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Advances in the neurobiology of hearing disorders: Recent developments regarding the basis of tinnitus and hyperacusis

Marlies Knipper [a,*], Pim Van Dijk [b], Isidro Nunes [c], Lukas Rüttiger [a], Ulrike Zimmermann [a]

[a] University of Tübingen, Department of Otolaryngology, Head and Neck Surgery, Tübingen Hearing Research Centre (THRC), Molecular Physiology of Hearing, Tübingen, Germany
[b] University of Groningen, Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Groningen & Graduate School of Medical Sciences, Research School of Behavioural and Cognitive Neurosciences, Groningen, The Netherlands
[c] University of Porto, Faculty of Medicine, Department of Sensory Organs-Otorhinolaryngology, Porto, Portugal

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ABSTRACT

The prevalence of hearing problems in the Western world has, due to aging of the population, doubled over the past 30 years. Thereby, noise-induced hearing loss is an important factor that worsens over time in addition to age-related hearing loss. Hearing loss is usually measured as an elevation of a person's hearing thresholds, expressed in decibel (dB). However, recent animal studies have unraveled a type of permanent cochlear damage, without an elevation of hearing thresholds. This subtle damage is linked to a permanent and progressive degeneration of auditory fibers that occurs in association with damage of the inner hair cell synapse. Afferent neuronal degeneration has been suggested to be involved in hyperacusis (over sensitivity to sound) and tinnitus (a phantom sound percept). Hyperacusis and tinnitus are potentially devastating conditions that are still incurable. The main risk factors to develop tinnitus or hyperacusis are hearing loss, social stress and age. Both tinnitus and hyperacusis have been discussed in the context of a pathological increased response gain in subcortical brain regions as a reaction to deprivation of sensory input. Novel studies confirm the involvement of peripheral deafferentation for tinnitus and hyperacusis, but suggest that the disorder results from different brain responses to different degrees of deafferentation: while tinnitus may arise as a failure of the brain to adapt to deprived peripheral input, hyperacusis may result from an 'over-adaptive' increase in response gain. Moreover, moderate and high stress levels at the time of acoustic trauma have been suggested to play a pivotal role in the vulnerability of the cochlea to acoustic damage and therefore for the development of tinnitus and hyperacusis.

Contents

Abbreviations: ABR, auditory brainstem response; AC, auditory cortex; AN, auditory nerve; Arc/Arg3.1, activity-regulated cytoskeleton-associated protein/activity-regulated gene 3.1; BLA, basolateral amygdala; CN, cochlear nucleus; DCN, dorsal cochlear nucleus; DPOAE, distortion product otoacoustic emission; fMRI, functional magnetic resonance imaging; HPA axis, hypothalamic-pituitary-adrenal axis; IC, inferior colliculus; IHC, inner hair cell; MGB, medial geniculate body; MNTB, medial nucleus of the trapezoid body; NIHL, noise-induced hearing loss; OHC, outer hair cell; SOC, superior olivary complex; SR, spontaneous (discharge) rate; VCN, ventral cochlear nucleus.

* Corresponding author at: Universität Tübingen, HNO-Klinik, Elfriede-Aulhorn-Straße 5, 72076 Tübingen, Germany. Tel.: +49 7071 2988244; fax: +49 7071 294950.
E-mail address: marlies.knipper@uni-tuebingen.de (M. Knipper).

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1. Advances in the neurobiology of hearing disorders

1.1. Permanent elevation of hearing threshold after cochlear damage

Hearing impairment is a considerable disease burden. It has been estimated that adult-onset hearing impairment is the third leading cause of disability (WHO, 2008). Forty-two previous reports published between 1973 and 2010 in 29 countries have revealed increased hearing loss with age; developing countries report higher rates of moderate and moderately-severe hearing impairment due to higher rates of pre- and postnatal childhood infections such as rubella, measles and meningitis, and from the use of ototoxic drugs (Stevens et al., 2013). However, in industrialized countries, noise-induced hearing loss (NIHL) is a common cause of hearing impairments (Lu et al., 2005), with a prevalence that is second to presbycusis (Stanbury et al., 2008). Unfortunately, opportunities for sound overexposure abound and the sounds that damage hearing are not necessarily painful or even annoying. Thus, damage may occur in situations that are not easily recognized as potentially harmful. NIHL can also be caused by a one-time exposure to excessive sound pressure, such as explosions, gunfire, a large drum forcefully hit, or fire crackers. However, NIHL is more often caused by repeated exposures to medium- and high-intensity sounds (Flamme et al., 2009; Phillips and Mace, 2008). Exposure to high sound levels does not lead to NIHL in everyone. Apparently, the susceptibility to NIHL varies among individuals (Henderson et al., 1993). The variable susceptibility may have a genetic cause, as confirmed by several studies (Konings et al., 2007; Sliwinska-Kowalska et al., 2008; Sliwinska-Kowalska and Pawelczyk, 2013; Van Laer et al., 2006; Yang et al., 2006).

NIHL has been, in a previous view, typically defined by a permanent loss of hearing thresholds. Normal thresholds rely on the proper function of outer hair cells (OHCs) (Dallos and Harris, 1978). Per inner ear, there are approximately 11,000 OHCs, which are, in the human cochlea, typically arranged in 3 rows (Fig. 1, OHC). OHC function is to nonlinearly amplify basilar membrane vibration in response to soft sounds near the place of characteristic frequency within the cochlea (Ashmore, 2008). OHCs are therefore crucial for the high sensitivity of the hearing organ, its frequency selectivity, and understanding speech in noise (Ashmore, 2008; Dallos, 2008).

After mild acoustic overexposure, hearing function can recover within 2–3 weeks (Miller et al., 1963). This corresponds to a temporary threshold shift due to reversible damage to the mechanosensory hair bundles of hair cells (Fig. 1, stereocilia) (Liberman and Dodds, 1984a,b; Schneider et al., 2002). After intense or repeated acoustic overstimulation, however, hearing function stabilizes at an elevated value, leading to permanent threshold shift that mostly occurs due to destruction of OHCs (Spoendlin, 1985).

In the daily clinical routine, permanent hearing loss is typically detected through the increase of hearing thresholds as tested by tone-audiometry. More detailed clinical diagnostic testing may also include auditory brainstem response (ABR) testing or recording distortion product otoacoustic emissions (DPOAEs). ABR responses represent the summed activity of neurons in the ascending auditory pathways (see Section 1.3). ABRs can either be evoked by short click or noise sounds, or frequency-specific tone bursts. The specific function of intact OHCs can be measured by amplitudes of DPOAEs. DPOAEs are acoustic signals that arise from distortions in the OHCs' mechanoelectrical response to two continuous tones. These distortion products, which are at frequencies not present in the input stimulus, are generated by the OHCs' biological motors and can be detected with a microphone in the ear canal. DPOAEs responses thus reflect the electromotile properties of OHCs (Fitzgerald et al., 1993; Huang et al., 2005). DPOAE responses can be intact while ABRs dramatically decline, due to dysfunction of inner hair cell (IHC) synapses in, for example, DFNB9 patients during auditory neuropathy (Denoyelle and Petit, 2002; Smith et al., 1993). DFNB9 patients are suffering from non-syndromic autosomal recessive deafness due to dysfunction of otoferlin, a multi-C2 domain protein that acts as a calcium sensor in cochlear inner hair cells (Roux et al., 2006). Also, when DPOAEs are maximally reduced, ABRs nevertheless exist to a distinct degree, as OHC loss presumably contributes a maximum of ~40 dB to total threshold loss.

We can conclude that loss of hearing thresholds after noise exposure is mostly linked to OHC loss, which specifically can be measured by DPOAEs. Through DPOAE and ABR measurements, in combination, a differential damage of OHCs and IHCs can be detected.

1.2. Permanent cochlear damage without elevation of hearing threshold

Regarding more recent findings on NIHL, it is most important to remember that OHC loss can be accompanied by IHC (Fig. 1, IHC) damage (Liberman and Dodds, 1984a,b).

The IHCs are the primary sensory hair cells of the cochlea that transmit sound information over an intensity range spanning 12 orders of magnitude (120 dB) and 3 orders of magnitude of frequency (20 Hz to 20 kHz) (Robles and Ruggero, 2001). This powerful capacity of IHC synapses is achieved through their numerous specialized afferent contacts. Each IHC is innervated by 8 (human) or up to 20 (rodents) (Glowatzki and Fuchs, 2002) unbranched spiral ganglion neurons, which represent about 90–95% of all afferent fibers (AF) in the auditory nerve (AN) (Fig. 1, AN; Figs. 1 and 2, AF type I). Each IHC contains electron-dense presynaptic subcellular structures, so-called ribbons (Figs. 1 and 2, red) that tether >100 synaptic vesicles (Glowatzki and Fuchs, 2002). This specialized presynaptic machinery thereby maintains a large releasable pool of neurotransmitter, allowing afferent

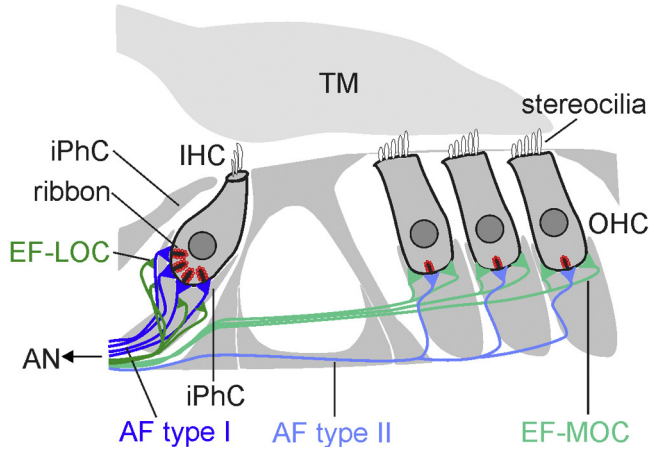

Fig. 1. Schematic illustration of the adult organ of Corti. The mammalian cochlea in the inner ear is a snail shell-shaped, bony duct that contains the organ of Corti, the sensory organ of hearing. The organ of Corti contains two types of sensory cells, the inner (IHC) and outer hair cells (OHC). Along the organ of Corti, there is one row of IHCs and three rows of OHCs. The human cochlea has about 3500 IHCs and 12,000 OHCs. IHCs and OHCs are characterized by a cuticular plate with hair bundles at their upper end, the stereocilia. The tectorial membrane is a semi-gelatinous structure overlying the hair cells. The lower portion of a hair cell is innervated: the nerve fibers of IHCs send information to the brain, whereas the nerves of OHCs mainly receive information from the brain. IHCs are, therefore, the true sensory cells of hearing. OHCs are characterized by their electromotile properties; they are responsible for the amplification of the acoustic signal, which in turn activates IHCs. The IHCs transmit electrical signals in a frequency-specific manner to higher auditory brain areas. The auditory nerve is a bundle of approximately 30,000 nerve fibers that carries hearing information between the cochlea and the brain. There are two types of afferent nerve fibers (blue): type I (AF type I) and type II (AF-type II). 90–95% are type I fibers projecting to IHCs; the residual type II afferent fibers project to OHCs only. In addition to the afferent innervation, there is also an efferent innervation of the hair cells. Originally efferent fibers (green) project from the region of the superior olive in the brainstem and transmit information from higher auditory brain areas to the hair cells. Below the IHCs, efferent fibers from the LSO (EF-LOC) mainly make axodendritic contact with afferent type I fibers, whereas OHCs are directly contacted by efferent fibers from the MSO (EF-MOC), which have modulating effect on sound amplification, AF, afferent fiber; AN, auditory nerve; EF, efferent fiber; IHC, inner hair cell; iPhC, inner phalangeal cells; LOC, lateral olivary complex; LSO; lateral superior olive; MOC, medial olivary complex; MSO, medial superior olive; OHC, outer hair cell; TM, tectorial membrane. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

auditory neurons to code the temporal characteristics of sound with high reliability and temporal precision (Buran et al., 2010). IHC ribbons also have been shown to cluster $Ca_V1.3$ calcium channels (Fig. 2, $Ca_V1.3$) and stabilize contacts with afferent neurons (Sheets et al., 2011), a finding that may be important in the context of IHC ribbon loss after NIHL (see Section 2.3).

The afferent fibers that innervate IHCs are classified based on their response threshold and spontaneous discharge rate (or spontaneous rate, SR). Approximately 17,000 high-SR fibers (~60% of the total number) have an SR above 18 action potentials (APs) per second (Fig. 2, low-threshold, high-SR fibers). These neurons are sensitive to low sound pressure levels, with thresholds between 0 and 20 dB SPL. In contrast, approximately 4500 low-SR and medium-SR fibers (~40%) with an SR between <0.5 and 18 AP/s have elevated thresholds, between 20 and 40 dB (Fig. 2, high-threshold, low-, medium-SR fibers), (Heinz and Young, 2004; Liberman, 1978; Merchan-Perez and Liberman, 1996; Müller and Robertson, 1991; Sachs and Abbas, 1974; Schroeder et al., 2001; Spoendlin and Schrott, 1989; Yates, 1991).

