B., Zhang, N., & Gao, X. (2005). Identification of a novel point mutation of mouse proto-oncogene c-kit through *N*-ethyl-*N*-nitrosourea mutagenesis. *Genetics*, 169(2), 819–831.
- Rubel, E. W., & Fritzsche, B. (2002). Auditory system development: Primary auditory neurons and their targets. *Annual Review of Neuroscience*, 25, 51–101.
- Rubel, E. W., Lippe, W. R., & Ryals, B. M. (1984). Development of the place principle. *Annals of Otology, Rhinology and Laryngology*, 93(6), 609–615.
- Russell, F. A., & Moore, D. R. (1995). Afferent reorganization within the superior olivary complex of the gerbil—development and induction by neonatal, unilateral cochlear removal. *Journal of Comparative Neurology*, 352(4), 607–625.
- Ryugo, D. K., & Fekete, D. M. (1982). Morphology of primary axosomatic endings in the anteroventral cochlear nucleus of the cat: A study of the endbulbs of Held. *Journal of Comparative Neurology*, 210(3), 239–257.
- Ryugo, D. K., & Sento, S. (1991). Synaptic connections of the auditory nerve in cats: Relationship between endbulbs of held and spherical bushy cells. *Journal of Comparative Neurology*, 305(1), 35–48.
- Ryugo, D. K., & May, S. K. (1993). The projections of intracellularly labeled auditory nerve fibers to the dorsal cochlear nucleus of cats. *Journal of Comparative Neurology*, 329(1), 20–35.
- Ryugo, D. K., & Parks, T. N. (2003). Primary innervation of the avian and mammalian cochlear nucleus. *Brain Research Bulletin*, 60(5–6), 435–456.
- Ryugo, D. K., & Spirou, G. A. (2009). Auditory system: Giant synaptic terminals, Endbulbs, and Calyces. In L. R. Squire (Ed.), *Encyclopedia of Neuroscience* (Vol. 1, pp. 759–770). Oxford: Academic Press.
- Ryugo, D. K., & Limb, C. J. (2009). Brain plasticity: The impact of the environment on the brain as it relates to hearing and deafness. In J. K. Niparko (Ed.), *Cochlear implants: Principles and practices* (2nd ed., pp. 19–37). Philadelphia: Lippincott Williams & Wilkins.
- Ryugo, D. K., Wu, M. M., & Pongstaporn, T. (1996). Activity-related features of synapse morphology: A study of endbulbs of held. *Journal of Comparative Neurology*, 365(1), 141–158.
- Ryugo, D. K., Pongstaporn, T., Huchton, D. M., & Niparko, J. K. (1997). Ultrastructural analysis of primary endings in deaf white cats: Morphologic alterations in endbulbs of Held. *Journal of Comparative Neurology*, 385(2), 230–244.
- Ryugo, D. K., Rosenbaum, B. T., Kim, P. J., Niparko, J. K., & Saada, A. A. (1998). Single unit recordings in the auditory nerve of congenitally deaf white cats: Morphological correlates in the cochlea and cochlear nucleus. *Journal of Comparative Neurology*, 397(4), 532–548.
- Ryugo, D. K., Cahill, H. B., Rose, L. S., Rosenbaum, B. T., Schroeder, M. E., & Wright, A. L. (2003). Separate forms of pathology in the cochlea of congenitally deaf white cats. *Hearing Research*, 181(1–2), 73–84.
- Ryugo, D. K., Kretzmer, E. A., & Niparko, J. K. (2005). Restoration of auditory nerve synapses in cats by cochlear implants. *Science*, 310(5753), 1490–1492.
- Ryugo, D. K., Baker, C. A., Montey, K. L., Chang, L. Y., Coco, A., Fallon, J. B., & Shepherd, R. K. (2010). Synaptic plasticity after chemical deafening and electrical stimulation of the auditory nerve in cats. *Journal of Comparative Neurology*, 518(7), 1046–1063.
