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REVIEW

Auditory neuroplasticity, hearing loss and cochlear implants

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Abstract Data from our laboratory show that the auditory brain is highly malleable by experience. We establish a base of knowledge that describes the normal structure and workings at the initial stages of the central auditory system. This research is expanded to include the associated pathology in the auditory brain stem created by hearing loss. Utilizing the congenitally deaf white cat, we demonstrate the way that cells, synapses, and circuits are pathologically affected by sound deprivation. We further show that the restoration of auditory nerve activity via electrical stimulation through cochlear implants serves to correct key features of brain pathology caused by hearing loss. The data suggest that rigorous training with cochlear implants and/or hearing aids offers the promise of heretofore unattained benefits.

Keywords Auditory · Brain · Cochlear · Implants · Deafness · Synapse

Introduction

During the nearly 65 years since Levi-Montalcini (1949) reported on the importance of afferent fibers for the development of acoustic centers in the chick embryo, a tremendous body of data has amassed indicating that the structural and functional integrity of neurons are radically altered by changes in the amount of afferent input that they receive. When a fiber system is damaged, atrophic changes may appear in the cells to which it is connected. Such transneuronal degeneration has been produced in a variety of brain structures, including the cochlear nucleus, olfactory bulb, spinal cord, lateral geniculate, subcortical trigeminal centers and pyriform cortex (Mathews and Powell 1962; Cook et al. 1965; Gelfan et al. 1972; Lund et al. 1973; Belford and Killackey 1979; Westenbroek et al. 1988). These effects are more striking in young animals and importantly, pathologic changes can occur in the absence of actual tissue damage. The observation that abnormalities can be produced by functional deprivation has emphasized the role of neural activity in the development and/or maintenance of brain structure.

Substantial alterations at the cellular level occur following manipulations of afferent activity. With regard to the auditory system of birds and mammals, deafening in neonates (ferrets, Moore and Kowalchuk 1988; cats, Lustig et al. 1994; guinea pigs, Lesperance et al. 1995) or adults (cats, Powell and Erulkar 1962; chickens, Parks 1979; Born et al. 1991; mice, Trune 1982a, 1982b; ferrets, Moore 1990; rats, Hildebrandt et al. 2011) produces atrophic and reactive changes in the central pathways. The expression of these changes can appear as the atrophy of dendrites (Benes et al. 1977; Deitch and Rubel 1984, 1989), somatic shrinkage (Parks 1979; Trune 1982a, 1982b; Saada et al. 1996), chromatolysis (Powell and Erulkar 1962), RNA downregulation (Steward and Rubel 1985) and altered axonal projections along the central pathway (Nordeen et al. 1983; Moore and Kowalchuk 1988; Parks et al. 1990; Illing et al. 1997; Tirko and Ryugo 2012). Such changes are much more striking when deafness is induced in neonates compared with in adults (Powell and Erulkar 1962; Trune 1982a, 1982b; Hashisaki and Rubel 1989; Mostafapour et al. 2000). Acute pharmacologic blockade of electrical activity in the auditory nerve is also capable of producing central structural changes (Sie and Rubel 1992; Pasic et al. 1994). A broad range of homeothermic species appear dependent on

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neural activity to maintain normal brain organization and function. Furthermore, the similarity of neural reactions to manipulations of the sensory environment indicate that common principles are involved. The generality of effects signifies that neuroplasticity can be studied by using a variety of species, methods and tools to yield important contributions and insights.

In contrast to the effects of deprivation, stimulation paradigms (such as conditioning to certain frequencies) often produce expanded representations of neural regions or increased sensitivity that are specific to the conditioning frequencies (e.g., Robertson and Irvine 1989; Bakin and Weinberger 1990; Recanzone et al. 1993; Suga et al. 2002; Suga 2011). These studies emphasize the extent to which the brain is selectively responsive to the type and amount of afferent activity, although the cellular and molecular mechanisms underlying these changes have not been revealed. Nevertheless, these kinds of plastic changes are speculated to be controlled by balancing excitation and inhibition, by exerting centrifugal influences on ascending pathways and/or by modulating sensory receptors by way of the auditory efferents.

Historically, experimental studies of acoustic deprivation or deafferentation have been performed on phenotypically normal subjects. Cochlear ablation, auditory nerve section and pharmacologic blockade of the cochlea are known to produce central changes that are hypothesized to result from such deprivation (Rubel and Parks 1988). Invasive surgical effects, however, can be complicated by variables such as direct and/or indirect insults to the blood supply, collateral surgical damage, inflammation and infection. Chemical deafening by the neurotoxic effects of drug application raises caveats because of the multiple modes of pharmacologic action. Ototoxic drugs that kill auditory receptors in the inner ear potentially have "downstream" effects that act directly or indirectly on structures of interest, even if they are remote from the site of application. Thus, we need to consider both the direct and indirect consequences of experimentally induced deafness in order to interpret the results properly.

Over the last several decades, the use of gene mutations that result in deafness has been growing. Many forms of hereditary deafness are accompanied by other abnormalities, such as blindness (*Usher's syndrome*, Keats and Corey 1999) or motor pathologies (*Ames Waltzer*, Osako and Hilding 1971; *Whirler*, Fleming et al. 1994). "Uncomplicated" forms of deafness have assumed greater prominence because they better resemble deafness found in humans (Fraser 1976). Today, a "cornucopia" of gene candidates that are associated with deafness is available (Eisen and Ryugo 2007; Lewis and Steel 2012). A myriad of possible genetic events, any of which may appear innocuous, can nevertheless initiate certain downstream processes that result in deafness.

In this context, there may be no perfect model that can be used to study the effects of deafness expressed by inner ear pathology and that is free of potential complications of indirect effects on the very brain structure under study. That said, however, models of deafness that selectively block auditory nerve activity will serve as the strongest argument for a causal link between deafness, neural activity and brain structure and function. A corollary is that the restoration of activity to a deaf system should propel the system back towards normal with the caveat that timing (e.g., age of deafness onset and duration of deafness), environment and innate abilities will influence the outcome. This review reports on work conducted in my laboratory that addresses brain alterations as a result of changes in auditory nerve activity and documents synapse plasticity when spike activity is restored.

In order to study the relationship between brain morphology and auditory nerve activity, a structure needs to be selected that has functional significance and is readily identifiable. The endbulb of Held of auditory nerve fibers meets the criteria by virtue of its large size, characteristic axosomatic architecture and evolutionary conservation (Ryugo and Fekete 1982; Ryugo and Parks 2003). Endbulbs are revealed by using intracellular dyes; they arise from the ascending branch of a single type I auditory nerve fiber and terminate by clasping the soma of a bushy cell in the anteroventral cochlear nucleus (Fig. 1). Each endbulb is formed by the simultaneous emergence of several thick gnarled branches that divide repeatedly to form a network of *en passant* and terminal swellings; the resulting arborization spreads over much of the surface of the associated cell body. Indeed, the endbulb forms up to 2000 release sites (Ryugo et al. 1996). The numerous synapses imply that depolarization of the endbulb causes the synchronous release of many synaptic vesicles. Presynaptic activity

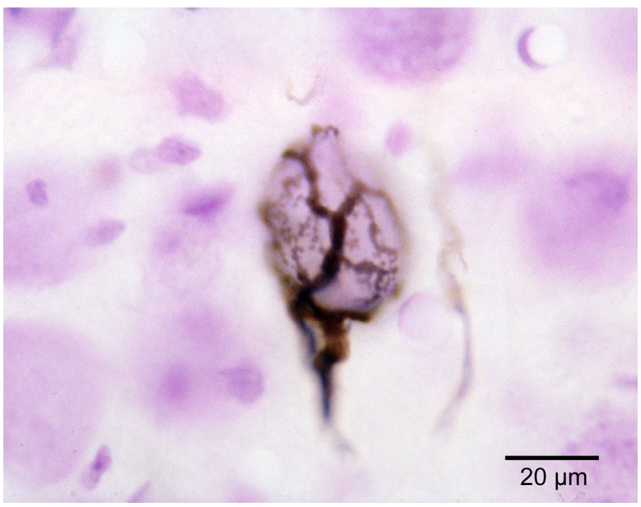

Fig. 1 Light micrograph of an endbulb of Held in the anteroventral cochlear nucleus of an adult cat; the endbulb is stained *brown* by horseradish peroxidase (HRP) and diaminobenzidine (DAB) histochemistry. Note the complex branching and the varicosities on the tertiary branches. The endbulb encircles the cell body of the spherical bushy cell, stained *light purple* and gives rise to hundreds of synapses (modified from Ryugo and Fekete 1982)

would therefore produce a prominent and dependable postsynaptic response because of the flood of neurotransmitters. The reliable linkage of neural activity to acoustic events subserves the ability of mammals to detect interaural timing differences on the order of 10s of microseconds (Joris and Yin 1998; Drapal and Marsalek 2011).

The importance of this large auditory nerve terminal is underscored by its presence in every terrestrial vertebrate examined. They have been observed in turtles, lizards, birds and mammals including rodents, carnivores and primates (Fig. 2). Consequently, they are inferred to have an important role in auditory processing and, thus, the survival of the organism.