It is important to consider that not only IHC synapses but also OHC synapses comprise functional afferent neuronal projections to the brain, exhibiting Ca^{2+} currents (Knirsch et al., 2007) as well as ribbon-like presynaptic structures (Weisz et al., 2012). Electron microscopy has shown relatively few vesicles tethered to ribbons

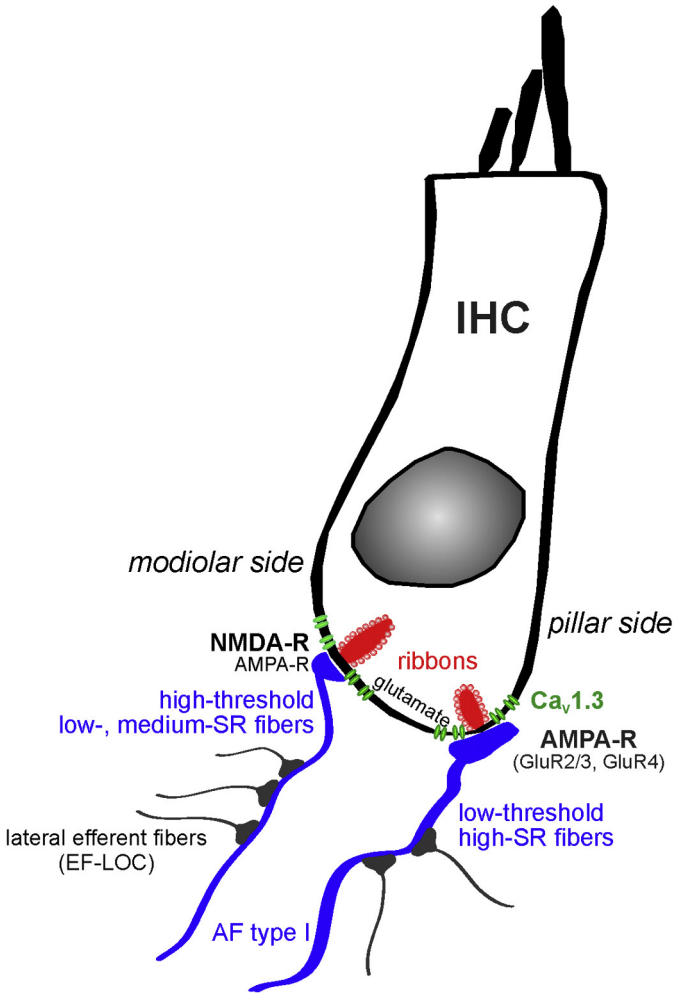

Fig. 2. Predicted subcellular positions of high- and low-SR fibers at the inner hair cell (IHC). IHC ribbon synapses have synaptic active zones that are characterized by a presynaptic electron-dense subcellular structure known as synaptic ribbon (red), to which synaptic vesicles are tethered. Ribbon synapses are glutamatergic, wherein glutamate is released at high and sustained rates. Glutamate released by the IHC synapses in response to the receptor potential drives the firing pattern of the primary auditory neurons upon binding to the AMPA- or NMDA receptors of their afferent boutons. Afferent auditory nerve fibers of IHCs are classified according to their spontaneous action potential discharge rate (SR). High-threshold, low- and medium-SR fibers are presumably preferentially located at the modiolar side of the IHC, where larger ribbons are associated with smaller patches of NMDA-R and AMPA-R. Low-threshold, high-SR fibers are presumably preferentially located at the pillar side of the IHC, where smaller ribbons oppose larger AMPA-R patches. Also characteristic of ribbon synapses, $Ca_V1.3$ channels are clustered near synaptic ribbons, and thereby stabilize the contact with afferent neurons. Modified after Liberman et al., 2011. AF, afferent fiber; AMPA-R, AMPA receptor; EF, efferent fiber; IHC, inner hair cell; LOC, lateral olivary complex; NMDA-R, NMDA receptor; SR, spontaneous (discharge) rate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

in equivalent OHCs of the prehearing rat cochlea (Weisz et al., 2012). Each afferent neuron connects to an estimated seven presynaptic OHCs. It has been suggested that if these reach the action potential threshold at all, the threshold is only reached if the entire pool of presynaptic OHCs are maximally depolarized, such as during the loudest sounds (Weisz et al., 2012).

IHC damage would doubtless dramatically compromise cochlear transduction and lower the firing rates of auditory nerve fibers (Fig. 2, blue) (Liberman and Kiang, 1984; Sewell, 1984). The ~3500 IHCs (Figs. 1 and 2, IHC) in the cochlea rarely die from NIHL, however. Instead, the innervated dendrites of the auditory nerve fibers undergo neurodegeneration (Kujawa and Liberman, 2009; Lin et al., 2011). This process has been revealed to be tightly

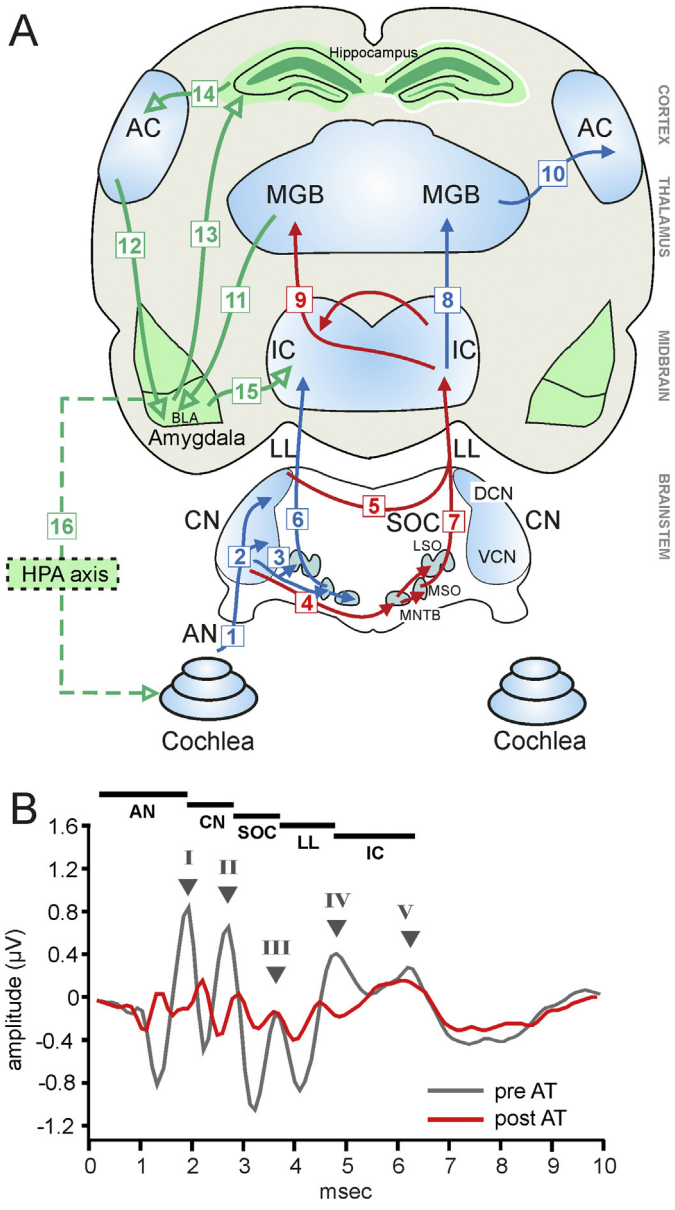

Fig. 3. Central auditory circuits and auditory brainstem responses. (A) Sound is transmitted from the cochlea by the auditory nerve (AN, [1]) to the cochlear nucleus (CN, [2]). In the brainstem, the AN bifurcates to the dorsal (DCN) and ventral (VCN) part of the CN. The processed information is forwarded to the ipsilateral (blue, [3]) and contralateral (red, [4]) lateral superior olive (LSO) and medial superior olive (MSO), and to the medial nucleus of the trapezoid body (MNTB), which are all part of the superior olivary complex (SOC). The inferior colliculus (IC) in the midbrain gets contralateral (red, [5]) input from the DCN as well as ipsilateral (blue, [6]) and contralateral (red, [7]) input from the SOC. Fibers from the IC project to the ipsilateral (blue, [8]) and contralateral (red, [9]) medial geniculate body (MGB), which is located in the thalamus. From here, signals are then transmitted to the auditory cortex (AC) (blue, [10]). Additionally, there are also auditory-limbic interactions (drawn in green). The basolateral amygdala (BLA) receives direct neural inputs from the auditory thalamus (MGB, green, [11]) and the (AC, [12]). The BLA, in turn, contacts the hippocampus [13], which has direct contact with the AC [14]. The BLA also projects to the IC [15], thereby generating an amygdalar-auditory feedback loop. The BLA also activates (e.g. due to noise-induced stress) the hypothalamic-pituitary-adrenal axis (HPA axis, [16]), thereby influencing the level of blood cortisol (human) or corticosterone (rodents), as well as the cochlea (green dashed lines). (B) The auditory signal along the auditory pathway can be measured by ABRs providing information regarding auditory function and hearing sensitivity. The normal ABR consists of five prominent waves that occur during the first 10 ms after presentation of a transient sound. These ABR waves are labeled by Roman numerals (I–V). The different peaks of the waves can be assigned to different parts of the ascending auditory pathway. Wave I is generated exclusively by the auditory nerve, whereas waves II, III, IV, and V have contributions from more than one anatomical structure of the ascending auditory pathways. Wave II is mainly generated by the CN, wave III by the SOC, wave IV by the lateral lemniscus (LL), and wave V by the lateral lemniscus and its termination in the IC. After an acoustic trauma (post AT, red) all amplitudes of ABR waves are reduced compared with untraumatized control animals (pre AT, gray). ABR, auditory brainstem response; AC, auditory cortex; AN, auditory nerve; BLA, basolateral amygdala; CN, cochlear nucleus; DCN, dorsal part of the CN; HPA axis, hypothalamic-pituitary-adrenal axis; IC, inferior colliculus; LL, lateral lemniscus; LSO; lateral superior olive; MGB, medial geniculate body; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; SOC, superior olivary complex; VCN, ventral part of the CN.

correlated with an altered number of transmitter release sites in IHC nerve terminals (Fig. 2, blue) (Jaumann et al., 2012; Kujawa and Liberman, 2009; Lin et al., 2011; Rüttiger et al., 2013; Zuccotti et al., 2012). So far, a loss of active release sites at the level of the OHCs has not been described.

Secondary to degeneration of the afferent dendrites of auditory fibers, spiral ganglion cells undergo neurodegeneration as shown after glutamate-induced excitotoxic trauma in vitro (Wang and Green, 2011), after intense tone exposure (Godfrey et al., 2012), reviewed in (Puel et al., 2002), or after long-term mild trauma (Lin et al., 2011). Indeed, the long-standing dogma that cochlear nerve degeneration is a consequence of IHC death after acoustic trauma was only recently overturned, as degeneration can occur when IHCs are present. It has been proposed that the glial supporting cells that surround IHCs, the inner phalangeal cells (Fig. 1, iPhC), are crucial for auditory nerve survival (Zilberstein et al., 2012). Consistent with this, after acoustic trauma, these phalangeal cells also are important to stabilize exocytosis and the number of transmitter release sites in IHCs in the intact cochlea, as well as to destabilize stable pre-and postsynaptic IHC/afferent contacts (Zuccotti et al., 2012).

In conclusion, the role of the OHC ribbon synapses and their afferent fibers is not yet understood. A complete set of functional, intact IHC ribbon synapses and their proper contacts to auditory fibers are crucial elements to achieve the full dynamic loudness range, as well as high precision of temporal sound information. Evidence from recent animal experiments shows that extensive and even moderate noise-induced cochlear damage can cause persistent and progressive deafferentation of auditory nerves, a deafferentation process that is associated with a deterioration of active transmitter release sites from the IHC synapse. We explain in the next chapter the consequences of these subtle changes in the cochlea for brain responses, and ways to detect these changes with non-invasive methods in humans and animals.

1.3. Altered central brain responses to cochlear damage

In the central auditory system, activity spreads directly from the auditory nerve (AN) (Fig. 3A, [1]) via the cochlear nucleus (CN) (Fig. 3A, [2]) to higher brain regions. The first ABR wave (Fig. 3B, ABR wave I) represents the summed activity of the auditory nerve, whereas later ABR waves arise from synchronous neural activity in the auditory brainstem (Melcher and Kiang, 1996). In the brainstem, the auditory nerve bifurcates to the dorsal and ventral part of the cochlear nucleus. Within the dorsal cochlear nucleus (DCN) (Fig. 3A), sound-induced activity patterns spread via projection neurons (Kaltenbach, 2007) and T-stellate neurons (Brunso-Bechtold et al., 1981) to the contralateral side (Fig. 3A, [5], red) toward the inferior colliculus (IC) (Fig. 3A) in the midbrain. Notably, when hearing function is measured through ABRs, the spreading, sound-induced activity through the ventral cochlear nucleus (VCN) (Fig. 3A) to ascending nuclei is measured (Melcher and Kiang, 1996). From VCN neurons, sound-induced activity (Fig. 3B, ABR wave II) spreads either via ipsilateral (Fig. 3A, [6], blue) or contralateral (Fig. 3A, [7], red) projections, crossing either the medial nucleus of the trapezoid body (MNTB) (Fig. 3A) as part of the superior olivary complex (SOC) (Fig. 3A) or the lateral

lemniscus (LL) (Fig. 3A and B, ABR wave III) (Coleman and Clerici, 1987) toward the IC (Fig. 3B, ABR wave IV). Fibers from the IC project to the ipsi- (Fig. 3A, [8], blue) and contralateral (Fig. 3A, [9], red) medial geniculate body (MGB) in the thalamus. From the MGB, signals are transmitted (Fig. 3A, [10], blue) to the auditory cortex (AC) (reviewed for animals in Malmierca and Merchan, 2004) For differences in ABR wave numbering in humans, see (Hashimoto et al., 1981; Kaga and Tanaka, 1980).

Sound processing can also activate limbic structures (Fig. 3A, drawn in green). The amygdala and the hippocampus, two major regions of the limbic system, receive direct and indirect neural input from the central auditory system. The basolateral amygdala (BLA) receives direct neural inputs from the auditory thalamus (Fig. 3A, MGB, [11], green) and the auditory cortex (Fig. 3A, AC, [12]). The basolateral amygdala, in turn, contacts the hippocampus (Fig. 3A, [13]), which has direct contact with the auditory cortex (Fig. 3A, [14]). Noise-induced stress can activate the basolateral amygdala through the hypothalamic-pituitary-adrenal axis (HPA axis) (Fig. 3A, [16]). Thus, acoustic trauma can damage the cochlea and affect the basolateral amygdala and the hippocampus. (Kraus et al., 2010).