- Saada, A. A., Niparko, J. K., & Ryugo, D. K. (1996). Morphological changes in the cochlear nucleus of congenitally deaf white cats. *Brain Research*, 736(1–2), 315–328.
- Sanchez-Martin, M., Rodriguez-Garcia, A., Perez-Losada, J., Sagrera, A., Read, A. P., & Sanchez-Garcia, I. (2002). SLUG (SNAI2) deletions in patients with Waardenburg disease. *Human Molecular Genetics*, 11(25), 3231–3236.
- Sanes, D. H. (1993). The development of synaptic function and integration in the central auditory system. *Journal of Neuroscience*, 13(6), 2627–2637.

- Sanes, D. H., & Rubel, E. W. (1988). The ontogeny of inhibition and excitation in the gerbil lateral superior olive. *Journal of Neuroscience*, 8(2), 682–700.
- Sanes, D. H., & Siverls, V. (1991). Development and specificity of inhibitory terminal arborizations in the central nervous system. *Journal of Neurobiology*, 22(8), 837–854.
- Sanes, D. H., & Takacs, C. (1993). Activity-dependent refinement of inhibitory connections. *European Journal of Neuroscience*, 5(6), 570–574.
- Sanes, D. H., & Bao, S. (2009). Tuning up the developing auditory CNS. *Current Opinion in Neurobiology*, 19(2), 188–199.
- Sanes, D. H., & Kotak, V. C. (2011). Developmental plasticity of auditory cortical inhibitory synapses. *Hearing Research*, 279(1–2), 140–148.
- Sanes, D. H., Song, J., & Tyson, J. (1992a). Refinement of dendritic arbors along the tonotopic axis of the gerbil lateral superior olive. *Developmental Brain Research*, 67(1), 47–55.
- Sanes, D. H., Markowitz, S., Bernstein, J., & Wardlow, J. (1992b). The influence of inhibitory afferents on the development of postsynaptic dendritic arbors. *Journal of Comparative Neurology*, 321(4), 637–644.
- Sarro, E. C., Kotak, V. C., Sanes, D. H., & Aoki, C. (2008). Hearing loss alters the subcellular distribution of presynaptic GAD and postsynaptic GABAA receptors in the auditory cortex. *Cerebral Cortex*, 18(12), 2855–2867.
- Scheibe, A. (1892). A case of deaf-mutism, with auditory atrophy and anomalies of development in the membranous labyrinth of both ears. *Archives of Otolaryngology*, 21, 12–22.
- Schreiner, C. E., & Winer, J. A. (2007). Auditory cortex mapmaking: Principles, projections, and plasticity. *Neuron*, 56(2), 356–365.
- Schwartz, I. R. (1992). The superior olivary complex and lateral lemniscal nuclei. In D. B. Webster, A. N. Popper, & R. R. Fay (Eds.), *The mammalian auditory pathway: Neuroanatomy* (pp. 117–167). New York: Springer-Verlag.
- Schwartz, I. R., & Higa, J. F. (1982). Correlated studies of the ear and brainstem in the deaf white cat: Changes in the spiral ganglion and the medial superior olivary nucleus. *Acta Oto-Laryngologica*, 93(1–2), 9–18.
- Seeber, B. U., & Fastl, H. (2008). Localization cues with bilateral cochlear implants. *Journal of the Acoustical Society of America*, 123(2), 1030–1042.
- Seidl, A. H., & Grothe, B. (2005). Development of sound localization mechanisms in the mongolian gerbil is shaped by early acoustic experience. *Journal of Neurophysiology*, 94(2), 1028–1036.
- Sento, S., & Ryugo, D. K. (1989). Endbulbs of held and spherical bushy cells in cats: Morphological correlates with physiological properties. *Journal of Comparative Neurology*, 280(4), 553–562.
- Shannon, R. V., Zeng, F. G., Kamath, V., Wygonski, J., & Ekelid, M. (1995). Speech recognition with primarily temporal cues. *Science*, 270(5234), 303–304.