The endbulb does not start off as a highly arborized structure. In newborn cats, the immature endbulb resembles a growth cone, described as a club-shaped swelling with numerous filopodia and fine adventitious processes (Held 1893; Brawer and Morest 1975; Lorente de Nó 1981; Ryugo and

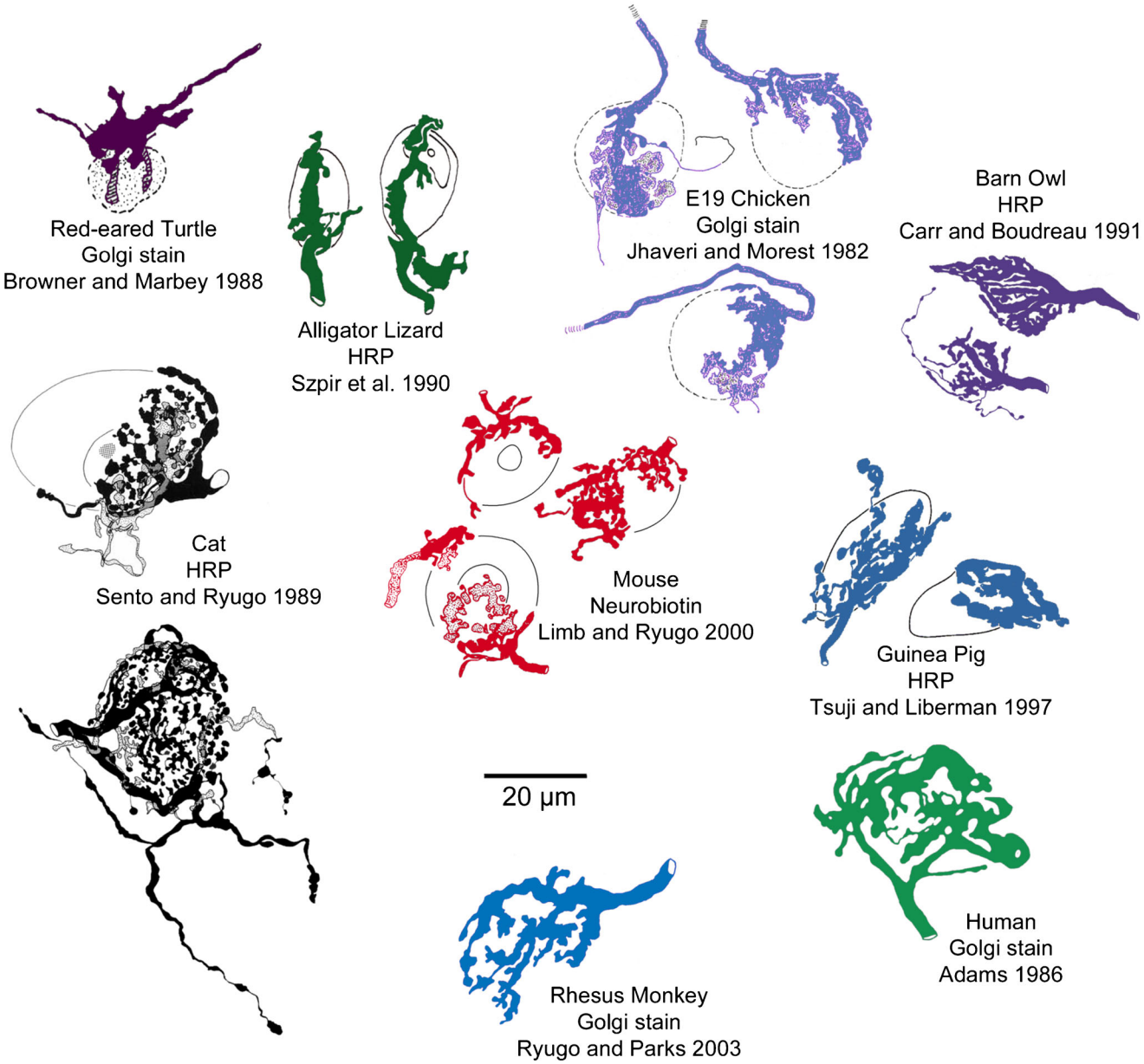

Fig. 2 Comparative view of endbulbs from terrestrial vertebrates, spanning amphibia to humans (Browner and Marbey 1988; Szpir et al. 1990; Jhaveri and Morest 1982; Carr and Boudreau 1991; Sento and Ryugo 1989; Limb and Ryugo 2000; Tsuji and Liberman 1997; Ryugo and Parks 2003; Adams 1986). These endbulbs have been stained by a variety of techniques and illustrate their large size and complex structure. The morphology implies faithful signal transmission to the postsynaptic neuron in which neural activity will be tightly linked to acoustic events. Accurate timing of spikes confers evolutionary advantages in the form of sound localization acuity and auditory discrimination (modified from Ryugo and Parks 2003)

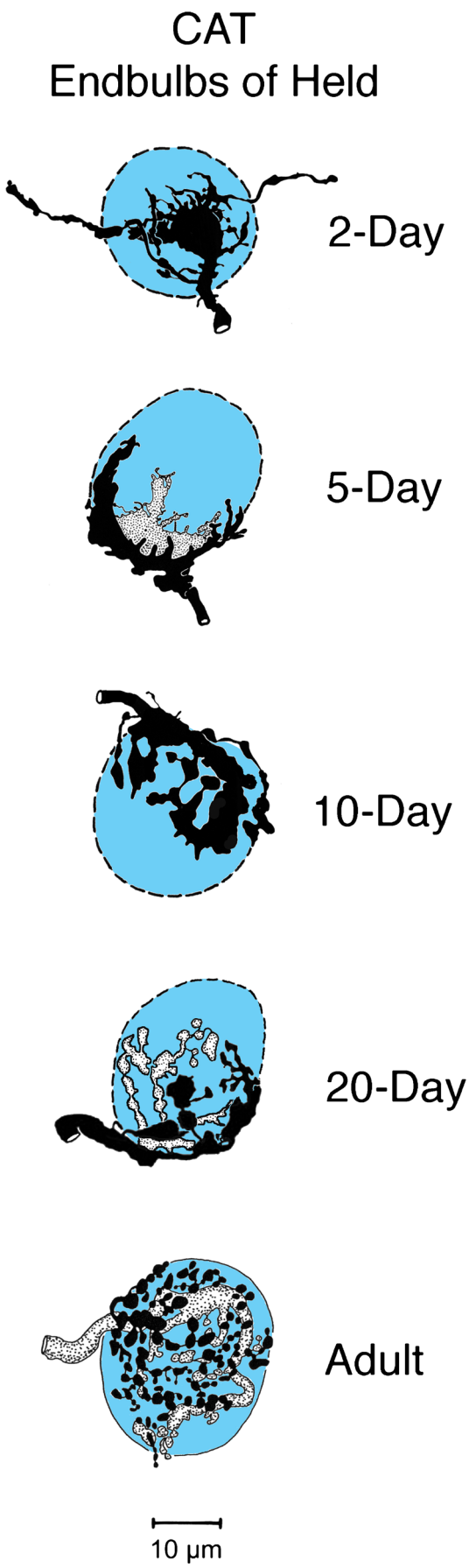

Fig. 3 Development of endbulbs of Held in cats. Endbulbs were originally described in Golgi-stained material as large spoon-shaped endings arising from the auditory nerve (Held 1893). We show, however, that the original description was based on immature endbulbs and that endbulbs pass through a sequence of postnatal developmental stages culminating in a highly branched, arborized structure (modified from Ryugo and Fekete 1982)

Fekete 1982). Over the next several days, the swelling develops fenestrations and fissures; irregular leaflets form between the fissures and the adolescent endbulb starts to resemble a floral calyx. By the third week, the endbulb can be described as a highly branched arborization. The structure is characterized by 3–5 main branches that divide repeatedly to form successively finer branches (Fig. 3). A period of developmental refinement occurs over the next 30 days during which irregular varicosities become elaborated and strung together by fine filaments to create a delicate reticulum into which nestles the postsynaptic cell body (Ryugo and Fekete 1982; Limb and Ryugo 2000).

Because of the relatively prolonged period over which the endbulb develops, the opportunity arises to investigate the way that neural activity affects the maturational process. The importance of neural activity for the normal development and function of synapses has received strong experimental support (e.g., Shatz and Stryker 1978; Goodman and Shatz 1993; Kandler 2004). Manipulations that deprive sensory systems of input produce striking atrophic effects (Powell and Erulkar 1962; Van der Loos and Woolsey 1973; LeVay et al. 1980; Benson et al. 1984; Born and Rubel 1985; Saada et al. 1996; Ryugo et al. 1997; Zhang et al. 2001), whereas selective activation can produce somatic enlargement (Wiesel and Hubel 1963; Moore 1985), terminal swelling (Heuser and Reese 1973; Boyne et al. 1975; Burwen and Satir 1977), dendritic spine alterations (Fifková and Van Harreveld 1977; Fifková and Morales 1992) and modifications in receptive field properties (Diamond and Weinberger 1986; Weinberger 1995; Suga 2011; Adab et al. 2014). These kinds of activity-related changes in the central nervous system argue that neuron structure and function can be influenced by the type and level of input activity.

Early studies sought to manipulate the hearing of normal subjects. In these cases, cochleae were ablated, auditory nerves were sectioned, or sound transduction blocked by pharmacologic agents (Rubel and Parks 1988). Alternative models of auditory deafferentation considered naturally occurring forms of hereditary deafness such as that observed in congenitally deaf white cats, Dalmatian dogs, blue-eyed white alpacas, waltzing guinea pigs and various strains (over 50) of mice carrying deafness genes. The congenitally deaf animal offered a challenging model of auditory deafferentation because it contained a broader spectrum of variables that affected brain structure and function, similar to the case in humans (Eisen and Ryugo 2007).