The central auditory system compensates for diminished input by upregulating its responsiveness in central circuitries (Salvi et al., 2000). Central compensation that follows reduced auditory nerve activity may occur first at the level of the auditory brainstem, from where altered activity patterns then spread to ascending auditory nuclei (Manzoor et al., 2013; Mulders and Robertson, 2013). In humans (Gu et al., 2012) and animals (Rüttiger et al., 2013; Singer et al., 2013), auditory nerve and brainstem function in response to sound, assessed by ABRs, have been used to analyze compensating central activity following cochlear damage. This is based on the observation that IHC ribbons (see Section 1.2) define the reliability and precision of auditory nerves discharge rates (Buran et al., 2010), and discharge rates and number of synchronously firing auditory fibers together define the ABR wave size changes (Johnson and Kiang, 1976). Thus, animals with a reduction in IHC ribbon number after acoustic trauma also show a reduction of ABR wave I (Buran et al., 2010) (Fig. 3B, post AT, red). Depending on the degree of deafferentation, a change of sound-induced activity can differentially spread within the ascending pathway (Buran et al., 2010; Kammerer et al., 2012; Lin et al., 2011; Rüttiger et al., 2013; Singer et al., 2013; Zuccotti et al., 2012).

Also, physiological findings in humans and neuroanatomical data in animals have suggested that the ratio of wave I (auditory nerve) to wave V (corresponding to wave IV in animals) reflects the degree of compensating hyperactivity generated in the VCN, which, via spherical bushy cells in particular (Gu et al., 2012; Schaette and McAlpine, 2011), spreads toward the inferior colliculus. As calculated in a computational model, this process of enhanced central responsiveness after auditory trauma is assumed to critically depend on the response characteristics of maintained afferent fibers (Schaette and McAlpine, 2011). Detailed wave analysis of ABRs in humans is not yet routinely used in clinical audiometry. Thus, the elucidation of deafferentation of cochlear hair cells is still lacking as a diagnostic tool for patients with hearing disorders.

In conclusion, the fine-structure analysis of individual ABR waves may reveal the first suitable approach to detect presumptive differences in central brain responses linked to different degrees of peripheral deafferentation. This has two crucial implications for future clinical studies or research of hearing disorders in humans and animals. First, improved ABR wave analysis may allow the diagnosis of tinnitus, hyperacusis, and troubles communicating in a noisy environment that may be linked to neurodegeneration. Second, animal screening for hereditary or acquired hearing disorders that currently uses only threshold as a tool to define hearing loss may overlook individual neural disorders. Routine assessment of ABR wave analysis could sub-classify the sensory/neural deficits in more detail.

2. Tinnitus and hyperacusis

2.1. Epidemiology of tinnitus and hyperacusis

Tinnitus is a disorder of perception of phantom sound that is also known as ringing in the ear or head. Tinnitus affects 10–20% of the general population (Galazyuk et al., 2012; Shargorodsky et al., 2010); reviewed in (Lockwood et al., 2002). According to the American Tinnitus Association, an estimated 50 million people in the United States have chronic tinnitus, persisting for longer than six months (Shargorodsky et al., 2010). For 12 million individuals, it is severe enough to interfere with daily activities. Tinnitus can occur in children (Shetye and Kennedy, 2010) and prevalence increases with age (Adams et al., 1999; Ahmad and Seidman, 2004).

Hearing loss and stress (emotional as well as psychosocial) are important risk factors for tinnitus (Hébert et al., 2012; Jastreboff, 2007; Langguth et al., 2009; Leaver et al., 2011; Lockwood et al., 2002; Meltser et al., 2009; Møller, 2003; Puel and Guitton, 2007; Zenner et al., 2006), although tinnitus can occur independently from broad increase of hearing thresholds (Geven et al., 2011; Langers et al., 2012; Lockwood et al., 2002). Since the prevalence of hearing loss increases with age, the prevalence of tinnitus also increases with age, peaking between 60 and 69 years of age (Shargorodsky et al., 2010). The prevalence of frequent tinnitus is highest among older adults, more common in men than in women, more likely in former smokers, and in adults with hypertension, hearing impairment, loud noise exposure, or generalized anxiety disorder (Shargorodsky et al., 2010). Loud noises, such as those from heavy equipment, chain saws and firearms, are common sources of noise-related hearing loss, as are portable music players and earphones (Breinbauer et al., 2012; Gilles et al., 2012; Harrison, 2012), and increase the risk of tinnitus. Tinnitus caused by short-term noise exposure, such as attending a loud concert, usually goes away. In contrast, long-term exposure to loud sound can cause permanent damage and thereby increase the risk of developing tinnitus.

Hyperacusis is a disorder of loudness perception, in which sound intensities that are considered comfortable by most people are perceived unbearably loud (Baguley, 2003). Hyperacusis does not imply a higher than normal threshold sensitivity to sound, nor loudness recruitment (the rapid growth in perceived loudness with increasing sound intensity that occurs with sensorineural hearing loss) (Tyler and Conrad-Armes, 1983). Instead, in hyperacusis, sounds are not simply a bit loud, but truly unbearable. Hyperacusis can occur without a loss of hearing thresholds (Gu et al., 2010). Statistics on hyperacusis are scarce, and although it is often coincident with tinnitus, limited evidence has supported the co-occurrence of the two conditions (Andersson et al., 2002; Gu et al., 2010; Nelson and Chen, 2004). With an approximate prevalence of about 10–15% of the population (Gilles et al., 2012), the prevalence of hyperacusis is comparable to tinnitus (Shargorodsky et al., 2010). For tinnitus and hyperacusis, hearing loss, however, is a major risk factor. As the incidence of hearing loss will increase with the aging of the population, also the incidence of tinnitus and hyperacusis may increase.

In conclusion, *hyperacusis* and *tinnitus* both often occur in conjunction with a loss of threshold hearing sensitivity (Dauman and Bouscau-Faure, 2005), but neither hearing threshold loss nor OHC loss is essential to develop either condition. This suggests that their etiologies may be related. However, evidence suggests that there are also important differences between the mechanisms involved in tinnitus and hyperacusis (see later in this review).

2.2. Research on tinnitus or hyperacusis in animals

Research for investigating neural and biological mechanisms of tinnitus or hyperacusis in humans is limited for obvious ethical reasons. Therefore, animal models are needed to study both these conditions' pathologies and therapies. In both humans and animals, determining the presence of tinnitus and hyperacusis is a challenge. Humans can, of course, indicate the presence of tinnitus, but it is not possible to confirm this with an objective measurement. Animals are unable to report the presence of tinnitus, and hence behavioral models have been developed for this purpose. Invariably, these models depend on an animal's learned or reflex-like behavior in the presence of tinnitus. Various animal models have been developed to detect tinnitus which include either a conditioned behavioral response to silence (Bauer and Brozoski, 2001; Bauer et al., 1999; Guitton et al., 2003; Heffner and Harrington, 2002; Heffner and Koay, 2005; Jastreboff and Brennan, 1994; Jastreboff et al., 1988; Middleton et al., 2011; Rüttiger et al., 2003; Yang et al., 2011) or the failure of a pre-pulse gap to suppress a sound-pulse-evoked startle reflex (Berger et al., 2013; Dehmel et al., 2012a; Engineer et al., 2011; Kraus et al., 2010; Lobarinas et al., 2013; Middleton et al., 2011; Nowotny et al., 2011; Turner et al., 2006; Turner and Parrish, 2008); reviewed in (Turner, 2007). Gaps in noise bands serves as pre-pulses to suppress a sound pulse-evoked startle reflex, assuming that ongoing tinnitus masks the gap and results in impaired gap detection. However, the startle reflex is mediated by subcortical areas only. Therefore, it is unclear whether the conditions that lead to an abnormal startle response also correspond to abnormal activity in the auditory cortex, which, in humans, presumably underlies tinnitus (Eggermont, 2013). However, a study directly comparing the outcome of the startle reflex method and a conditioned response method has shown similar results (Turner et al., 2006), despite the lack of involvement of cortical circuits in the startle response.

Both approaches are assumed to generally reflect the putative electrophysiological basis of tinnitus. Recent findings have emphasized, however, that it is necessary to move beyond the detection of startle responses, because this startle response may be linked to hyperacusis, in addition to tinnitus (Berger et al., 2013; Eggermont, 2013; Heffner and Heffner, 2012; Lobarinas et al., 2013). For example, the pre-pulse inhibition-gap detection relies on the percept of tinnitus to reduce the typical inhibition of an animal's startle response that is caused by a short sound gap (Turner et al., 2006). With acoustic trauma, the spontaneous firing rate within the ascending auditory pathway can be increased (this effect correlates with hyperacusis, for example; see Section 3.2). This increase could also lead to inhibition of the startle response, thereby generating a false-positive result (Eggermont, 2013). Response inhibition could occur by the activation of an inhibitory cholinergic pathway from the pedunculopontine tegmental nucleus or by the activation of the amygdala via the MGB in the thalamus (Eggermont, 2013). False-positive results arising from the methods to detect tinnitus may be one explanation for the differences in the rates of animals that appear to have developed tinnitus after noise trauma (ranging from 30% to 80%) (Dehmel et al., 2012b; Engineer et al., 2011; Middleton et al., 2011; Rüttiger et al., 2013; Singer et al., 2013).

Animal models that explicitly investigate hyperacusis are still rare. As hyperacusis is defined as altered sensitivity to sound, behavioral correlates of abnormally rapid growth of loudness and impaired sound tolerance are currently used in humans (Penner, 1986a,b; Sun et al., 2011). For future hyperacusis animal models, a method of choice would be measurement of altered amplitudes of ABR waves with increasing sound stimulation after acoustic trauma, in combination with behavioral studies. Alternatively, a defined paradigm of acoustic trauma-induced altered gap-detection for identifying hyperacusis may be used in animals in future studies (Turner and Parrish, 2008).

In conclusion, research on tinnitus animal models is an active field of investigation with an expanding number of models. Animal behavioral models to detect tinnitus and hyperacusis are still urgently needed, along with studies of the molecular basis and the biological mechanisms involved. These models could be a tool for initial preclinical studies in a search for therapeutic intervention for both disorders.

2.3. Deafferentation of auditory nerve fibers in the context of tinnitus and hyperacusis

Tinnitus is primarily linked to damage in the periphery of the auditory system (Axelsson and Ringdahl, 1989; Demeester et al., 2007; Sirimanna et al., 1996), but as mentioned above, loss of sensitivity at threshold is not a necessary condition for tinnitus. This has been confirmed in animal models (Bauer et al., 2007; Geven et al., 2011; Knipper et al., 2012; Roberts et al., 2010; Rüttiger et al., 2013; Singer et al., 2013) and human studies (Geven et al., 2011; Kim et al., 2011; Langers et al., 2012; Lockwood et al., 2002; Roberts et al., 2010; Saunders, 2007; Shiomi et al., 1997; Tan et al., 2013; Weisz et al., 2006). The same is true for hyperacusis: people with clinically normal auditory thresholds can have hyperacusis (Gu et al., 2010; Zeng, 2013).

A link between deafferentation of IHCs and tinnitus has been suggested by various studies in humans and animals (Bauer et al., 2007; Rüttiger et al., 2013; Singer et al., 2013; Tan et al., 2013; Weisz et al., 2006). In recent animal studies, a higher degree of deafferentation and IHC ribbon loss in high-frequency regions of the cochlea has been shown in animals with behaviorally-tested tinnitus, while a lower IHC ribbon loss was found in equally exposed animals without tinnitus (Rüttiger et al., 2013). So far, ribbon loss of OHCs after noise exposure has not been investigated. Noise-induced OHC ribbon loss and the neurodegeneration of afferent type II fibers, contacting OHCs, have previously been suggested as a cause of tinnitus (Jastreboff, 1995). Accordingly, we hypothesize an increased noise vulnerability through loss of the protective function of efferent fibers, whose function has been suggested to depend on afferent type II fibers (Maison et al., 2013).

The more severe loss of ribbons in tinnitus animals (Rüttiger et al., 2013; Singer et al., 2013) has also been linked to an abnormal large ribbon size (Rüttiger et al., 2013) and a reduction of the basolateral length of IHCs in two different noise exposure paradigms (Fig. 4). Animals with tinnitus were either exposed to sound of 1 h, 10 kHz, 120 dB SPL and were analyzed 6 days after exposure (Fig. 4A and C) or were exposed for 1.5 h, 10 kHz, 120 dB SPL, and analyzed 30 days after exposure (Fig. 4B and D). Both groups exhibited reduced length of the basolateral pole of IHCs in high-frequency cochlear turns (Rüttiger et al., 2013). A reduced number of ribbons, reduction in basolateral length of IHCs, and abnormally large ribbons resemble the IHC phenotype of mutant mice with disturbed endocytosis and replenishment of vesicles after myosin VI or otoferlin deletion (Heidrych et al., 2009; Johnson et al., 2010). The metabolically demanding maintenance of proper IHC surface area through appropriate exocytosis/endocytosis cycles therefore may be considered in future studies as a risk factor for ribbon loss and tinnitus.