- Shepherd, R. K., & Javel, E. (1997). Electrical stimulation of the auditory nerve. I. Correlation of physiological responses with cochlear status. *Hearing Research*, 108(1–2), 112–144.
- Shepherd, R. K., & Hardie, N. A. (2001). Deafness-induced changes in the auditory pathway: Implications for cochlear implants. *Audiology and Neuro-Otology*, 6(6), 305–318.
- Shepherd, R. K., Baxi, J. H., & Hardie, N. A. (1999). Response of inferior colliculus neurons to electrical stimulation of the auditory nerve in neonatally deafened cats. *Journal of Neurophysiology*, 82(3), 1363–1380.
- Shepherd, R. K., Meltzer, N. E., Fallon, J. B., & Ryugo, D. K. (2006). Consequences of deafness and electrical stimulation on the peripheral and central auditory system. In S. B. Waltzman & J. T. Roland, Jr. (Eds.), *Cochlear implants* (2nd ed., pp. 25–39). New York: Thieme.
- Sie, K. C., & Rubel, E. W. (1992). Rapid changes in protein synthesis and cell size in the cochlear nucleus following eighth nerve activity blockade or cochlea ablation. *Journal of Comparative Neurology*, 320(4), 501–508.
- Silvers, W. K. (1979). *The coat colors of mice: A model for mammalian gene action and interaction*. New York: Springer-Verlag.

- Smith, P. H., Joris, P. X., & Yin, T. C. (1993). Projections of physiologically characterized spherical bushy cell axons from the cochlear nucleus of the cat: Evidence for delay lines to the medial superior olive. *Journal of Comparative Neurology*, 331(2), 245–260.
- Snyder, R. L., Rebscher, S. J., Cao, K. L., Leake, P. A., & Kelly, K. (1990). Chronic intracochlear electrical stimulation in the neonatally deafened cat. I: Expansion of central representation. *Hearing Research*, 50(1–2), 7–33.
- Snyder, R., Leake, P., Rebscher, S., & Beitel, R. (1995). Temporal resolution of neurons in cat inferior colliculus to intracochlear electrical stimulation: Effects of neonatal deafening and chronic stimulation. *Journal of Neurophysiology*, 73(2), 449–467.
- Snyder, R. L., Sinex, D. G., McGee, J. D., & Walsh, E. W. (2000). Acute spiral ganglion lesions change the tuning and tonotopic organization of cat inferior colliculus neurons. *Hearing Research*, 147(1–2), 200–220.
- Southard-Smith, E. M., Kos, L., & Pavan, W. J. (1998). *Sox10* mutation disrupts neural crest development in Dom Hirschsprung mouse model. *Nature Genetics*, 18(1), 60–64.
- Spoendlin, H. (1984). Factors inducing retrograde degeneration of the cochlear nerve. *Annals of Otolaryngology, Rhinology, and Laryngology*, 112(Supplement), 76–82.
- Stakhovskaya, O., Hradek, G. T., Snyder, R. L., & Leake, P. A. (2008). Effects of age at onset of deafness and electrical stimulation on the developing cochlear nucleus in cats. *Hearing Research*, 243(1–2), 69–77.
- Suga, F., & Hattler, K. W. (1970). Physiological and histopathological correlates of hereditary deafness in animals. *Laryngoscope*, 80(1), 81–104.
- Syrris, P., Carter, N. D., & Patton, M. A. (1999). Novel nonsense mutation of the endothelin-B receptor gene in a family with Waardenburg-Hirschsprung disease. *American Journal of Medical Genetics*, 87(1), 69–71.
- Tachibana, M., Hara, Y., Vyas, D., Hodgkinson, C., Fex, J., Grundfast, K., & Arnheiter, H. (1992). Cochlear disorder associated with melanocyte anomaly in mice with a transgenic insertional mutation. *Molecular and Cellular Neurosciences*, 3(5), 433–445.