The congenitally deaf white cat mimics the Scheibe deformity in humans and features early onset, progressive cochleo-saccular degeneration and severe sensorineural hearing impairment (Scheibe 1895; Bosher and Hallpike 1965; Deol 1970; Suga and Hattler 1970; Beighton et al. 1991). The *Dominant White* locus (*W*) in the domestic cat demonstrates pleiotropic effects that are transmitted in an autosomal dominant pattern with complete penetrance for the absence of coat pigmentation and incomplete penetrance for deafness and iris hypopigmentation. Linkage analysis of a pedigree segregating *White* identified *KIT* as the feline *W* locus. Segregation and sequence analysis of the *KIT* gene in two pedigrees (P1 and P2) revealed a retrotransposition and evolution of a feline endogenous retrovirus (FERV1) as being responsible for two distinct phenotypes of the *W* locus, Dominant White and White Spotting (David et al. 2014). Deafness is attributable to inner ear pathology ranging from variable hair cell loss to complete collapse of the organ of Corti with evidence of spiral ganglion cell loss (Rawitz 1896; Bosher and Hallpike 1965; Bergsma and Brown 1971; Mair 1973; Pujol et al. 1977; Rebillard et al. 1981; Chen et al. 2010). Our interest was in the structural changes in neurons of the central auditory pathway as a result of the deafness (West and Harrison 1973; Schwartz and Higa 1982; Larsen and Kirchhoff 1992; Saada et al. 1996).

Cats with hearing loss

Auditory nerve recordings We examined the structure of the organ of Corti and the activity of the auditory nerve in order to relate their influence on the morphology of primary ending morphology in the cochlear nucleus. Single unit recordings were made in normal hearing cats, in cats with elevated thresholds and in totally deaf cats. Because unit activity is not driven by sound in deaf cats, we used intracellular recording techniques for this project. An abrupt negative shift in the DC potential to around −30 mV indicated contact with an auditory nerve fiber. Once the pipette penetrated an axon, the DC potential gradually moved towards 0 mV, typically within 3–5 min and sometimes sooner. During this period, however, we were able to collect 10 s of spontaneous activity (SR) and run an automated tuning curve program. Three types of auditory nerves were encountered: those with fibers having a normal distribution of frequency sensitivity and thresholds being collected from hearing cats; those with fibers having elevated (40–95 dB) thresholds that were collected from cats with hearing loss; and those with fibers that were completely unresponsive to sound arose from cats that were profoundly deaf.

Endbulb morphology Endbulb structure is correlated to the fiber's hearing status (Fig. 4). Auditory nerve fibers from normal hearing cats exhibit a complex terminal arborization

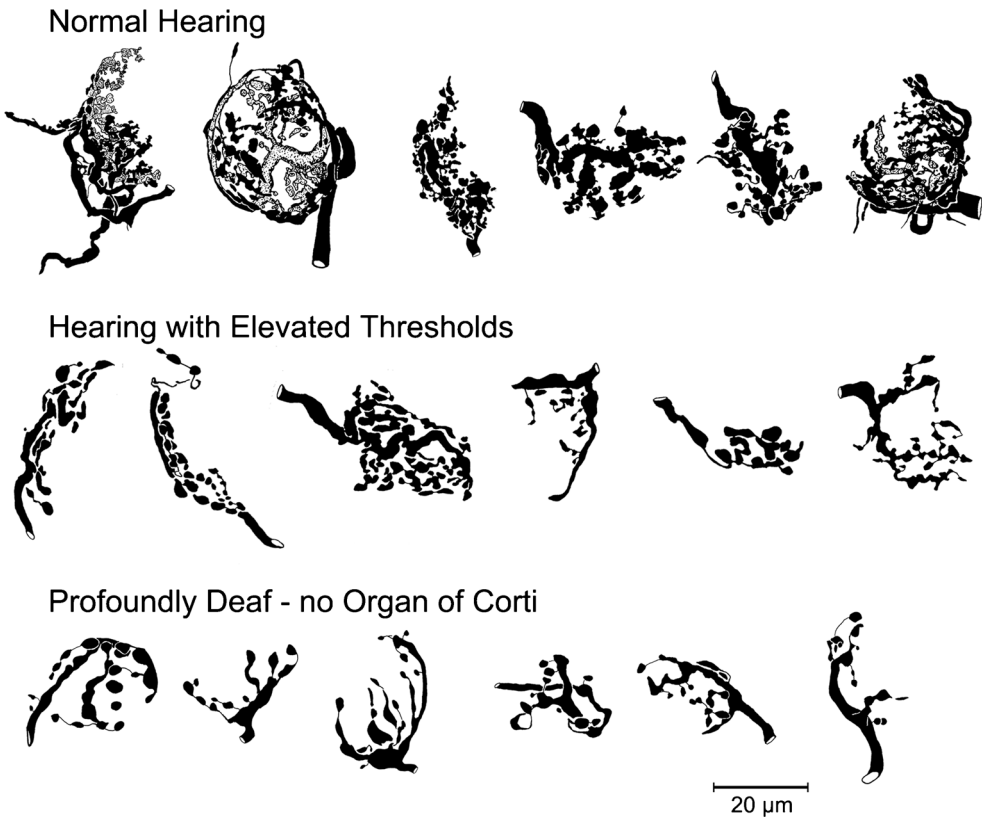

Fig. 4 Reconstructions of endbulbs stained by HRP reveal that hearing status influences the development of endbulb structure. The complexity of branching as assessed by fractal analysis is demonstrably affected by hearing loss. The greater the loss, the greater the structural atrophy (modified from Ryugo et al. 1998)

marked by several thick branches (2–3 μm in diameter) stemming from a single trunk. Numerous irregular varicosities varying in size and shape (1–5 μm in diameter) occur along these branches, strung together by fine processes. This elaborate network of interconnected terminal swellings (fractal index 1.430±0.048; silhouette area 390.3±177 μm^2) expands to contact much of the soma of the spherical bushy cell (Ryugo et al. 1997, 1998).

In contrast, the endbulbs from cats with hearing loss were decidedly atrophic. Those from cats with elevated thresholds exhibited fewer branches and fewer varicose swellings. The resulting endbulbs were less complex (fractal index 1.318±0.066; silhouette area 193.81±49.3 μm^2). Endbulbs from congenitally deaf cats were the most severely attenuated. They had the least complex branching structure (fractal index 1.288±0.056) and the smallest average silhouette area (171.8 ±61 μm^2). Average endbulb complexity was significantly different between the separate cohorts of cats by fractal dimension values ($P<0.05$, analysis of variance). This effect of hearing loss on endbulb morphology is similar to that observed in mice (Limb and Ryugo 2000).

Endbulb synapses The synapses of normal auditory nerve terminals are characterized by an accumulation of clear round synaptic vesicles in close proximity to a slightly curved but prominent membrane thickening that arches into the presynaptic terminal (Fig. 5). Parallel to the presynaptic membrane thickening is a pronounced postsynaptic membrane thickening, which emphasizes the asymmetric nature of the thickened membrane segments. The associated vesicles are relatively uniform in shape and size (approximately 50 nm in diameter) and cluster in variable numbers around the dome-shaped membrane thickening. The extracellular space between these membranes, called the synaptic cleft, is slightly widened and filled by a dense flocculent material. The dome-shaped synapses of auditory nerve fibers are characteristic of many

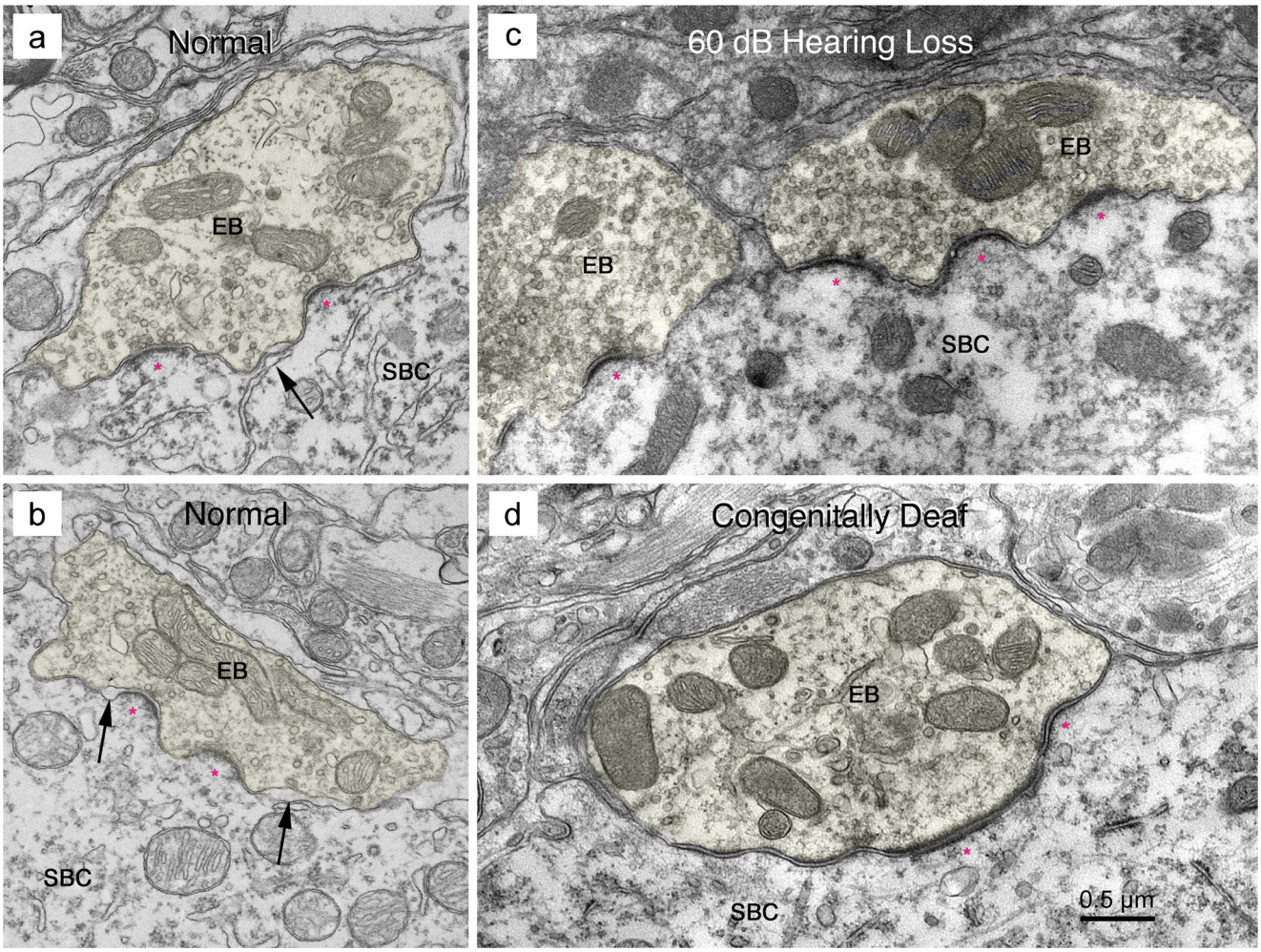

Fig. 5 Electron micrographs of endbulbs (*pale yellow*) from cats with normal hearing and those with hearing loss. Note the flattening and lengthening of synapses (*pink stars*) in cats with hearing loss. Channels between pre- and postsynaptic membranes (*arrows*) are common in hearing animals but rare or absent in animals with hearing loss (*EB* endbulb, *SBC* spherical bushy cell; from Ryugo et al. 1998 and O'Neil et al. 2010)