For now, described in animals only, deafferentation can occur after auditory trauma but also after various other influences that contribute to causing tinnitus, such as ototoxic drugs (Wang et al., 2002). It may be challenging in future studies to consider that several types of tinnitus, differing in etiology and development (Mazurek et al., 2008) are collectively caused by peripheral deafferentation. Beside noise, hearing impairments as a result of hypoxia, ischemia (Mazurek et al., 2006), carotic dissections, and

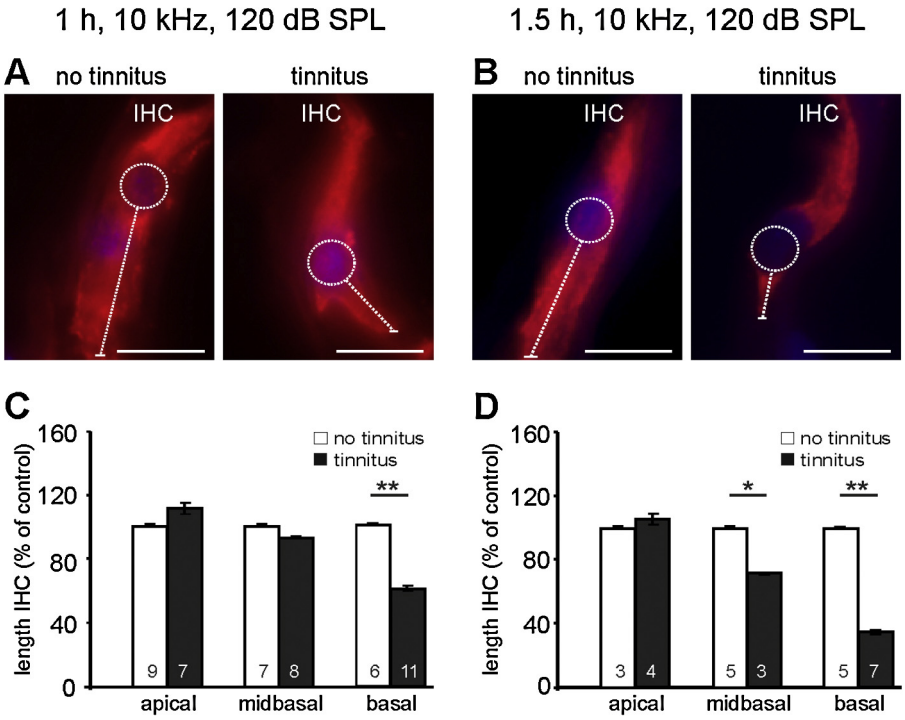

Fig. 4. Comparison of the basolateral pole length of inner hair cells (IHCs) from rats with or without tinnitus in indicated cochlear turns. Animals were exposed to sound of either 1 h, 10 kHz, 120 dB SPL and analyzed 6 days after noise exposure (A, C) or 1.5 h, 10 kHz, 120 dB SPL and analyzed 30 days after noise exposure (B, D). Note the significant reduction of the basolateral pole length in tinnitus animals in high-frequency cochlear turns (two-way ANOVA $p < 0.001$; post-test two-sided Student's t-test, $p < 0.02$). IHCs are immunostained with anti-otoferlin antibody, red. Nuclei are stained in blue with DAPI and delineated by dotted circles. Scale bars, 20 μm. The number in the bars represents the IHCs analyzed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

vascular diseases (Shulman and Strashun, 2009) should be tested in future studies for increasing the risk of neuronal deafferentation, tinnitus, or hyperacusis. This may provide a plausible first explanation of enhanced baseline tinnitus rates in patients with chemotherapy with cisplatin and carboplatin (Dille et al., 2010).

We conclude that in animal studies, deafferentation is linked to tinnitus, but may also occur without evidence of tinnitus. A larger extent of deafferentation appears to be correlated with tinnitus. A lesser extent of deafferentation may not lead to tinnitus, but rather be linked to hyperacusis. More evidence for this hypothesis that deafferentation primarily causes tinnitus and hyperacusis in humans, has to be accumulated by detailed audiometric assessments.

3. Differences in subcortical activity patterns between hyperacusis and tinnitus

3.1. Does deafferentation of auditory fibers influence central compensating responses?

Following acoustic trauma, the response rates at the peripheral auditory nerve are reduced (Liberman and Kiang, 1978). The central responses to auditory deprivation are still controversially discussed. As stated above, the normal spontaneous discharge rate of auditory fibers diverges in those with high firing rates (low-threshold, high-SR fibers) and those with low firing rates (high-threshold, low-SR fibers) (Fig. 2). In various studies, the low-SR, high-threshold fibers (~40%) have been suggested to exhibit particularly high vulnerability for noise damage (Furman et al., 2013; Heinz et al., 2005; Heinz and Young, 2004; Ruel et al., 2008).

In a computational model, a favored loss of low-SR, high-threshold fibers has been predicted to preferably correlate with a pathological increase in central gain and tinnitus (Schaette and McAlpine, 2011), as otherwise the generation of a sufficient increase in discharge rate to compensate for deprived auditory input may be hampered (Schaette and Kempter, 2009, 2012). The earliest point at which such a compensation of reduced mean neuronal activity at the level of the auditory nerve can occur is the target cells of auditory nerves in the brainstem (Brigande and Heller, 2009). Indeed, spontaneous hyperactivity occurs after auditory trauma in the target neurons, which are the projection neurons (fusiform and giant cells) in the DCN (Fig. 3A, DCN) (Brigande and Heller, 2009), and the spherical bushy cells in the VCN (Fig. 3A, VCN) (Cai et al., 2009; Mulders and Robertson, 2011; Vogler et al., 2011). Even modest auditory deprivation can induce an increase in hyperactivity in DCN projection neurons after auditory trauma, making these cells most suitable for feed-forward responses (Kaltenbach, 2007). These rapidly arising responses of DCN neurons have also been suggested to occur only in the fusiform cells that receive convergent somatosensory and auditory input (Shore, 2011; Shore et al., 2008).

If the loss of low-SR, high-threshold fibers in the auditory nerve causes tinnitus-related hyperactivity in the cochlear nucleus, what would be the role of a loss of the high-SR, low-threshold fibers in the generation of tinnitus? Recent animal studies have suggested that a critical loss of high-SR, low-threshold fibers may correlate with tinnitus, based on a high degree of IHC ribbon loss (Rüttiger et al., 2013; Singer et al., 2013). A loss of high-SR fibers has also been observed in other tinnitus studies in animals (Bauer et al., 2007). As a consequence of the more severe damage of the IHC synapse in animals with tinnitus, amplitudes of central ABR waves did not restore and molecular markers for plasticity of synaptic strength were not mobilized (see Section 4.2) (Rüttiger et al., 2013; Singer et al., 2013).

Interesting in this context is that only recently, in a mouse model, it has been observed that the central brain responds in two

different ways to auditory deprivation and IHC ribbon loss, depending on the presence or absence of brain-derived neurotrophic factor (BDNF) that stabilizes or destabilizes IHC/auditory nerve contacts (Zuccotti et al., 2012).

In conclusion, future studies in humans and animals may carefully consider the possibility that the central nervous system can respond in two different ways to auditory deprivation, depending on the degree of deafferentation. First, it can respond with an increase in response gain (synaptic strength) maintaining the stable neuronal circuit, and second, it can respond with a failure to appropriately adapt the central response gain, which may cause tinnitus or hyperacusis.

3.2. Is central compensating response gain linked to hyperacusis or tinnitus?

Hyperacusis needs for generation an external sound that produces an abnormally loud percept, even though the same sound is deemed acceptable by a normal-hearing person. Converging physiological evidence indicates that intensifying central responsiveness to an existing sound causes loudness recruitment in subjects with hyperacusis (Buus and Florentine, 2002). This occurs through a process that leads to elevated midbrain activity, as shown by functional magnetic resonance imaging (fMRI) studies in patients with a main complaint of hyperacusis (Gu et al., 2010). Animal studies suggest that loudness recruitment results from increases in discharge rates of projecting target neurons in the brainstem after acoustic trauma (Cai et al., 2009). The elevated spontaneous activity has been shown to spread to neurons in the IC and AC (Eggermont, 2012a; Qiu et al., 2000; Szczepaniak and Møller, 1996). It needs to be shown how these observed hyperactivities contribute to altered central responses observed after auditory trauma in the cat. For example, VCN neurons exhibit elevated maximum discharge rates and steeper rate-level functions for frequencies at and near best frequency (Cai et al., 2009). It is also unclear if these hyperactivities are associated with a better restoration of ABR waves and greater mobilization of activity-dependent plasticity genes as Arc/Arg3.1 (see Section 4.2 for more information about Arc/Arg3.1) that are essential for increasing synaptic strength as observed in rats without tinnitus, although these animals are suffering from persistent deafferentation (Rüttiger et al., 2013; Singer et al., 2013).

Elevated maximum discharge rates and steeper rate-level functions observed after auditory trauma have been suggested to originate from disinhibition (Cai et al., 2009). Therefore, both increased rate-level function and increased ABR waves could be part of a homeostatic adaptation process that leads to an increased discharge rate after decreased inhibition (Jakawich et al., 2010; Lindskog et al., 2010; Tyagarajan and Fritschy, 2010). This homeostatic process aims to stabilize the input/output neuronal activity within a functional combined circuit by scaling the strength of excitatory and inhibitory synapses (Turrigiano, 1999). A number of studies have described neurophysiological changes that are attributed to tinnitus: an increase in spontaneous and evoked spike rate after acoustic trauma has been linked to decreased inhibition (Middleton et al., 2011), reduction in inhibitory glycinergic synaptic transmission in the DCN (Wang et al., 2009), and upregulation of AMPA receptors in the DCN (Whiting et al., 2009). Also, a decline of GABAergic input has been shown in the IC (Milbrandt et al., 2000; Mossop et al., 2000), which has been suggested to be a part of a tinnitus-inducing activity change in subcortical neurons.

Recently, a first indication was brought that elevated subcortical central gain, previously linked to tinnitus (Lanting et al., 2008; Melcher et al., 2009), may in fact be related to hyperacusis, rather than tinnitus. Thus, fMRI studies that analyzed midbrain activation in subjects with preferential hyperacusis or preferential tinnitus observed sound-induced elevated activity only in subjects with hyperacusis (Gu et al., 2010); reviewed in (Eggermont, 2012a,b).

Also consistent with these results, psychophysical studies have analyzed the loudness recruitment in humans with tinnitus and or hyperacusis. Penner (1986a,b) found steeper than normal loudness growth at the tinnitus frequency in 8 out of 10 subjects who had concomitant hearing loss and tinnitus but normal growth at the tinnitus frequency without hearing loss in the remaining 2 subjects. Ward and Baumann (2009) confirmed Penner's finding by showing steeper growth in tinnitus subjects with 50 dB hearing loss, but normal growth in tinnitus subjects with 15 dB loss (Ward and Baumann, 2009). In 16 tinnitus subjects without hearing loss, Nischalk & Stoll found shallower than normal growth (Nieschalk and Stoll, 1996). Together, these studies indicate that hyperacusis, but probably not tinnitus, is linked to elevated sound-induced subcortical evoked activity or steeper loudness growth in humans, a feature that has been confirmed through a computational model (Zeng, 2013).

In conclusion, novel findings suggest that an over-adaptive compensating central gain that spreads from the brainstem toward ascending pathways may be associated with hyperacusis, but not with tinnitus.

3.3. When central compensating response gain fails: the link to tinnitus or hyperacusis

There are currently two different views how central gain is linked to tinnitus, outlined in different computational models. In the first view, the tinnitus-related hyperactivity in the cortex is the result of a pathological increase in spreading response gain generated in the brainstem (reviewed in (Schaette and Kempter, 2012). Within this view, abnormal spontaneous activity in the auditory cortex arises because spontaneous activity in the cochlear nucleus is over-amplified along the auditory pathway. In the second view, increased central gain causes hyperacusis but not tinnitus. In this view, tinnitus is instead the result of elevated central noise (Zeng, 2013). The source of elevated central noise is elusive in the second model (Zeng, 2013). In previous animal studies that for the first time directly compared equally acoustically exposed animals with and without tinnitus (Rüttiger et al., 2013), the tinnitus group exhibited features of a failure to increase central synaptic strength (gain). Accordingly, a loss of more than 50% of IHC ribbons in the tinnitus group was linked to permanently reduced amplitude of central ABR waves and reduced markers for synaptic strength (Fig. 5) (Rüttiger et al., 2013; Singer et al., 2013). Overall, the studies have strongly indicated a failure to centrally compensate for auditory fiber loss in tinnitus animals (Rüttiger et al., 2013; Singer et al., 2013). A failure to increase central response activity in tinnitus would explain why no elevated sound-induced midbrain activity has been observed in patients with tinnitus using fMRI studies (Gu et al., 2010) and why an increase in tinnitus loudness has been associated with a decrease in MGB activity (Van Gendt et al., 2012).

In conclusion, studies in animals and humans may directly or indirectly support the notion that tinnitus is related to a failure of the central auditory pathway to adapt to a critical loss of afferent peripheral fibers. For hyperacusis and tinnitus we thus hypothesize compensating and non-compensating central changes, respectively. It is important to note that the changes may occur within the same individual in parallel regions of the auditory system representing different frequencies. Within the octave frequency resolution that is commonly used in clinical audiometric testing, hyperacusis and tinnitus channels may co-exist. This hypothesis needs further testing in future experiments.