- Tachibana, M., Perez-Jurado, L. A., Nakayama, A., Hodgkinson, C. A., Li, X., Schneider, M., Miki, T., Fex, J., Francke, U., & Arnheiter, H. (1994). Cloning of MITF, the human homolog of the mouse microphthalmia gene and assignment to chromosome 3p14.1–p12.3. *Human Molecular Genetics*, 3(4), 553–557.
- Tait, L. (1873). Note on a polydactylous cat from Cookham-Dean. *Nature*, 7(174), 323.
- Tait, L. (1883). Note on deafness in white cats. *Nature*, 29(737), 164.
- Takesian, A. E., Kotak, V. C., & Sanes, D. H. (2009). Developmental hearing loss disrupts synaptic inhibition: Implications for auditory processing. *Future Neurology*, 4(3), 331–349.
- Tillein, J., Hubka, P., Syed, E., Hartmann, R., Engel, A. K., & Kral, A. (2010). Cortical representation of interaural time difference in congenital deafness. *Cerebral Cortex*, 20(2), 492–506.
- Tirko, N. N., & Ryugo, D. K. (2012). Synaptic plasticity in the medial superior olive of hearing, deaf, and cochlear-implanted cats. *Journal of Comparative Neurology*, 520(10), 2202–2217.
- Tollin, D. J. (2003). The lateral superior olive: A functional role in sound source localization. *Neuroscientist*, 9(2), 127–143.
- Tritsch, N. X., Yi, E., Gale, J. E., Glowatzki, E., & Bergles, D. E. (2007). The origin of spontaneous activity in the developing auditory system. *Nature*, 450(7166), 50–55.
- Trune, D. R. (1982). Influence of neonatal cochlear removal on the development of mouse cochlear nucleus: I. Number, size, and density of its neurons. *Journal of Comparative Neurology*, 209(4), 409–424.
- Tsuji, J., & Liberman, M. C. (1997). Intracellular labeling of auditory nerve fibers in guinea pig: Central and peripheral projections. *Journal of Comparative Neurology*, 381(2), 188–202.
- Tsujimura, T., Hirota, S., Nomura, S., Niwa, Y., Yamazaki, M., Tono, T., Morii, E., Kim, H. M., Kondo, K., Nishimune, Y., & Kitamura, Y. (1991). Characterization of *Ws* mutant allele of rats: A 12-base deletion in tyrosine kinase domain of *c-kit* gene. *Blood*, 78(8), 1942–1946.

- Tucci, D. L., & Rubel, E. W. (1990). Physiologic status of regenerated hair cells in the avian inner ear following aminoglycoside ototoxicity. *Otolaryngology-Head and Neck Surgery*, 103(3), 443–450.
- Tyler, R. S., & Summerfield, A. Q. (1996). Cochlear implantation: Relationships with research on auditory deprivation and acclimatization. *Ear and Hearing*, 17(3), 38S–50S.
- Van der Loos, H., & Woolsey, T. A. (1973). Somatosensory cortex: Structural alterations following early injury to sense organs. *Science*, 179(4071), 395–398.
- van Hoesel, R. J. (2004). Exploring the benefits of bilateral cochlear implants. *Audiology and Neuro-Otology*, 9(4), 234–246.
- Vollmer, M., Leake, P. A., Beitel, R. E., Rebscher, S. J., & Snyder, R. L. (2005). Degradation of temporal resolution in the auditory midbrain after prolonged deafness is reversed by electrical stimulation of the cochlea. *Journal of Neurophysiology*, 93(6), 3339–3355.
- Waardenburg, P. J. (1951). A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. *American Journal of Human Genetics*, 3(3), 195–253.
- Walmsley, B., Berrntson, A., Leao, R. N., & Fyffe, R. E. (2006). Activity-dependent regulation of synaptic strength and neuronal excitability in central auditory pathways. *Journal of Physiology*, 572(2), 313–321.
- Waltzman, S. B., Cohen, N. L., Gomolin, R. H., Shapiro, W. H., Ozdamar, S. R., & Hoffman, R. A. (1994). Long-term results of early cochlear implantation in congenitally and prelingually deafened children. *American Journal of Otology*, 15(Supplement 2), 9–13.