mammals (Lenn and Reese 1966; Gulley et al. 1978; Cant and Morest 1979; Ryugo and Fekete 1982; Gomez-Nieto and Rubio 2011).

Extracellular dilations were frequently observed between the pre- and postsynaptic membranes that formed narrow channels near synapses (Fig. 5a, b). Finger-like glial processes were often seen within the space, prompting the thought that such cisternae could aid in the dispersal of excess neurotransmitters. Puncta adeherentia and mitochondrial adherens complexes also characterized these auditory terminals. Several layers of thin astrocytic sheets ensheathed the terminals. Away from the axosomatic synapses, synapses could be found on nearby dendrites (Lenn and Reese 1966; Gulley et al. 1978; Cant and Morest 1979; Ryugo and Sento 1991; Rowland et al. 2000).

Endbulb synapses with hearing loss and deafness In the congenitally deaf adult cat, endbulb synapses retain many of the features found in the normal hearing cat. Prominent contacts are found on the somata of spherical bushy cells associated with large round synaptic vesicles (Ryugo et al. 1997, 1998; O'Neil et al. 2010). Distinctly abnormal features of endbulbs in deaf cats include the appearance of enlarged and flattened postsynaptic densities (PSDs), a lack of intercellular cisternae and increased clustering of synaptic vesicles in the immediate vicinity of the PSDs (Fig. 5d). A notable increase also occurs in synaptic vesicle density (63.0±41.8 vesicles per μm^2) when compared to that of endbulbs from normal hearing cats (45.0± 12.4, $P<0.01$, Kruskal-Wallis tests).

Some white cats from families with a history of congenital deafness were impaired but not profoundly deaf. These animals exhibited a loss of hair cell receptors in the basal 20 % of the organ of Corti, were unresponsive to frequencies between 10 and 40 kHz but had an average of 60 dB elevated single unit thresholds for tones below 10 kHz. SR rates varied considerably but were independent of best frequency thresholds (Ryugo et al. 1997). The synapses of cats with elevated thresholds were different from those of either the normal or profoundly deaf cats. The density of presynaptic vesicles was consistently elevated (mean 92.9±25.2 vesicles/μm^2). The PSDs exhibited asymmetric membrane densities and many were clearly dome-shaped but they were sometimes longer and not as curved (Fig. 5c). A reduction was observed in the intermembraneous cisternae.

Individual synapses were reconstructed in three dimensions by collecting high-magnification serial electron micrographs through the PSD digitizing and drawing the outline of the presynaptic terminal and the PSD and then stacking and aligning the images by using computer graphics. When the stack of images was rotated by 90° and viewed *en face*, the area of postsynaptic membrane contacting the presynaptic terminal and the PSDs was revealed and individual PSDs could be measured (Fig. 6). In this way, the difference in PSD size was quantified by comparing the mean values from normal hearing cats, cats with hearing loss and profoundly deaf cats. The PSDs of endbulbs from normal hearing cats were generally round-to-oval in shape and small in size (0.06 ±0.04 μm^2). Those PSDs from cats with hearing loss were more oval in shape and slightly larger (0.1±0.08 μm^2) but not statistically so ($P=0.10$). In contrast, those PSDs in profoundly deaf cats were much larger (0.34±0.37 μm^2) and strikingly irregular in shape. Because the PSDs of congenitally deaf cats often extended beyond the scope of our tissue section series, our measurements underestimated their actual size. These differences in PSD size between our cohorts reflected pathologic conditions of hearing loss, which were related to the amount of neural activity.

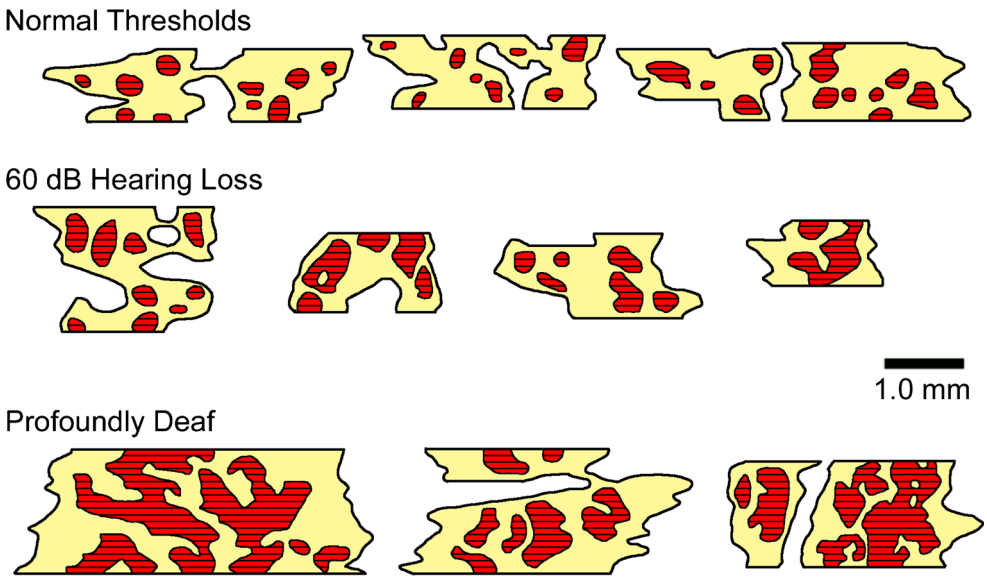

Fig. 6 Images of reconstructed endbulb synapses from serial electron micrographs that were aligned, stacked and then rotated. The view shows the area of postsynaptic membrane that lies adjacent to the endbulb (*yellow*) and the areas with *horizontal lines* (marking an individual section) represent the postsynaptic density (PSD, *red*). Synapses from cats with hearing loss are on average slightly larger than those of normal hearing cats but the difference is not statistically significant. The PSDs from congenitally deaf cats, however, are significantly larger (Ryugo et al. 1998)

Cats with normal hearing

The auditory nerve is an excellent model with which to study activity-related features of synaptic structure. The myelinated fibers convey acoustic information into the brain and individual fibers can be described by two fundamental properties: frequency selectivity and spontaneous discharge rate. Frequency selectivity is represented by that pure tone frequency to which the fiber is most sensitive, known as the best or characteristic frequency (CF). CF reflects the longitudinal position along the cochlea at which the peripheral process terminates (Liberman 1982). Spontaneous discharge rate (SR) is defined as the spike activity (in spikes/s) occurring in the absence of experimentally controlled acoustic stimulation (Kiang et al. 1965; Liberman 1978). SR can range from near zero to greater than 100 spikes/s and across the audible frequency range, a bimodal distribution of SR occurs in the population of auditory nerve fibers (Kiang et al. 1965; Evans and Palmer 1980; Schmiedt et al. 1996). We defined one group as having low SRs (≤ 18 spikes/s) and the other as having high SRs (> 18 spikes/s). The low SR fibers have relatively high thresholds for evoked activity and the high SR fibers have relatively low thresholds. Thus, in silence or noise, the low SR fibers presumably exhibit lower levels of spike activity in comparison with that of high SR fibers. Moreover, because high and low SR fibers are present for fibers of all CFs, they could subserve different functions in sound processing. We reasoned that the two fiber groups could be compared in order to study the relationship between neural activity and synaptic morphology.

Endbulb morphology Intracellular recordings were made in the auditory nerves of normal hearing cats. Our strategy was to inject dye into 1–3 low SR fibers in the left nerve whose CFs differed by at least an octave, and into 1–3 high SR fibers in the right nerve of similar CFs. This technique minimized individual variations. Moreover, the recovered labeled fibers yielded endbulbs whose morphology could be correlated with their activity levels (Fig. 7): low activity was associated with complex arborizations (as defined by fractal analysis), whereas high activity fibers were associated with simpler arborizations (cat, Sento and Ryugo 1989; guinea pig, Tsuji and Liberman 1997). These results provide convincing data that activity influences endbulb structure but the significance of the differences remains to be determined.

Endbulb synapses Electron microscopic analyses of the synapses from these endbulbs also revealed distinct structural differences (Fig. 8). Synapses from high SR fibers exhibited the characteristic dome-shaped PSDs with clear round synaptic vesicles clustered along the presynaptic membrane. In contrast, synapses from low SR fibers exhibited more irregular PSDs. Some PSDs were dome-shaped and small, whereas many were flattened or wavy and longer. The curvature of the PSD was quantified: on average, that of PSDs of high SR fibers was significantly greater than that for low SR fibers ($P<0.003$, Mann–Whitney U test; Ryugo et al. 1996). Intermembraneous cisternae were typically near the synaptic release sites.