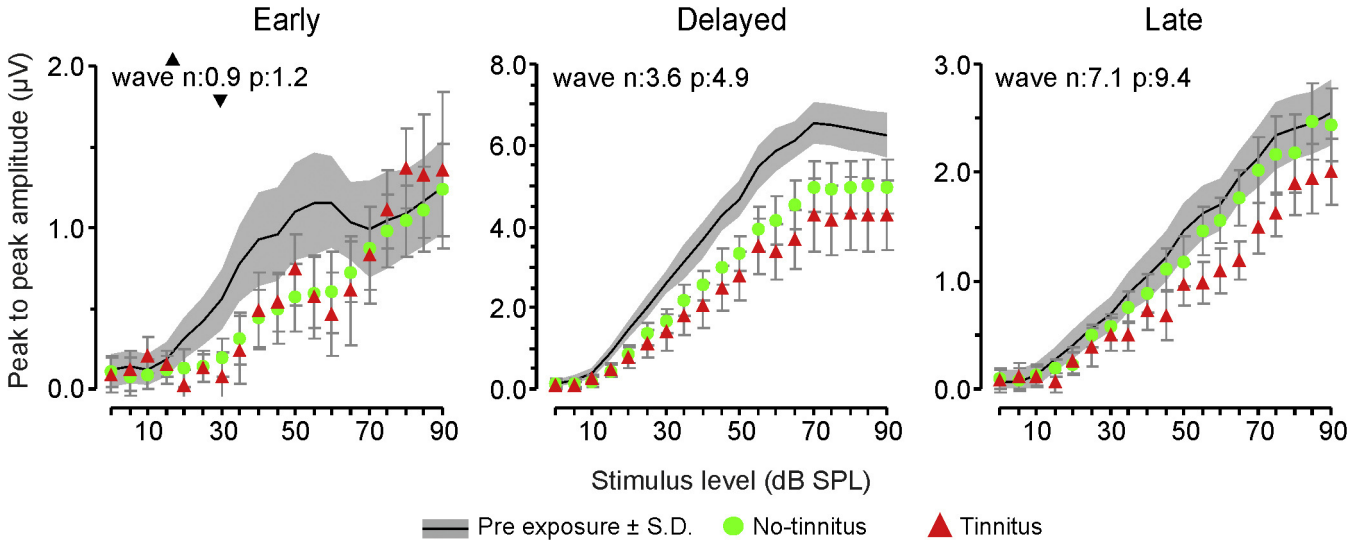

Fig. 5. Comparison of the early, delayed, and late peak-to-peak ABR wave amplitudes in rats with and without tinnitus. Peak-to-peak amplitudes of late peaks of ABR waves remain reduced following noise exposure in animals with tinnitus. Mean peak growth input/output (I/O) function (±S.D.) for early, delayed, and late ABR waves is shown before exposure (black line and gray shaded area) and after 1 h or 1.5 h exposures. Three selected peak-to-peak amplitude growth functions (μV) with increasing stimulus levels (dB SPL) are shown for rats without tinnitus (no-tinnitus, green) or with tinnitus (tinnitus, red). In the rats with tinnitus, the peak-to-peak amplitudes remain reduced up to late waves (right panel). The peak latencies are given in each panel for negative (n) and positive (p) peaks. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

4. Differences in cortical activity patterns between hyperacusis and tinnitus

4.1. To what extent is cortical map reorganization causally linked to tinnitus or hyperacusis?

After strong acoustic trauma, the cortical tonotopic map is altered, such that high frequencies are no longer represented (in terms of characteristic frequencies of central neurons) and the edge frequency of the hearing loss is over-represented. The over-representation at the audiometric edge is linked to a larger number of cortical units that are activated and spread out over a larger surface area than other stimulus frequencies (Rajan, 1998; Schwaber et al., 1993). Whether activity from the edge frequency is the source for permanently elevated spontaneous activity ("hyperactivity") in the expanded cortical area to which they project (Noreña and Eggermont, 2003; Noreña et al., 2003; Rajan et al., 1993; Robertson and Irvine, 1989; Snyder et al., 2008; Snyder and Sinex, 2002; Snyder et al., 2000; Weisz et al., 2006), is an open question. Cortical reorganization is assumed to go hand-in-hand with a deprivation of excitatory and inhibitory inputs from the nuclei of the afferent auditory pathway, causing down-regulation of inhibition and an increase of excitability in several subcortical nuclei (Gerken, 1996; Salvi et al., 2000; Zacharek et al., 2002) and the auditory cortex (Rajan, 1998; Syka, 2002).

Many comprehensive studies argue that cortical reorganization correlates with tinnitus (Gerken, 1996; König et al., 2006; Moore et al., 2010; Moore and Vinay, 2009; Rauschecker et al., 2010; Yang et al., 2011). This view may be reassessed, however, for tinnitus and perhaps also for hyperacusis for the following reasons. First, neither tinnitus (Lockwood et al., 2002; Saunders, 2007; Shiomi et al., 1997) nor hyperacusis (Gu et al., 2010; Zeng, 2013) is necessarily linked to loss of hearing thresholds, which is likely a prerequisite for cortical reorganization. Second, while mild to moderate amounts of hearing loss in cats can produce a loss of surround inhibition in the affected cortical regions, importantly, this did *not* result in functional reorganization (Rajan, 1998). Third, also in humans, using psychophysical measurements, it has been shown that a 'shallow hearing loss slope' is insufficient to trigger cortical reorganization or improvement of frequency discrimination in the region of the tonotopic map (Thai-Van et al., 2003, 2002). Fourth, on the other side, subjects with a 'steep hearing loss slope' have shown an improvement of frequency discrimination in the region of the audiometric edge and enhanced fMRI steady state responses, compatible with (if not an argument for) cortical reorganization (Dietrich et al., 2001; Moore and Vinay, 2009). Fifth, in high resolution fMRI studies that determined tonotopic maps in the auditory cortex of tinnitus patients with clinically normal hearing thresholds, no evidence for macroscopic tonotopic reorganization has been found (Langers et al., 2012). Finally, tinnitus is assumed to occur instantaneously within a short period following noise (Atherley et al., 1968; Axelsson and Prasher, 2000; Demeester et al., 2007; Loeb and Smith, 1967; McFeely et al., 1999; Mrena et al., 2004; Nottet et al., 2006; Schreiber et al., 2010), and often exhibits a transient character (Axelsson and Ringdahl, 1989; Etchelecou et al., 2011; Hoffman and Reed, 2004; Ortmann et al., 2011). This is inconsistent with the much longer time (weeks or months) taken to generate cortical map plasticity, which requires refilling of deafferented regions and functional reorganization of primary auditory cortex (A1) (Eggermont, 2006; Rajan et al., 1993; Robertson and Irvine, 1989; Schwaber et al., 1993).

These observations argue against cortical reorganization as a primary cause for tinnitus. As hyperacusis can also occur independently of hearing threshold loss (see above), this conclusion may likely also hold for hyperacusis. We cannot exclude the possibility however, that cortical map reorganization is a risk factor for the development of both diseases. Thus, patients with clinically significant hearing loss, which has led to map reorganization, may be at risk for the development of tinnitus. Regarding IHC ribbon loss as a candidate correlate for tinnitus/hyperacusis in animals (Rüttiger et al., 2013; Singer et al., 2013), the progression of IHC ribbon loss over time (Kujawa and Liberman, 2009) may also be considered as a risk for a sudden onset of tinnitus.

We may conclude that cortical reorganization is not a prerequisite for the generation of tinnitus or hyperacusis, just like a loss of threshold sensitivity is not a necessary condition for either etiology. Functional cortical reorganization is possibly a

concomitant phenomenon and a risk factor for tinnitus and hyperacusis, rather than part of its origin.

4.2. Do cortical activities differ between hyperacusis and tinnitus?

In tinnitus subjects, cortical hyperactivity is expected to occur within the region of the perceived tinnitus tone close to the frequency range that covers the hearing loss (Diesch et al., 2004; Eggermont and Roberts, 2004; Henry et al., 1999; Moffat et al., 2009; Noreña et al., 2002, 2003; Roberts et al., 2006, 2008; Schaette and Kempter, 2009; Sereda et al., 2011), matching the pattern of threshold changes in behavioral audiograms (Kleinjung et al., 2012; Noreña et al., 2002). This is also the case for hyperacusis (Hellman, 1978; Moore et al., 1985; Zeng, 2013; Zeng and Turner, 1991). The altered central activity may occur within the auditory filters near the heard tone frequencies, rather than from spreading activity at or beyond the edge frequency. Also, in animal studies following auditory trauma, hyperexcitation has been shown to spread from the DCN (Manzoor et al., 2013) or VCN (Mulders and Robertson, 2013) toward higher brain regions, such as the IC, within the same frequency band that was used for damage. This indicates a tight relationship between the 'existence region' of hyperactivity and the tonotopic map (Manzoor et al., 2013; Mulders and Robertson, 2013).

Regarding this view, in the following chapter, we will discuss in more detail the different cortical activity patterns that occur after auditory trauma, including (i) increases in spontaneous firing rate, (ii) increase in synchronized firing rates, and (iii) increases in basal excitatory postsynaptic potentials (bEPSP). We will especially try here to correlate the patterns with either tinnitus or hyperacusis.

(i) Increased spontaneous firing rates have been described to occur in the auditory cortex after acoustic trauma in various animal studies. However, the immediate appearance of tinnitus following noise (Atherley et al., 1968; Loeb and Smith, 1967; McFeely et al., 1999; Mrena et al., 2004; Nottet et al., 2006; Schreiber et al., 2010) is a first crucial argument that increased spontaneous firing rates is not a direct correlate of tinnitus, as they arise with a delay.

An increase in spontaneous firing rates in the primary auditory cortex after acoustic trauma in cats could be observed only hours after trauma, and in a much more expanded region than the trauma-tone frequency (Eggermont and Roberts, 2004); reviewed in (Eggermont, 2012a,b). Consistent with this result, an increase in spontaneous firing rates after auditory trauma occurred in the IC and VCN in rodents also only after a delay (Mulders and Robertson, 2011; Robertson et al., 2013). This work has led to the conclusion that the model of cortical hyperactivity as a result of subcortical hyperactivity cannot provide a neural basis for sudden onset tinnitus (Robertson et al., 2013).

Could the observed increase in spontaneous firing rates in the primary auditory cortex of, for example, cats, after acoustic trauma therefore be a correlate of hyperacusis? If we regard hyperacusis as a hypersensitivity to sound that is independent of hearing threshold loss, the sound-induced elevated cortical activity in low-frequency regions of tinnitus patients (Hébert et al., 2013; Langers et al., 2012), as well as increased spontaneous firing rates in low-frequency regions of the cochlea in rats (Noreña and Eggermont, 2003; Seki and Eggermont, 2003), may be viewed as correlates of hyperacusis. In humans and animals, the elevated activity in low-frequency cortical regions occurs subsequent to damage in the high-frequency range of the cochlea. In acoustically traumatized gerbils, an increase of cortical spontaneous firing rates has been directly correlated with increased glutamatergic sensitivity and synaptic strength of cortical pyramidal neurons in layer II and III (Kotak et al., 2005). Increased glutamatergic sensitivity and synaptic strength has been shown in the visual cortex following visual deprivation (Gao et al., 2010) and has been shown to correlate with increased expression levels of the activity-regulated gene Arc/Arg3.1 (Goel and Lee, 2007; Nichols et al., 2007). Arc/Arg3.1 is a cytoskeletal protein that is mobilized after LTP-like activity to scale AMPA receptors in postsynapses up and down, a process essential for long-term potentiation (LTP) consolidation. This process is also a prerequisite for long-term increases in strength of a synapse in response to reduced firing rate (Beique et al., 2011) or to visual deprivation (Gao et al., 2010); reviewed in (Bramham et al., 2008, 2010; Korb and Finkbeiner, 2011; Tzingounis and Nicoll, 2006). Mobilized cortical Arc/Arg3.1 after acoustic trauma was exclusively observed in frequency-deprived cortical regions of animals *without* tinnitus but not *with* tinnitus (Rüttiger et al., 2013; Singer et al., 2013). This observation suggests that the increased cortical spontaneous firing rates that follow auditory trauma may be linked to enhanced glutamatergic sensitivity of pyramidal neurons in regions of moderate deafferentation. More detailed studies are required to support this hypothesis. Yet, increased cortical spontaneous firing rates and mobilized cortical Arc/Arg3.1 in frequency-deprived regions may already be viewed as an attractive candidate molecular correlate of increased gain during hyperacusis, as has been suggested by a computational model (Zeng, 2013).

(ii) High synchronization and epileptic-like neuronal activity has been observed following auditory trauma in sensory-deprived frequency regions of the primary auditory cortex in the cat (Borsello et al., 2003; Eggermont and Roberts, 2004; Noreña et al., 2003; Ochi and Eggermont, 1997). In contrast to enhanced spontaneous firing rates, the enhanced synchrony of neurons occurs instantaneously (Eggermont, 2013). Accordingly, within minutes after an 1-h exposure of 120 dB SPL 6 kHz tone, the cross-correlation coefficient between simultaneously recorded spontaneous firings of pyramidal neurons in the primary auditory cortex on different electrodes (reflecting neural synchrony) was increased for neuron pairs with characteristic frequencies above the trauma-tone frequency (Noreña and Eggermont, 2003, 2005; Noreña et al., 2003). Therefore, the generation of enhanced synchrony between neurons would provide a better explanation of the instantaneous character of tinnitus than, for example, an increase in spontaneous firing rates (Eggermont, 2013). Enhanced synchrony of cortical pyramidal neurons would be achieved when cortical pyramidal cells are released from perisomatic inhibition by their interneurons (basket cells). In this case, pyramidal neurons would fire in concert, as many interneurons contact all pyramidal cells within their local field (Packer and Yuste, 2011), a feature that has to be proved for the auditory cortex in the situation of tinnitus. The perisomatic inhibition of pyramidal neurons is accomplished first by auditory experience, in a BDNF-dependent step that leads to the mature spatial and temporal cortical specialization in the central auditory system (Xu et al., 2010). This process occurs similarly in all mammalian sensory systems, including the visual system (Heimel et al., 2011; Huang et al., 1999; Lein et al., 1999) and somatosensory system (Jiao et al., 2011); reviewed in (Lehmann et al., 2012). Future studies should reinvestigate the relation of high synchronization of cortical activity in the primary auditory cortex during tinnitus to a possible reversal of the input-dependent increase in perisomatic cortical inhibition that occurs during development. Regarding cortical theta and gamma oscillations, which are dependent on perisomatic inhibition (Gonzalez-Burgos et al., 2009), in patients with gaze-induced tinnitus, hypometabolic theta activity and reduced inhibition in the auditory cortex may be reconsidered in the context of reduced perisomatic inhibition of pyramidal neurons in these patients (Van Gendt et al., 2012).