- Wang, Y., & Manis, P. B. (2005). Synaptic transmission at the cochlear nucleus endbulb synapse during age-related hearing loss in mice. *Journal of Neurophysiology*, 94(3), 1814–1824.
- Wang, Y., & Manis, P. B. (2006). Temporal coding by cochlear nucleus bushy cells in DBA/2J mice with early onset hearing loss. *Journal of the Association for Research in Otolaryngology*, 7(4), 412–424.
- Webster, M., & Webster, D. B. (1981). Spiral ganglion neuron loss following organ of Corti loss: A quantitative study. *Brain Research*, 212(1), 17–30.
- Weller, W. L., & Johnson, J. I. (1975). Barrels in cerebral-cortex altered by receptor disruption in newborn, but not in 5-day-old mice (Cricetidae and Muridae). *Brain Research*, 83(3), 504–508.
- Werthat, F., Alexandrova, O., Grothe, B., & Koch, U. (2008). Experience-dependent refinement of the inhibitory axons projecting to the medial superior olive. *Developmental Neurobiology*, 68(13), 1454–1462.
- West, C. D., & Harrison, J. M. (1973). Transneuronal cell atrophy in the congenitally deaf white cat. *Journal of Comparative Neurology*, 151(4), 377–398.
- Wiesel, T. N., & Hubel, D. H. (1963). Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *Journal of Neurophysiology*, 26(6), 978–993.
- Wilson, T. G., & Kane, F. (1959). Congenital deafness in white cats. *Acta Oto-Laryngologica*, 50(3–4), 269–275.
- Winer, J. A. (2006). Decoding the auditory corticofugal systems. *Hearing Research*, 212(1–2), 1–8.
- Winer, J. A. (2011). A profile of auditory forebrain connections and circuits. In J. A. Winer & C. E. Schreiner (Eds.), *The auditory cortex* (pp. 41–74). New York: Springer.
- Winer, J. A., & Schreiner, C. E., Eds. (2005). *The inferior colliculus*. New York: Springer.
- Winer, J. A., & Schreiner, C. E., Eds. (2011). *The auditory cortex*. New York: Springer.
- Wolff, D. (1942). Three generations of deaf white cat. *Journal of Heredity*, 33(2), 39–43.
- Wright, D. D., & Ryugo, D. K. (1996). Mossy fiber projections from the cuneate nucleus to the cochlear nucleus in the rat. *Journal of Comparative Neurology*, 365(1), 159–172.
- Ylikoski, J., & Savolainen, S. (1984). The cochlear nerve in various forms of deafness. *Acta Oto-Laryngologica*, 98(5–6), 418–427.
- Young, E. D., & Oertel, D. (2003). The cochlear nucleus. In G. M. Shepherd (Ed.), *The synaptic organization of the brain* (5th ed., pp. 125–163). New York: Oxford University Press.

- Young, S. R., & Rubel, E. W. (1986). Embryogenesis of arborization pattern and topography of individual axons in N. laminaris of the chicken brain stem. *Journal of Comparative Neurology*, 254(4), 425–459.
- Youssoufian, M., Couchman, K., Shivdasani, M. N., Paolini, A. G., & Walmsley, B. (2008). Maturation of auditory brainstem projections and calyces in the congenitally deaf (dn/dn) mouse. *Journal of Comparative Neurology*, 506(3), 442–451.
- Zhou, Y., Carney, L. H., & Colburn, H. S. (2005). A model for interaural time difference sensitivity in the medial superior olive: Interaction of excitatory and inhibitory synaptic inputs, channel dynamics, and cellular morphology. *Journal of Neuroscience*, 25(12), 3046–3058.
- Zilberstein, Y., Liberman, M. C., & Corfas, G. (2012). Inner hair cells are not required for survival of spiral ganglion neurons in the adult cochlea. *Journal of Neuroscience*, 32(2), 405–410.