The synaptic active zone is represented by a subcellular membrane density that appears as a thickening of electron-dense material attached to the postsynaptic membrane. The PSD is a scaffold of modular proteins that contain the receptors for neurotransmitters and is associated with Ca^{++}/calmodulin-dependent protein kinases (Seitanidou et al. 1988; Flucher and Daniels 1989; Kennedy 1989; Nusser et al. 1994; Cho et al. 2009). The differential expression of these proteins at excitatory and inhibitory synapses must underlie the differences in the ultrastructural appearance for the two types of synapses. Likewise, these kinds of variations will be reflected in the structural changes observed in synapses undergoing remodeling, such as in cases of atrophy of disuse, compensatory hypertrophy, or plasticity of habituation, sensitization and learning (Markus and Petit 1989). The postsynaptic membrane also houses molecules involved in signal transduction including other G-protein-coupled receptors (e.g., metabotropic receptors), voltage- and ligand-gated ion channels, transporters and pumps. The presynaptic membrane is involved in the vesicular release of transmitters for synaptic transmission and also contains substrates for inactivating synaptic transmission such as re-uptake receptors and transporters. The number and spatial distribution of these molecules are presumed to determine synaptic mechanisms and modes of intercellular communication.

Synaptic vesicles Synaptic vesicles were analyzed on micrographs at a magnification of ×138,000. The mean diameter of synaptic vesicles for endbulbs of high SR fibers was greater when the profile contained a synapse (48±8 nm, $n=764$) than not (46±7 nm, $n=380$). Likewise, the mean diameter for vesicles of low SR fibers was greater (48±9 nm, $n=939$) when the ending profile contained a synapse than not (44±7 nm, $n=164$). No difference was seen in vesicle size when comparing high versus low SR endbulbs. These observations are consistent with the idea that synaptic vesicles more distant from the active zone and representing the reserve vesicle pool are not yet completely filled with transmitters.

The number of synaptic vesicles per ending profile and per square micrometer within 0.5 μm of the PSD was determined. We calculated an average of 67.2±16.9 vesicles/μm^2 for high SR endings and 62.2±24.4 vesicles/μm^2 for low SR endings. On average, more synaptic vesicles are found in high SR endbulbs than in low SR endbulbs ($P<0.05$).

Synapse size and number We reconstructed endbulb profiles through serial ultrathin sections by using methods, as

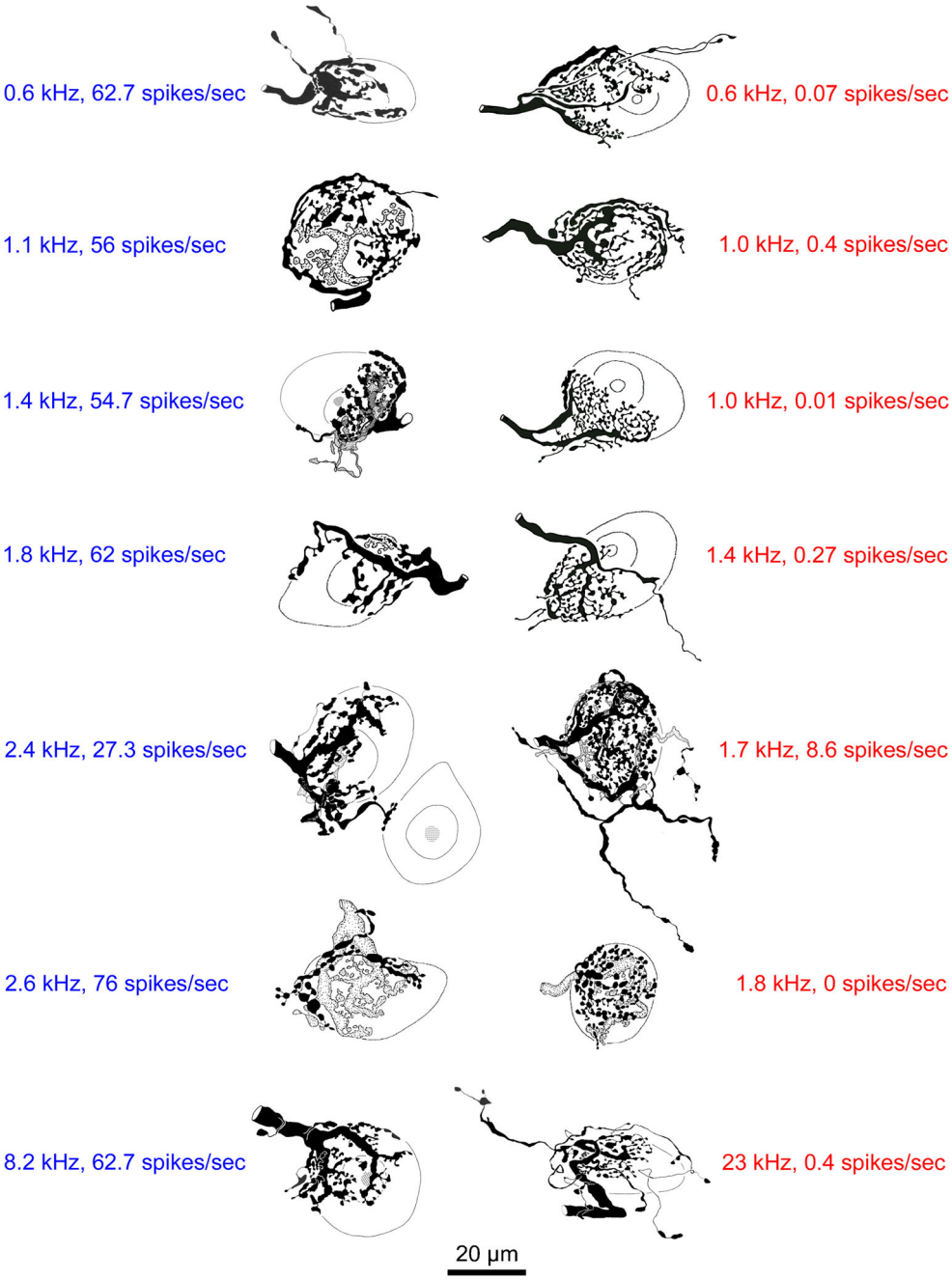

Fig. 7 Images of reconstructed endbulbs from intracellular recording and dye injection experiments illustrate the structural differences between endbulbs of "active" (*left*) and "inactive" (*right*) auditory nerve fibers. Pairs of endbulbs from separate auditory nerves of the same cat are roughly matched in frequency sensitivity but have striking differences in thresholds and general activity. Note the way that the structure of high threshold, low activity endbulbs is more complex in their branching pattern compared to those of low threshold and high activity (Sento and Ryugo 1989; Ryugo and Sento 1991; Ryugo et al. 1996)

previously described, in order to calculate synapse size. The *en face* area of each synapse was measured, the entire PSD being contained within the section series, i.e., there was a start and finish (Fig. 9). A total of 74 synapses were reconstructed from the endbulbs of high SR fibers and these were, on average, 0.089±0.02 μm^2. In contrast, 65 synapses were reconstructed from the endbulbs of low SR fibers and they were significantly larger (0.179±0.02 μm^2, $P<0.01$). These differences were reliable across many cats and terminals.

The number of axosomatic synapses per endbulb was calculated in the following way. First, we counted the number of synapses per unit apposition area through serial section reconstructions of portions of each endbulb (Fig. 9). The resulting values were relatively constant and revealed that synapse density was uniform over the entire endbulb. We multiplied this density value for each endbulb by its corresponding silhouette area because we estimated that the silhouette area approximated the endbulb contact surface with the postsynaptic cell body. This method revealed that the high SR endbulbs had an average of 1720±395 synapses, whereas the low SR endbulbs had an average of 407±139 synapses. The data indicated that high SR endbulbs have roughly four times the number of axosomatic synapses contacting spherical bushy cells as do low SR endbulbs.