(iii) Increased basal cortical activity has been suggested by animal studies (Rüttiger et al., 2013; Singer et al., 2013) and a computational model (Zeng, 2013) to occur in frequency-deprived

regions during tinnitus. Consistent with this, in rodents behaviorally determined to experience tinnitus, there are reduced levels of Arc/Arg3.1 in pyramidal neurons of the auditory cortex in regions that likely correspond to frequency-deprived cochlear regions (Rüttiger et al., 2013). Reduced Arc/Arg3.1 levels (i.e. in Arc/Arg3.1 knockout mice) lead to increased basal miniature excitatory postsynaptic potential (mEPSP), highly synchronized epileptic-like network activity, hyperexcitability and increased susceptibility to seizures, (Peebles et al., 2010) due to disturbed regulation of AMPA receptor endocytosis in postsynapes (reviewed in Korb and Finkbeiner, 2011). The increased basal mEPSP in the absence of Arc/Arg3.1 has been suggested to be a result of a failure of homeostatic scaling down of excitatory synapses, a process that typically occurs in the visual cortex with visual experience (Desai et al., 2002; Gao et al., 2010; Goel and Lee, 2007). Enhanced basic cortical activity has been indeed observed in tinnitus animals close to the exposed tone frequency (Yang et al., 2011). In this study, however, a coincident change in miniature inhibitory postsynaptic currents (mIPSC) in higher frequency regions was suggested to cause tinnitus behavior (Yang et al., 2011), an interpretation that may be revisited in the context of the above discussion. Also in a computational model, 'increased central noise' was proposed as a neural correlate of tinnitus (Zeng, 2013). To what extent elevated bEPSP (Yang et al., 2011) and reduced Arc/Arg3.1 levels in the auditory cortex (Rüttiger et al., 2013; Singer et al., 2013) are direct correlates of increased central noise (Zeng, 2013) awaits further investigation.

In conclusion, increased sound-evoked or spontaneous firing rates in the auditory cortex may occur after moderate deafferentation. This process may be considered to originate from an increased subcortical response gain, linked to increased hypersensitivity of glutamatergic cortical pyramidal neurons during hyperacusis (Fig. 6, left side). A failure to increase central gain after a critical degree of deafferentation may be discussed in the context of increased cortical bEPSP and the epileptic-like, highly synchronous cortical activity that follows unscaled postsynapses within the frequency-deprived cortical region during tinnitus (Fig. 6, right side).

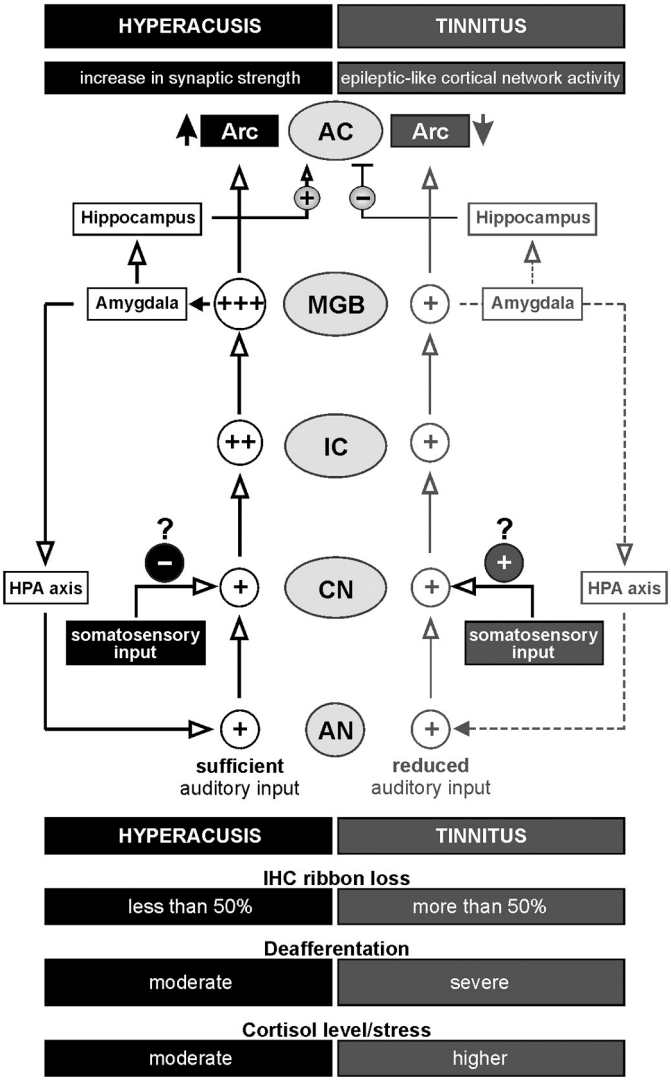

Fig. 6. Abstract illustration depicting the current hypothesis and conclusions drawn in the manuscript. For further details see Sections 4.2 and 5.1 AC, auditory cortex; AN, auditory nerve; CN, cochlear nucleus; HPA axis, hypothalamic-pituitary-adrenal axis; IC, inferior colliculus; MGB, medial geniculate body.

5. Influence of stress on hearing disorders like tinnitus and hyperacusis

5.1. What is known about the influence of social stress on tinnitus/hyperacusis in humans and animals?

Some clinical observations have long favored the view that tinnitus may be triggered and modulated by stress (Jastreboff, 2007; Leaver et al., 2011; Meltser et al., 2009; Møller, 2003; Puel and Guitton, 2007; Zenner et al., 2006). Only recently, large population studies have established that emotional exhaustion and long-term stress are predictors of hearing disorders, including tinnitus (Hasson et al., 2011; Hébert et al., 2012; Jastreboff et al., 1996; Simoens and Hébert, 2012). Stress exposure and emotional exhaustion have also been shown to enhance the risk for hyperacusis (Hasson et al., 2013a,b; Wagenaar et al., 2010; Wallén et al., 2012).

The neural networks involved in normal emotional behavior that can be altered in mood disorders involve the medial prefrontal cortex, the medial and caudolateral orbital cortex (medial prefrontal network), anterior cingulate, amygdala, hippocampus, and ventromedial parts of the basal ganglia (Drevets et al., 2008; Hinton et al., 2006; Jastreboff, 1990; Neigh et al., 2009). Imaging performed in humans with tinnitus provides evidence that tinnitus-related and distress-related brain networks overlap, such as the limbic and paralimbic regions (Rauschecker et al., 2010), the amygdala (Mirz et al., 2000; Shulman et al., 1995), the hippocampus (Landgrebe et al., 2009; Lockwood et al., 1998), the basal ganglia (Cheung and Larson, 2010; Lowry et al., 2004), and the subcallosal region, including the nucleus accumbens (Leaver et al., 2011; Mühlau et al., 2006). Also, various animal studies provide evidence for altered activity within the limbic system structures (Mahlke and Wallhäusser-Franke, 2004; Singer et al., 2013); reviewed in (Knipper et al., 2012; Kraus and Canlon, 2012).

In favor of a presumptive influence of cross-modal interactions of the limbic system on central responsiveness to auditory trauma, we may reconsider the influence on sound processing through its direct thalamic/amygdala projections. Co-activation along the HPA axis and the amygdala (Wolf, 2009) could intervene with the responsiveness of auditory circuitries. Sound, through the MGB, can activate the basolateral amygdala and via its efferent projections, indirectly influence the hippocampus and thereby the auditory cortex. This process increases the number of sound-responsive cortical neurons following environmental enrichment (Chavez et al., 2009; Turner, 1986). Through the amygdaloid output projections, the basolateral amygdala feeds back to the hypothalamus and the glucocorticoid levels in the blood (Chavez et al., 2009; Turner, 1986); reviewed in (Canlon et al., 2013). This

means that sound, but also stress, through the basolateral amygdala projections, can influence cortisol-responsive receptors such as glucocorticoid receptors and mineralocorticoid receptors in the brain. Glucocorticoid and mineralocorticoid receptors are expressed in the hippocampus or basolateral amygdala (Groeneweg et al., 2011) as well as in the mature IHCs and spiral ganglion neurons (Terakado et al., 2011; Yao and Rarey, 1996).

Therefore, stress can also affect the peripheral sensory organs. An influence of stress on the IHC synapse has only recently been shown in rodents: two days after a stress priming there was an elevated number of release sites (ribbons) at IHC synapses when animals exhibited high corticosterone levels (Singer et al., 2013). Elevated corticosterone levels also led to a smaller variance of ABR wave amplitudes and elevated Arc/Arg3.1 levels in the hippocampus (Singer et al., 2013), indicating a positive influence of stress on sound processing and potentiating hippocampal activity in a healthy system. An influence of corticosteroid on the stability of the IHC synapse may also explain the slightly improved response of the auditory nerve response (recorded through compound action potentials, CAP) that follows elevated corticosterone levels in rodents (Wang and Liberman, 2002). A direct influence of stress on the vulnerability of the IHC synapse during acoustic trauma has also been concluded from the observation that high stress levels at the time of a moderate auditory trauma led to a 'tinnitus-specific' central responsiveness, including more severe IHC ribbon loss, less restored ABR amplitudes and the decline of Arc/Arg3.1 expression levels in the hippocampal CA1 or auditory cortex (Singer et al., 2013). In contrast, moderate stress levels at the time of trauma could prevent such a tinnitus-specific central response and restore adaptive central responses (Fig. 6) (Singer et al., 2013).

The influence of different stress levels on Arc/Arg3.1 expression after acoustic trauma is reminiscent of studies that observed that weak stressors led to a moderate increase of cortisol levels and mobilize Arc/Arg3.1 in hippocampal CA1 and basolateral amygdala (Kozlovsky et al., 2008; Ons et al., 2010), while stronger stressors failed to do so (Ons et al., 2010; Yilmaz-Rastoder et al., 2011). LTP-like activity in the hippocampus was moreover switched to long-term depression (LTD) activity patterns by the influence of high stressors (Kozlovsky et al., 2008; Ons et al., 2010).

It remains to be investigated whether these observations also apply to humans. Depotentiating activity patterns in the hippocampus could be discussed as a first evidence of reduced gray matter observed in the hippocampus of hearing-impaired matched tinnitus patients (Boyen et al., 2013; Landgrebe et al., 2009). Gray matter, comprising neural cell bodies and neuropil (dendrites and unmyelinated axons), is also decreased in the hippocampus of patients with mild cognitive impairment (de Rover et al., 2011). This observation may be regarded in the context of the ~90% of tinnitus patients who exhibit reduced cognitive function as a main distress-related symptom, including concentration, attention, working memory and episodic memory deficits (Andersson and McKenna, 2006; Hallam et al., 2004; Rossiter et al., 2006; Schecklmann et al., 2013; Zirke et al., 2013). This would explain why many tinnitus patients report a reduced tinnitus severity if cognitive functions such as concentration and/or attention are improved (Cima et al., 2012; Langguth, 2012; Zenner et al., 2006; Zirke et al., 2013).

In conclusion: Activation of the basolateral amygdala projections (through either sound or disturbance of the body) can influence cortisol-responsive receptors such as glucocorticoid receptors and mineralocorticoid receptors in the brain. Elevated cortisol levels may, however, also reach the cochlea and influence the vulnerability of the IHC synapse and the degree of deafferentation. The combined network activity that circles between the inner hair cell synapse (input side) and cortex (output side) includes the emotional/memory pathway and would be influenced by adaptive or non-adaptive responsiveness to auditory deprivation. Thus, alterations in the cognitive functions during tinnitus or hyperacusis may be regarded in the context of an alteration of potentiating or depotentiating activity following auditory deprivation and subsequent changes of connectivities.

6. Conclusion

We outlined a possibly universal model for the pathomechanisms of tinnitus and hyperacusis. However, it has been repeatedly suggested that tinnitus may have a range of such mechanisms, leading to a number of tinnitus subtypes. Possibly, the peripheral pathology (deafferentiation) that is described in this review is caused by various phenomena besides acoustic trauma that could be classified as different tinnitus subtypes. In this case, the model would be universal. Alternatively, this review describes only one of the possible tinnitus subtypes and other causes of hearing loss besides acoustic trauma may trigger different pathological pathways and thereby different forms of tinnitus. Future studies will show whether the mechanisms proposed in this review are universal or constitute a subtype of tinnitus. Given the widespread presence of noise-induced hearing loss among hearing deficits, the clinical relevance of the mechanisms described in this review are expected to play a major role in tinnitus and hyperacusis.

The following conclusions can be drawn from our model and are discussed in this review:

(i) Hearing disorders can be linked with cochlear damage without an elevation of hearing thresholds.
(ii) Noise-induced cochlear damage can cause persistent and progressive deafferentation of auditory nerves without detectable elevation of hearing thresholds.
(iii) A larger extent of deafferentation may trigger tinnitus. A lesser extent of deafferentation may rather be linked to hyperacusis.
(iv) The central nervous system may respond in two different ways to auditory deprivation, depending on the degree of deafferentation. First, it can respond with an increase in response gain (synaptic strength) maintaining the stable neuronal circuit, a feature that may lead to hyperacusis. Second, it can respond with a failure to appropriately adapt the central response gain, which may cause tinnitus.
(v) Tinnitus and hyperacusis often occur within a single individual. As the proposed mechanisms for tinnitus and hyperacusis are different, it must be assumed that these occur in closely-spaced frequency band. Moreover, parallel pathways within an octave frequency band possibly cause tinnitus and hyperacusis, respectively. Detailed future studies of the physiology and psychoacoustic characteristics of tinnitus and hyperacusis need to provide support for this hypothesis .
(vi) Cortical reorganization may not be an essential prerequisite for the generation of tinnitus or hyperacusis, just like a loss of threshold sensitivity is not a necessary condition for either etiology. Functional cortical reorganization is possibly a concomitant phenomenon and a risk factor for tinnitus and hyperacusis, rather than part of its origin.
(vii) Increased sound-evoked or spontaneous firing rates in the auditory cortex may occur after moderate deafferentation as a result of increased subcortical response gain and may be linked to hyperacusis. A failure to increase central gain after a critical degree of deafferentation may be discussed in the context of increased cortical bEPSP and the epileptic-like, highly synchronous cortical activity that follows unscaled postsynapses within the sound-deprived cortical region during tinnitus.

(viii) Elevated cortisol levels (stress) may be regarded in the context of exhibiting an impact on the vulnerability of the IHC synapse and degree of deafferentation, thereby changing the risk for the generation of an either adaptive (hyperacusis) or non-adaptive (tinnitus) central circuitry response, including subsequent influence on the emotional/memory pathway.

(ix) The disturbance of central homeostatic adaptation and the influence of cortisol (stress) at the input side of a functional combined circuitry may also be a model for other brain disorders.

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References

Adams, P.F., Hendershot, G.E., Marano, M.A., 1999. Current estimates from the National Health Interview Survey, 1996. Vital Health Stat. 10, 1–203.
Ahmad, N., Seidman, M., 2004. Tinnitus in the older adult: epidemiology, pathophysiology and treatment options. Drugs Aging 21, 297–305.
Andersson, G., McKenna, L., 2006. The role of cognition in tinnitus. Acta Otolaryngol. Suppl. 556, 39–43.
Andersson, G., Lindvall, N., Hursti, T., Carlbring, P., 2002. Hypersensitivity to sound (hyperacusis): a prevalence study conducted via the Internet and post. Int. J. Audiol. 41, 545–554.
Ashmore, J.F., 2008. Cochlear outer hair cell motility. Physiol. Rev. 88, 173–210.
Atherley, G.R., Hempstock, T.I., Noble, W.G., 1968. Study of tinnitus induced temporarily by noise. J. Acoust. Soc. Am. 44, 1503–1506.
Axelsson, A., Prasher, D., 2000. Tinnitus induced by occupational and leisure noise. Noise Health 2, 47–54.
Axelsson, A., Ringdahl, A., 1989. Tinnitus – a study of its prevalence and characteristics. Br. J. Audiol. 23, 53–62.
Baguley, D.M., 2003. Hyperacusis. J. Roy. Soc. Med. 96, 582–585.
Bauer, C.A., Brozoski, T.J., 2001. Assessing tinnitus and prospective tinnitus therapeutics using a psychophysical animal model. J. Assoc. Res. Otolaryngol. 2, 54–64.
Bauer, C.A., Brozoski, T.J., Rojas, R., Boley, J., Wyder, M., 1999. Behavioral model of chronic tinnitus in rats. Otolaryngol. Head Neck Surg. 121, 457–462.
Bauer, C.A., Brozoski, T.J., Myers, K., 2007. Primary afferent dendrite degeneration as a cause of tinnitus. J. Neurosci. Res. 85, 1489–1498.
Beique, J.C., Na, Y., Kuhl, D., Worley, P.F., Huganir, R.L., 2011. Arc-dependent synapse-specific homeostatic plasticity. Proc. Natl. Acad. Sci. U. S. A. 108, 816–821.
Berger, J.I., Coomber, B., Shackleton, T.M., Palmer, A.R., Wallace, M.N., 2013. A novel behavioural approach to detecting tinnitus in the guinea pig. J. Neurosci. Methods 213, 188–195.
Borsello, T., Clarke, P.G., Hirt, L., Vercelli, A., Repici, M., Schorderet, D.F., Bogousslavsky, J., Bonny, C., 2003. A peptide inhibitor of c-Jun N-terminal kinase protects against excitotoxicity and cerebral ischemia. Nat. Med. 9, 1180–1186.
Boyen, K., Langers, D.R., de Kleine, E., Van Dijk, P., 2013. Gray matter in the brain: differences associated with tinnitus and hearing loss. Hear. Res. 295, 67–78.
Bramham, Worley, C.R., Moore, P.F., Guzowski, M.J.J.F., 2008. The immediate early gene arc/arg3.1: regulation, mechanisms, and function. J. Neurosci. 28, 11760–11767.
Bramham, C.R., Alme, M.N., Bittins, M., Kuipers, S.D., Nair, R.R., Pai, B., Panja, D., Schubert, M., Soule, J., Tiron, A., Wibrand, K., 2010. The arc of synaptic memory. Exp. Brain Res. 200, 125–140.
Breinbauer, H.A., Anabalon, J.L., Gutierrez, D., Carcamo, R., Olivares, C., Caro, J., 2012. Output capabilities of personal music players and assessment of preferred listening levels of test subjects: outlining recommendations for preventing music-induced hearing loss. Laryngoscope 122, 2549–2556.
Brigande, J.V., Heller, S., 2009. Quo vadis, hair cell regeneration? Nat. Neurosci. 12, 679–685.
Brunso-Bechtold, J.K., Thompson, G.C., Masterton, R.B., 1981. HRP study of the organization of auditory afferents ascending to central nucleus of inferior colliculus in cat. J. Comp. Neurol. 197, 705–722.
Buran, B.N., Strenzke, N., Neef, A., Gundelfinger, E.D., Moser, T., Liberman, M.C., 2010. Onset coding is degraded in auditory nerve fibers from mutant mice lacking synaptic ribbons. J. Neurosci. 30, 7587–7597.
Buus, S., Florentine, M., 2002. Growth of loudness in listeners with cochlear hearing losses: recruitment reconsidered. J. Assoc. Res. Otolaryngol. 3, 120–139.
Cai, S., Ma, W.L., Young, E.D., 2009. Encoding intensity in ventral cochlear nucleus following acoustic trauma: implications for loudness recruitment. J. Assoc. Res. Otolaryngol. 10, 5–22.
Canlon, B., Theorell, T., Hasson, D., 2013. Associations between stress and hearing problems in humans. Hear. Res. 295, 9–15.
Chavez, C.M., McGaugh, J.L., Weinberger, N.M., 2009. The basolateral amygdala modulates specific sensory memory representations in the cerebral cortex. Neurobiol. Learn. Mem. 91, 382–392.
Cheung, S.W., Larson, P.S., 2010. Tinnitus modulation by deep brain stimulation in locus of caudate neurons (area LC). Neuroscience 169, 1768–1778.
Cima, R.F., Maes, I.H., Joore, M.A., Scheyen, D.J., El Refaie, A., Baguley, D.M., Anteunis, L.J., Van Breukelen, G.J., Vlaeyen, J.W., 2012. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. Lancet 379, 1951–1959.
Coleman, J.R., Clerici, W.J., 1987. Sources of projections to subdivisions of the inferior colliculus in the rat. J. Comp. Neurol. 262, 215–226.
Dallos, P., 2008. Cochlear amplification, outer hair cells and prestin. Curr. Opin. Neurobiol. 18, 370–376.
Dallos, P., Harris, D., 1978. Properties of auditory nerve responses in absence of outer hair cells. J. Neurophysiol. 41, 365–383.
Dauman, R., Bouscau-Faure, F., 2005. Assessment and amelioration of hyperacusis in tinnitus patients. Acta Otolaryngol. 125, 503–509.
de Rover, M., Pironti, V.A., McCabe, J.A., Acosta-Cabronero, J., Arana, F.S., Morein-Zamir, S., Hodges, J.R., Robbins, T.W., Fletcher, P.C., Nestor, P.J., Sahakian, B.J., 2011. Hippocampal dysfunction in patients with mild cognitive impairment: a functional neuroimaging study of a visuospatial paired associates learning task. Neuropsychologia 49, 2060–2070.
Dehmel, S., Eisinger, D., Shore, S.E., 2012a. Gap prepulse inhibition and auditory brainstem-evoked potentials as objective measures for tinnitus in guinea pigs. Front. Syst. Neurosci. 6, 42.
Dehmel, S., Pradhan, S., Koehler, S., Bledsoe, S., Shore, S., 2012b. Noise overexposure alters long-term somatosensory - auditory processing in the dorsal cochlear nucleus - possible basis for tinnitus-related hyperactivity? J. Neurosci. 32, 1660–1671.
Demeester, K., Van Wieringen, A., Hendrickx, J.J., Topsakal, V., Fransen, E., Van Laer, L., De Ridder, D., Van Camp, G., Van de Heyning, P., 2007. Prevalence of tinnitus and audiometric shape. B-Ent 3 (Suppl. 7) 37–49.
Denoyelle, F., Petit, C., 2002. Dfnb9. Adv. Otorhinolaryngol. 61, 142–144.
Desai, N.S., Cudmore, R.H., Nelson, S.B., Turrigiano, G.G., 2002. Critical periods for experience-dependent synaptic scaling in visual cortex. Nat. Neurosci. 5, 783–789.
Diesch, E., Struve, M., Rupp, A., Ritter, S., Hulse, M., Flor, H., 2004. Enhancement of steady-state auditory evoked magnetic fields in tinnitus. Eur. J. Neurosci. 19, 1093–1104.
Dietrich, V., Nieschalk, M., Stoll, W., Rajan, R., Pantev, C., 2001. Cortical reorganization in patients with high frequency cochlear hearing loss. Hear. Res. 158, 95–101.
Dille, M.F., Konrad-Martin, D., Gallun, F., Helt, W.J., Gordon, J.S., Reavis, K.M., Bratt, G.W., Fausti, S.A., 2010. Tinnitus onset rates from chemotherapeutic agents and ototoxic antibiotics: results of a large prospective study. J. Am. Acad. Audiol. 21, 409–417.
Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118.
Eggermont, J.J., 2006. A time-line of auditory cortical reorganization after noise-induced hearing loss. In: Lomber, S.G., Eggermont, J.J. (Eds.), Reprogramming the Cerebral Cortex: Adaptive Plasticity Following Central and Peripheral Lesions. Oxford University Press, Oxford, pp. 143–158.
Eggermont, J.J., 2012a. Cortex: Way station or locus of the tinnitus percept? In: Eggermont, J.J., Zeng, F.-G., Popper, A.N. (Eds.), Springer Handbook of Auditory Research: Tinnitus. R.R. Fay, New York, pp. 137–162.
Eggermont, J.J., 2012b. The Neuroscience of Tinnitus. Oxford University Press, Oxford, UK.
Eggermont, J.J., 2013. Hearing loss, hyperacusis, or tinnitus: what is modeled in animal research? Hear. Res. 295, 140–149.
Eggermont, J.J., Roberts, L.E., 2004. The neuroscience of tinnitus. Trends Neurosci. 27, 676–682.
Engineer, N.D., Riley, J.R., Seale, J.D., Vrana, W.A., Shetake, J.A., Sudanagunta, S.P., Borland, M.S., Kilgard, M.P., 2011. Reversing pathological neural activity using targeted plasticity. Nature 470, 101–104.
Etchelecou, M.C., Coulet, O., Derkenne, R., Tomasi, M., Noreña, A.J., 2011. Temporary off-frequency listening after noise trauma. Hear. Res. 282, 81–91.
Fitzgerald, J.J., Robertson, D., Johnstone, B.M., 1993. Effects of intra-cochlear perfusion of salicylates on cochlear microphonic and other auditory responses in the guinea pig. Hear. Res. 67, 147–156.
Flamme, G.A., Wong, A., Liebe, K., Lynd, J., 2009. Estimates of auditory risk from outdoor impulse noise II. Civilian firearms. Noise Health 11, 231–242.
Furman, A.C., Kujawa, S.G., Liberman, M.C., 2013. Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates. J. Neurophysiol. 10, 577–586.
Galazyuk, A.V., Wenstrup, J.J., Hamid, M.A., 2012. Tinnitus and underlying brain mechanisms. Curr. Opin. Otolaryngol. Head Neck Surg. 20, 409–415.
Gao, M., Sossa, K., Song, L., Errington, L., Cummings, L., Hwang, H., Kuhl, D., Worley, P., Lee, H.K., 2010. A specific requirement of Arc/Arg3.1 for visual experience-induced homeostatic synaptic plasticity in mouse primary visual cortex. J. Neurosci. 30, 7168–7178.

Gerken, G.M., 1996. Central tinnitus and lateral inhibition: an auditory brainstem model. Hear. Res. 97, 75–83.

Geven, L.I., de Kleine, E., Free, R.H., Van Dijk, P., 2011. Contralateral suppression of otoacoustic emissions in tinnitus patients. Otol. Neurotol. 32, 315–321.

Gilles, A., De Ridder, D., Van Hal, G., Wouters, K., Kleine Punte, A., Van de Heyning, P., 2012. Prevalence of leisure noise-induced tinnitus and the attitude toward noise in university students. Otol. Neurotol. 33, 899–906.

Glowatzki, E., Fuchs, P.A., 2002. Transmitter release at the hair cell ribbon synapse. Nat. Neurosci. 5, 147–154.

Godfrey, D.A., Kaltenbach, J.A., Chen, K., Ilyas, O., Liu, X., Licari, F., Sacks, J., McKnight, D., 2012. Amino acid concentrations in the hamster central auditory system and long-term effects of intense tone exposure. J. Neurosci. Res. 90, 2214–2224.

Goel, A., Lee, H.K., 2007. Persistence of experience-induced homeostatic synaptic plasticity through adulthood in superficial layers of mouse visual cortex. J. Neurosci. 27, 6692–6700.