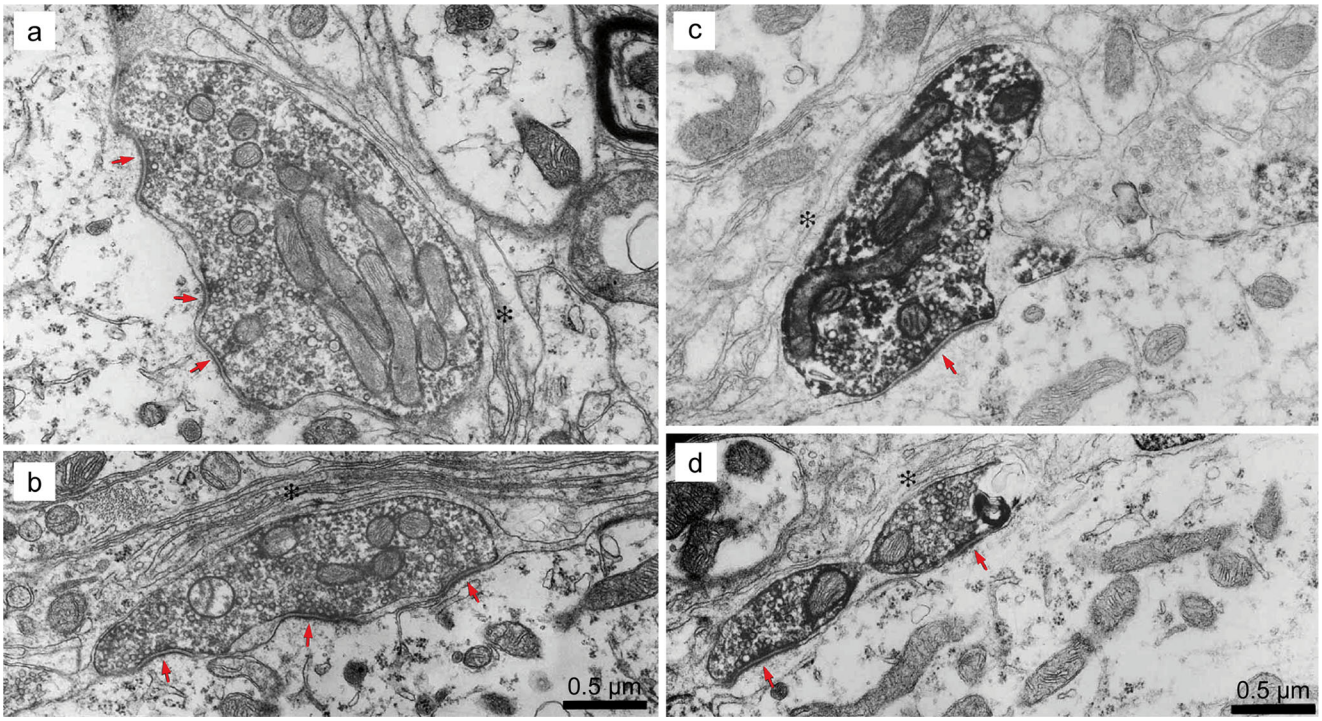

Fig. 8 Electron micrograph of endbulbs labeled after intracellular recording and HRP injections. Parts of the labeled endbulbs are *dark* because of the presence of HRP-DAB reaction product. Synapses (*red arrows*) are characterized by a thickened curved postsynaptic membrane associated with an accumulation of synaptic vesicles on the presynaptic side. The postsynaptic membranes of the synapses of high SR fibers (**a**, **b**) are clearly dome-shaped and punctate, whereas those of low SR fibers (**c**, **d**) are longer and variably curved

The smaller and more numerous active zones for endbulbs of high SR fibers represent a striking contrast to those of low SR fibers. This difference raises questions about the role of activity in this arrangement. What purpose is served by arranging active zones into smaller but more numerous modules? We speculate that the arrangement will bring more non-active zone membranes into closer proximity to the PSDs and reduce the average distance from the PSD to the surrounding non-PDS area. The membrane containing PSDs is surrounded by a non-synaptic membrane that contains other

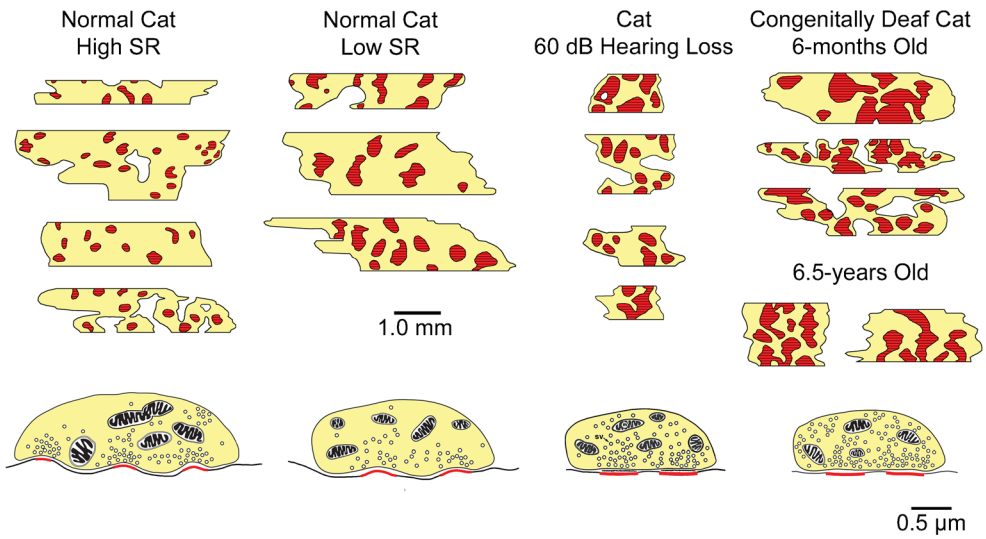

Fig. 9 Images of reconstructed endbulb synapses from serial electron micrographs from cats of various hearing status. The postsynaptic membrane has been rotated so that we are looking down on the PSDs beneath the presynaptic endbulb. The contact area is in *yellow*; the PSDs are *red*. Note that the most active fibers have the smallest PSDs. Normal low SR fibers and cats with hearing loss exhibit PSDs that are similar in size and shape. The congenitally deaf cats have PSDs that are distinctly hypertrophied. No difference is seen in PSD size between 6-month-old and 6-year-old cats. *Bottom row* Normal hearing cats have PSDs that are dome-shaped, whereas cats with hearing loss have flattened PSDs. Some synapses are normal in appearance regardless of the degree of hearing loss

ion channels, receptors and/or pumps. For example, metabotropic glutamate receptors (cerebellar cortex, Baude et al. 1993; Nusser et al. 1994) and Na^+ channels (neuromuscular junction, Flucher and Daniels 1989) are concentrated in the membrane immediately adjacent to PSDs. The increased interface between active and non-active membranes facilitates receptor and ion channel turnover because pertinent molecules simply migrate in and out. Molecules in the middle of the PSD have shorter distances to migrate. A pattern of multiple small active zones might also be more advantageous than a single large active zone for optimizing diffusion kinetics of ions, metabolites and/or transmitter molecules from PSD to non-PSD regions. Small PSD size would also concentrate receptor distribution and help synchronize receptor activation; it could also expedite transmitter inactivation by minimizing the time/distance that the transmitter molecule is exposed to receptor binding (Taflia and Holcman 2007). These ideas have an intuitive quality but remain to be verified.

Action potentials occurring in fibers that generally exhibit low rates of activity might require specialized transmission mechanisms to assure information transfer because each spike assumes greater relative importance. As a result, the synapses of low SR fibers associate with larger PSDs that house correspondingly larger numbers of transmitter receptors. Such an arrangement optimizes transmitter binding with each synaptic event. The relationship is exaggerated by the hypertrophied PSDs found in congenitally deaf cats and mice (Ryugo et al. 1997, 1998; Lee et al. 2003). For low SR fibers, structural features associated with synaptic efficiency that assure high spike rates might not be an issue because their maximal discharge rate is lowest among the other auditory nerve fibers (Liberman 1978). An upregulation of AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid) receptors observed with postsynaptic to auditory nerve synapses also occurs following conductive hearing loss (Whiting et al. 2009; Wang et al. 2011). These observations are consistent with the notion that the synapse is a dynamic structure whose form and composition are influenced by neural activity.

On the presynaptic side, this pattern of multiple small synapses allows sites for vesicle attachment and recycling to reside in closer proximity to each other and to synaptic vesicles but without overcrowding. This arrangement serves to keep transporters and/or re-uptake receptors near the transmitter release sites, thereby providing greater synaptic efficiency. Rapid removal of excess transmitters in the cleft also reduces desensitization of receptors at the synapse (Trussell and Fischbach 1989). Both pre- and postsynaptic specializations must orchestrate their own unique, yet complementary, spatial assemblage in response to neural activity or chemical signals when forming synapses. In the anteroventral cochlear nucleus, signals as yet unidentified would be exchanged in both directions between membrane patches of endbulbs and spherical bushy cells in order to accomplish this task. The necessary interactive construction of pre- and postsynaptic components of the active zone is evident not only in the case of adjacent excitatory and inhibitory synapses that differ substantially in their form (Uchizono 1965) but also for activity-related structural features.

The synapse is the crucial point of communication between neurons and so should exhibit features that optimize their function. In addition to the punctate size of auditory synapses, the curvature of the membrane at the release site is a prominent feature. In the vernacular, synapses have the form of "smiling", "flat", or "frowning", the presynaptic element being placed above the postsynaptic structure (Markus and Petit 1989). Auditory nerve synapses are characteristically "frowning" as the dome-shaped PSD pushes into the presynaptic terminal (Lenn and Reese 1966; Cant and Morest 1979). Central auditory neurons exhibit several specialized characteristics that are crucial to hearing function: they have high rates of activity even in the absence of sound stimulation (Bhattacharjee and Kaczmarek 2005; Harrison and Negandhi 2012). They convey information with high fidelity in order to maintain the precise temporal relationships to acoustic events required for localizing sound on the horizontal plane (Grothe 2000; Couchman et al. 2010). They change their shape during postnatal maturation (Ryugo et al. 2006) and in response to high rates of synaptic excitation in adulthood (Rees et al. 1985).

Synaptic curvature should be considered a principal feature and should prompt speculation about its significance. Fundamentally, the proper functioning of auditory synapses requires the faithful transmission of information. This transfer needs efficiency and precision. In a simplistic way, one could consider two critical links to this process: one on the presynaptic side and one on the postsynaptic side. Presynaptically, there is the demand for rapid membrane fusion of the synaptic vesicles to the site of release. Membrane fusion events require molecules that tether and dock membranes and bring them together. SNAREs and synaptotagamins must disturb the lipid bilayers of the presynaptic membrane for the initial tethering of the synaptic vesicles. This stage involves the formation of hydrophobic defects in the cytoplasmic membrane leaflet for insertion of the tethering "linker" proteins. This process could be promoted by "frowning" curvature stress that facilitates the insertion of the fusion protein into the plasma membrane (McMahon et al. 2010). Efficient synaptic vesicle fusion contributes to high rates of synaptic transmission.

The postsynaptic membrane is also curved (dome shaped) with the "cap" facing the presynaptic release site. This arrangement optimizes the packing of transmitter receptors into the PSD. AMPA receptors have a relatively narrow transmembrane domain and an expanded amino-terminal and ligand-

binding domain that extends into the synaptic cleft (Wollmuth and Traynelis 2009). The three-dimensional structure of the AMPA receptors has the transmembrane domain of the receptor embedded in the PSD. The dome-shaped curvature of the PSD boosts receptor density by separating the wider ends from each other for closer packing and high receptor density will favor ligand binding and thus, synaptic transmission.

Atrophy versus plasticity

Synaptic structure has been shown to be related to levels of spike discharges by analyzing the normal situation and comparing it with circumstances in which activity is reduced either naturally or experimentally (West and Harrison 1973; Trune 1982a, 1982b; Ryugo et al. 1997, 1998; Rubel et al. 2004). Abnormal auditory nerve synapses in the cochlear nucleus of deaf animals might simply reflect the "atrophy" of disuse. True plasticity implies that neuronal change is bidirectional and reflects increases and decreases in activity. Consequently, we sought to determine whether electrical stimulation of the auditory nerve of congenitally deaf cats via cochlear implants would restore synapses to their normal morphology.

Three- and six-month-old congenitally deaf cats received unilateral cochlear implants and were stimulated for 7 h a day, 5 days a week, for a period of 10–19 weeks by using human speech processors (courtesy of Advanced Bionics). All implanted cats exhibited startle responses to loud and sudden sounds. Moreover, they all learned to approach their food dish in response to the adjutant's bugle call. The stimulus was paired with a special food treat once or twice a day at random times; other bugle calls were played throughout the day and were not reinforced. An atonal version of the adjutant's call was occasionally played and the cats did not respond to this monotonic stimulus. This observation confirmed that some features of stimulus frequency were being processed that distinguished the tonal from the atonal melody for both early and late implanted cats. It does not indicate that the late implanted cats perceived the bugle call in a similar way as the early implanted cats. The signals were different and obviously, the late implanted cats were able to detect something about the difference in order to select the correct stimulus. This also demonstrates the power of experience and training.

Endbulb synapses were examined by using serial section electron microscopy from cohorts of cats with normal hearing, congenital deafness, or congenital deafness with a cochlear implant. Synapse restoration was evident in endbulb synapses on the stimulated side of cats implanted at 3 months of age (Fig. 10). In these cats, PSDs exhibited an obvious return of the small dome-shaped PSDs (Ryugo et al. 2005). Quantitative morphometric analyses further revealed that mean PSD curvature, mitochondrial volume fraction and synaptic vesicle density returned to values typical of hearing cats (O'Neil et al. 2010). These results demonstrated that electrical stimulation with a cochlear implant restored the synaptic structure of auditory nerve synapses. The generality of this phenomenon was demonstrated by observing similar results in ototoxically deafened cats (Ryugo et al. 2010). The interpretation that activity *restored* synapse structure can be made because pathologic synapses are present at 3 months of age in untreated congenitally deaf cats (Baker et al. 2010); the introduction of activity therefore does not preserve normal structure but reverses pathologic structure.

Serial section reconstructions of the PSDs were performed to determine if electrical stimulation of the auditory nerve returned the hypertrophied PSDs to their normal size and distribution (Fig. 11). In normal hearing and young implanted deaf cats, PSDs were small and uniformly dispersed over the surface of the postsynaptic target. Approximately 20 % of the endbulb synapses of untreated deaf and hard-of-hearing cats also expressed a normal morphology. These same cats exhibited hypertrophied PSDs without any type of systematic curvature. We infer that the acoustic startle responses and learned approach to the food bowl following specific sound stimuli in the late implanted cats were mediated by the remaining normal synapses when appropriately stimulated. We further speculate that learning to approach a food reward is such a natural part of a cat's behavioral repertoire that minimal neural elements were required for its performance.

Concluding comments

The results presented in this review have been collected over many years and several conclusions can be made. First, congenital deafness causes a pathologic hypertrophy and flattening of auditory nerve synapses in the cochlear nucleus. Moreover, synaptic vesicle density in the vicinity of the PSD increases and intermembraneous channels that form "channels" between the apposed neural membranes are lost. Second, early electrical stimulation with a cochlear implant has a dramatic effect on these synapses in congenitally deaf cats. Activation of auditory nerve fibers by a cochlear implant at 3 months of age restores many key features of synaptic morphology, whereas activation at 6 months of age has modest effects. These data are consistent with the concept of a "critical" or sensitive period for plasticity in auditory and visual cortex (Cynader and Mitchell 1980; Kral et al. 2002). In addition, moderate restorative effects have been observed for auditory synapses in the ipsilateral medial superior olive (Tirko and Ryugo 2012) and contralateral cochlear nucleus (O'Neil et al. 2010) revealing activity-dependent plasticity that occurs in the central auditory system, which is mediated by both direct and indirect pathways. Because our cats received only 2–3 months of stimulation, further progression of behavioral and brain restoration might occur if they had more experience with the cochlear implant.

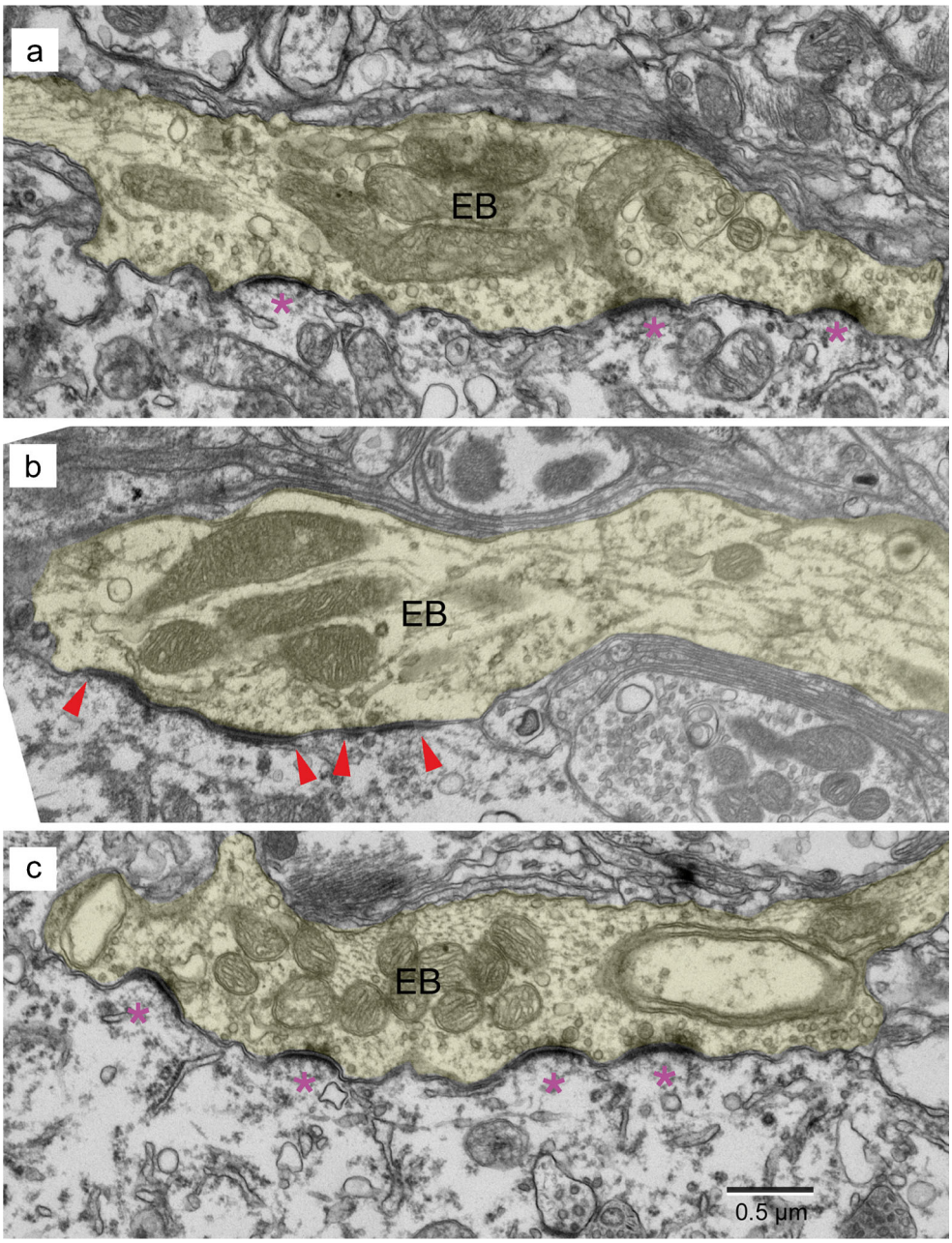

Fig. 10 Electron micrographs of auditory nerve synapses in the cochlear nucleus of the cat illustrating activity-associated plasticity. **a** Synapses (*pink stars*) in endbulbs (*pale yellow*) of normal hearing cats are characterized by their dome-shaped PSDs opposing an accumulation of synaptic vesicles in the presynaptic cytoplasm. **b** In congenitally deaf cats, synapses are hypertrophied and lose their characteristic curvature (*red arrowheads*). **c** Synapses (*pink stars*) in congenitally deaf cats are restored to the size and shape of normal hearing cats after electrical stimulation of their auditory nerves by way of cochlear implants

A third conclusion about hearing loss merits further discussion. Hearing loss is not simply the need for amplification and a return to sensation levels, because its consequences are not fully remedied by hearing aids and cochlear implants. Hearing loss results in (1) difficulty in understanding speech in noisy backgrounds, particularly when the noise is other speech sounds; (2) distortions in loudness perception; and (3) the frequent emergence of phantom sounds (tinnitus) in the form of buzzing, ringing, or hissing. These sequelae are undoubtedly created by alterations in the central nervous system. Evidence for such change emerges in terms of alterations in inhibitory circuits (Asako et al. 2005; Tirko and Ryugo 2012), a proliferation of excitatory terminals (Hildebrandt et al. 2011) and increased spontaneous activity in the inferior colliculus (Hancock et al. 2010; Robertson et al. 2012; Manzoor et al. 2013). Hyperactivity or tinnitus could be caused by diminished inhibitory terminals that "release" inhibition or the increased presence of excitatory terminals. The altered balance of excitation and inhibition could also perturb loudness perception and interfere with speech comprehension. These brain alterations represent a major challenge to the improvement of listening devices that aid hearing.

Activity and PSDs in spherical bushy cells In auditory nerve fibers of congenitally deaf cats and mice, the lack of

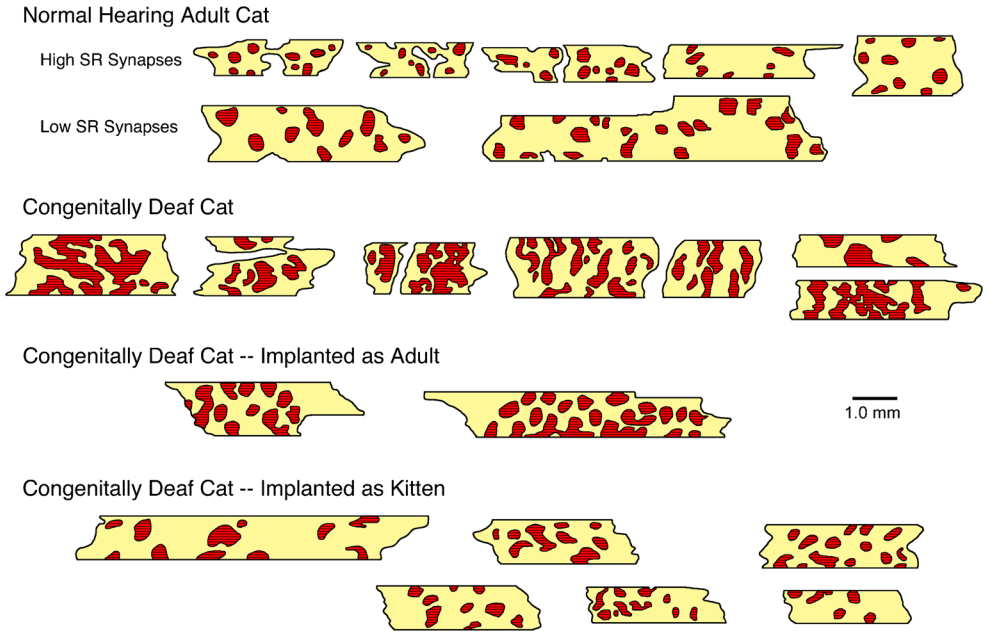

Fig. 11 Reconstructed endbulb synapses from serial electron micrographs of cats illustrate the influence of activity on synapse size and distribution. PSDs in normal hearing adult cats, when viewed as they reside in the postsynaptic membrane, are relatively small (< 0.5 μm in diameter) with smooth borders and round-to-oval in shape (*first panel*). Low activity fibers have larger PSDs compared with those of high activity fibers. In contrast, PSDs of congenitally deaf cats are generally hypertrophied with highly irregular shapes (*second panel*). Electrical stimulation via cochlear implantation re-introduces neural activity to the auditory nerve and restores PSDs to their normal size and shape when introduced to young kittens (*fourth panel*). Even when activity is introduced late (*third panel*), PSDs are reduced in size. Although not completely normal, the change suggests that neural activity, no matter when introduced, influences PSD size. Because cats were stimulated for a relatively short time (2–3 months), perhaps longer stimulation and training would also restore PSD morphology. The conclusion is that PSDs (indicators of synapses) are plastic and highly responsive to activity

spontaneous and sound-evoked activity was associated with an increase in PSD size (Ryugo et al. 1998; Lee et al. 2003). In cats with elevated thresholds (60–75 dB hearing loss), a situation in which neural activity is reduced, an increase occurred in the size of PSDs. Rats housed in a quiet room experienced normal spontaneous activity but minimal evoked activity and showed an increased PSD size (Rees et al. 1985). These findings suggest that PSD size in mammalian endbulbs is inversely proportional to the amount of spike activity in the parent fiber.

Synaptic strength and plasticity have been studied in other central synapses such as CA1 in the rat hippocampus in which the size of PSDs has been shown to increase in response to pharmacological blockade of spike activity (e.g., Murthy et al. 2001; Qin et al. 2001; Yasui et al. 2005). Quiescent synapses exhibit larger PSDs and increased numbers of synaptic vesicles and are accompanied by increases in synaptic strength. Consistent with this correlation, an increase in synaptic strength is seen in the anteroventral cochlear nucleus of the congenitally deaf mouse when compared to that of normal hearing mice (Oleskevich and Walmsley 2002; Oleskevich et al. 2004). This increase in synaptic strength might be related to an increase in the transmitter receptors that become distributed in the hypertrophied PSDs.

Trans-syna`tic effects on spherical bushy cells Spike activity and neural transmission in spiral ganglion cells and their fibers appear essential for the normal development of neurons of the cochlear nucleus (Rubel and Fritzsch 2002; West and Harrison 1973). Given that neuronal atrophy is a major consequence of sensory deprivation, we can reasonably predict that a recovery of neuronal activity should reverse the atrophy. Some studies involving ototoxic deafening of normal hearing cats have reported small but positive effects of electrical stimulation on cell size in the cochlear nucleus (Lustig et al. 1994; Leake et al. 1999; Stakhovskaya et al. 2008), whereas others using similar methods have shown no effects (Hultcrantz et al. 1991; Ni et al. 1993; Coco et al. 2007). Our data demonstrate that electrical stimulation of auditory nerve fibers via cochlear implants has no effect on the size of the spherical bushy cell neurons in this model of hereditary deafness. The differences in results from these research groups are not easily explained.

Critical period The observation that we can restore synaptic structure in congenitally deaf cats via electrical stimulation in kittens but not in young adult cats is consistent with observations with humans. It has long been known that young children receive significantly better benefits from cochlear implants when compared to those who receive implants as adolescents or adults (Waltzman et al. 1993; Tyler and

Summerfield 1996). The results from the human studies imply that deafness, when uncorrected, causes a fundamental change in the central auditory system such that, at some point, information from cochlear implants cannot be utilized. This phenomenon is consistent with the idea of a "critical period" in which some biological function is most severely affected during development. Critical periods have been shown in behavioral imprinting (Lorenz 1935), cortical barrel plasticity (Van der Loos and Woolsey 1973; Rice 1985), ocular dominance columns (LeVay et al. 1981; Raviola and Wiesel 1985), birdsong acquisition (Konishi 1985) and auditory cortex function (Klinke et al. 2001; Kral et al. 2002; Zhou et al. 2008). At least for the auditory system, we demonstrated a physical substrate that is found at the earliest stages of sound processing and that appears to be a prime candidate for determining, at least in part, the outcome of cochlear implants in humans.

Implications for cochlear implantation Several abnormalities have been demonstrated in the auditory system following deafness including reduced numbers of spiral ganglion neurons (Mair 1973; Leake and Hradek 1988; Heid et al. 1998; Ryugo et al. 1998), abnormal synaptic structure (Ryugo et al. 1997; Redd et al. 2000, 2002; Lee et al. 2003), physiological alterations of auditory nerve responses in the cochlear nucleus (Oleskevich and Walmsley 2002; Wang and Manis 2005) and ectopic projections in the ascending pathways (Nordeen et al. 1983; Moore and Kitzes 1985; Franklin et al. 2006). These changes undoubtedly affect synaptic transmission in which degraded responses in the inferior colliculus (Vollmer et al. 1999, 2005; Vale and Sanes 2002) and auditory cortex (Kral et al. 2006) have been observed. Nevertheless, the positive behavioral response of early and late implanted cats to their "dinner bell" is encouraging because it demonstrates "auditory learning" under pathologic conditions and leaves open the potential for late implanted children to gain benefit from cochlear implants.

Endbulbs have been implicated in mediating the precise temporal processing of sound (Molnar and Pfeiffer 1968) and are known to transmit from auditory nerve to postsynaptic cell with a high degree of fidelity (Babalian et al. 2003). The detection and identification of some sounds are not nearly as demanding as the processing of temporal cues needed for sound localization, pattern recognition, or speech comprehension. The introduction of synaptic jitter, delay, or failure by congenital deafness at the endbulb synapse could compromise such processing. The contribution of electrical activity to synaptic ultrastructure demonstrates that a cochlear implant can reverse some morphologic abnormalities in the auditory pathway when stimulation is started early. Moreover, effects are observed bilaterally at the earliest stage in the auditory pathway, demonstrating that 2–3 months of stimulation has a widespread trophic effect. We propose that systematic training by using interaural time disparities will improve sound localization among bilateral implant users.

Finally, we demonstrated that cats with only six electrodes are capable of recognizing and distinguishing one bugle call from many after several months of training. Moreover, frequency discrimination is involved because the atonal version of the call is also recognized as an unrewarded signal. Perhaps even more impressive is the observation that the late implanted cats, with structurally pathologic synapses, are also able to distinguish a rewarded signal from unrewarded ones. This latter feat, which is possibly mediated by a minority of normal synapses, nevertheless demonstrates that functionally significant behaviors can be achieved with training under less-than-ideal conditions. The take-away message is that the full potential of cochlear implants could be even greater with strategic training that exercises frequency and timing discrimination.

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