Gonzalez-Burgos, G., Rotaru, D.C., Zaitsev, A.V., Povysheva, N.V., Lewis, D.A., 2009. GABA transporter GAT1 prevents spillover at proximal and distal GABA synapses onto primate prefrontal cortex neurons. J. Neurophysiol. 101, 533–547.

Groeneweg, F.L., Karst, H., de Kloet, E.R., Joëls, M., 2011. Rapid non-genomic effects of corticosteroids and their role in the central stress response. J. Endocrinol. 209, 153–167.

Gu, J.W., Halpin, C.F., Nam, E.C., Levine, R.A., Melcher, J.R., 2010. Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity. J. Neurophysiol. 104, 3361–3370.

Gu, J.W., Herrmann, B.S., Levine, R.A., Melcher, J.R., 2012. Brainstem auditory evoked potentials suggest a role for the ventral cochlear nucleus in tinnitus. J. Assoc. Res. Otolaryngol. 13, 819–833.

Guitton, M.J., Caston, J., Ruel, J., Johnson, R.M., Pujol, R., Puel, J.L., 2003. Salicylate induces tinnitus through activation of cochlear NMDA receptors. J. Neurosci. 23, 3944–3952.

Hallam, R.S., McKenna, L., Shurlock, L., 2004. Tinnitus impairs cognitive efficiency. Int. J. Audiol. 43, 218–226.

Harrison, R.V., 2012. The prevention of noise induced hearing loss in children. Int. J. Pediatr. 2012, 473541.

Hashimoto, I., Ishiyama, Y., Yoshimoto, T., Nemoto, S., 1981. Brain-stem auditory-evoked potentials recorded directly from human brain-stem and thalamus. Brain 104, 841–859.

Hasson, D., Theorell, T., Wallen, M.B., Leineweber, C., Canlon, B., 2011. Stress and prevalence of hearing problems in the Swedish working population. BMC Public Health 11, 130.

Hasson, D., Theorell, T., Bergquist, J., Canlon, B., 2013a. Acute stress induces hyperacusis in women with high levels of emotional exhaustion. PLoS One 8, e52945.

Hasson, D., Theorell, T., Bergquist, J., Canlon, B., 2013b. Correction: acute stress induces hyperacusis in women with high levels of emotional exhaustion. PLoS One 8, e52945.

Hébert, S., Canlon, B., Hasson, D., 2012. Emotional exhaustion as a predictor of tinnitus. Psychother. Psychosom. 81, 324–326.

Hébert, S., Fournier, P., Noreña, A., 2013. The Auditory Sensitivity is Increased in Tinnitus Ears. J. Neurosci. 33, 2356–2364.

Heffner, H.E., Harrington, I.A., 2002. Tinnitus in hamsters following exposure to intense sound. Hear. Res. 170, 83–95.

Heffner, H.E., Heffner, R.S., 2012. Behavioral tests for tinnitus in animals. In: Eggermont, J.J., Zeng, F.-G., Popper, A.N., Fay, R.R. (Eds.), Springer Handbook of Auditory Research: Tinnitus. Springer, New York, pp. 21–58.

Heffner, H.E., Koay, G., 2005. Tinnitus and hearing loss in hamsters (Mesocricetus auratus) exposed to loud sound. Behav. Neurosci. 119, 734–742.

Heidrych, P., Zimmermann, U., Kuhn, S., Franz, C., Engel, J., Duncker, S.V., Hirt, B., Pusch, C.M., Ruth, P., Pfister, M., Marcotti, W., Blin, N., Knipper, M., 2009. Otoferlin interacts with myosin VI: implications for maintenance of the basolateral synaptic structure of the inner hair cell. Hum. Mol. Genet. 18, 2779–2790.

Heimel, J.A., Van Versendaal, D., Levelt, C.N., 2011. The role of GABAergic inhibition in ocular dominance plasticity. Neural Plast. 2011, 391763.

Heinz, M.G., Young, E.D., 2004. Response growth with sound level in auditory-nerve fibers after noise-induced hearing loss. J. Neurophysiol. 91, 784–795.

Heinz, M.G., Issa, J.B., Young, E.D., 2005. Auditory-nerve rate responses are inconsistent with common hypotheses for the neural correlates of loudness recruitment. J. Assoc. Res. Otolaryngol. 6, 91–105.

Hellman, R.P., 1978. Dependence of loudness growth on skirts of excitation patterns. J. Acoust. Soc. Am. 63, 1114–1119.

Henderson, D., Subramaniam, M., Boettcher, F.A., 1993. Individual susceptibility to noise-induced hearing loss: an old topic revisited. Ear Hear. 14, 152–168.

Henry, J.A., Meikle, M., Gilbert, A., 1999. Audiometric correlates of tinnitus pitch: insights from the tinnitus data registry. In: Hazell, J. (Ed.), Proceedings of the Sixth International Seminar. The Tinnitus and Hyperacusis Centre, London, pp. 51–57.

Hinton, D.E., Chhean, D., Pich, V., Hofmann, S.G., Barlow, D.H., 2006. Tinnitus among Cambodian refugees: relationship to PTSD severity. J. Trauma. Stress 19, 541–546.

Hoffman, H.J., Reed, G.W., 2004. Epidemiology of tinnitus. In: Snow., J.B., Decker, B.C. (Eds.), Tinnitus: Theory and Management. Hamilton, Ontario, Canada, pp. 16–41.

Huang, Z.J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M.F., Maffei, L., Tonegawa, S., 1999. BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. Cell 98, 739–755.

Huang, Z.W., Luo, Y., Wu, Z., Tao, Z., Jones, R.O., Zhao, H.B., 2005. Paradoxical enhancement of active cochlear mechanics in long-term administration of salicylate. J. Neurophysiol. 93, 2053–2061.

Jakawich, S.K., Nasser, H.B., Strong, M.J., McCartney, A.J., Perez, A.S., Rakesh, N., Carruthers, C.J., Sutton, M.A., 2010. Local presynaptic activity gates homeostatic changes in presynaptic function driven by dendritic BDNF synthesis. Neuron 68, 1143–1158.

Jastreboff, P.J., 1990. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci. Res. 8, 221–254.

Jastreboff, P.J., 1995. Tinnitus as a phantom perception: theories and clinical implications. In: Vernon, J.A., Møller, A.R. (Eds.), Mechanisms of Tinnitus. Allyn and Bacon, London, pp. 73–94.

Jastreboff, P.J., 2007. Tinnitus retraining therapy. Prog. Brain Res. 166, 415–423.

Jastreboff, P.J., Brennan, J.F., 1994. Evaluating the loudness of phantom auditory perception (tinnitus) in rats. Audiology 33, 202–217.

Jastreboff, P.J., Brennan, J.F., Coleman, J.K., Sasaki, C.T., 1988. Phantom auditory sensation in rats: an animal model for tinnitus. Behav. Neurosci. 102, 811–822.

Jastreboff, P.J., Gray, W.C., Gold, S.L., 1996. Neurophysiological approach to tinnitus patients. Am. J. Otol. 17, 236–240.

Jaumann, M., Dettling, J., Gubelt, M., Zimmermann, U., Gerling, A., Paquet-Durand, F., Feil, S., Wolpert, S., Franz, C., Varakina, K., Xiong, H., Brandt, N., Kuhn, S., Geisler, H.S., Rohbock, K., Ruth, P., Schlossmann, J., Hütter, J., Sandner, P., Feil, R., Engel, J., Knipper, M., Rüttiger, L., 2012. cGMP-Prkg1 signaling and Pde5 inhibition shelter cochlear hair cells and hearing function. Nat. Med. 18, 252–259.

Jiao, Y., Zhang, Z., Zhang, C., Wang, X., Sakata, K., Lu, B., Sun, Q.Q., 2011. A key mechanism underlying sensory experience-dependent maturation of neocortical GABAergic circuits *in vivo*. Proc. Natl. Acad. Sci. U. S. A. 108, 12131–12136.

Johnson, D.H., Kiang, N.Y., 1976. Analysis of discharges recorded simultaneously from pairs of auditory nerve fibers. Biophys. J. 16, 719–734.

Johnson, S.L., Franz, C., Kuhn, S., Furness, D.N., Rüttiger, L., Münkner, S., Rivolta, M.N., Seward, E.P., Herschman, H.R., Engel, J., Knipper, M., Marcotti, W., 2010. Synaptotagmin IV determines the linear Ca^{2+} dependence of vesicle fusion at auditory ribbon synapses. Nat. Neurosci. 13, 45–52.

Kaga, K., Tanaka, Y., 1980. Auditory brainstem response and behavioral audiometry. Developmental correlates. Arch. Otolaryngol. 106, 564–566.

Kaltenbach, J.A., 2007. The dorsal cochlear nucleus as a contributor to tinnitus: mechanisms underlying the induction of hyperactivity. Prog. Brain Res. 166, 89–106.

Kammerer, R., Rüttiger, L., Riesenberg, R., Schauble, C., Krupar, R., Kamp, A., Sunami, K., Eisenried, A., Hennenberg, M., Grunert, F., Bress, A., Battaglia, S., Schrewe, H., Knipper, M., Schneider, M.R., Zimmermann, W., 2012. Loss of mammal-specific tectorial membrane component carcinoembryonic antigen cell adhesion molecule 16 (CEACAM16) leads to hearing impairment at low and high frequencies. J. Biol. Chem. 287, 21584–21598.

Kim, D.K., Park, S.N., Kim, H.M., Son, H.R., Kim, N.G., Park, K.H., Yeo, S.W., 2011. Prevalence and significance of high-frequency hearing loss in subjectively normal-hearing patients with tinnitus. Ann. Otol. Rhinol. Laryngol. 120, 523–528.

Kleinjung, T., Langguth, B., Kreuzer, P., Landgrebe, M., Vielsmeier, V., Schecklmann, M., 2012. Relationship of tinnitus pitch and audiogram shape in patients with chronic tinnitus. In: Santi, P.A. (Ed.), 35th Annual Midwinter Research Meeting of the Association for Research in Otolaryngology. San Diego, CA, USA, Abstract No. 887, pp. 310.

Knipper, M., Müller, M., Zimmermann, U., 2012. Molecular mechanism of tinnitus. In: Eggermont, J.J., Zeng, F.-G., Popper, A.N., Fay, R.R. (Eds.), Springer Handbook of Audidory Research: Tinnitus. Springer, New York, pp. 59–82.

Knirsch, M., Brandt, N., Braig, C., Kuhn, S., Hirt, B., Münkner, S., Knipper, M., Engel, J., 2007. Persistence of $Ca_V1.3$ Ca^{2+} channels in mature outer hair cells supports outer hair cell afferent signaling. J. Neurosci. 27, 6442–6451.

König, O., Schaette, R., Kempter, R., Gross, M., 2006. Course of hearing loss and occurrence of tinnitus. Hear. Res. 221, 59–64.

Konings, A., Van Laer, L., Pawelczyk, M., Carlsson, P.I., Bondeson, M.L., Rajkowska, E., Dudarewicz, A., Vandevelde, A., Fransen, E., Huyghe, J., Borg, E., Sliwinska-Kowalska, M., Van Camp, G., 2007. Association between variations in CAT and noise-induced hearing loss in two independent noise-exposed populations. Hum. Mol. Genet. 16, 1872–1883.

Korb, E., Finkbeiner, S., 2011. Arc in synaptic plasticity: from gene to behavior. Trends Neurosci. 34, 591–598.

Kotak, V.C., Fujisawa, S., Lee, F.A., Karthikeyan, O., Aoki, C., Sanes, D.H., 2005. Hearing loss raises excitability in the auditory cortex. J. Neurosci. 25, 3908–3918.

Kozlovsky, N., Matar, M.A., Kaplan, Z., Kotler, M., Zohar, J., Cohen, H., 2008. The immediate early gene Arc is associated with behavioral resilience to stress exposure in an animal model of posttraumatic stress disorder. Eur. Neuropsychopharmacol. 18, 107–116.

Kraus, K.S., Canlon, B., 2012. Neuronal connectivity and interactions between the auditory and limbic systems. Effects of noise and tinnitus. Hear. Res. 288, 34–46.

Kraus, K.S., Mitra, S., Jimenez, Z., Hinduja, S., Ding, D., Jiang, H., Gray, L., Lobarinas, E., Sun, W., Salvi, R.J., 2010. Noise trauma impairs neurogenesis in the rat hippocampus. Neuroscience 167, 1216–1226.

Kujawa, S.G., Liberman, M.C., 2009. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. J. Neurosci. 29, 14077–14085.

Landgrebe, M., Langguth, B., Rosengarth, K., Braun, S., Koch, A., Kleinjung, T., May, A., de Ridder, D., Hajak, G., 2009. Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. Neuroimage 46, 213–218.

Langers, D.R.M., de Kleine, E., Van Dijk, P., 2012. Tinnitus does not require macroscopic tonotopic map reorganization. Front. Syst. Neurosci. 6, 1–15.
Langguth, B., 2012. Tinnitus: the end of therapeutic nihilism. Lancet 379, 1926–1928.
Langguth, B., Salvi, R., Elgoyhen, A.B., 2009. Emerging pharmacotherapy of tinnitus. Expert. Opin. Emerg. Drugs 14, 687–702.
Lanting, C.P., De Kleine, E., Bartels, H., Van Dijk, P., 2008. Functional imaging of unilateral tinnitus using fMRI. Acta Otolaryngol. 128, 415–421.
Leaver, A.M., Renier, L., Chevillet, M.A., Morgan, S., Kim, H.J., Rauschecker, J.P., 2011. Dysregulation of limbic and auditory networks in tinnitus. Neuron 69, 33–43.
Lehmann, K., Steinecke, A., Bolz, J., 2012. GABA through the ages: regulation of cortical function and plasticity by inhibitory interneurons. Neural Plast. 2012, 892784.
Lein, E.S., Finney, E.M., McQuillen, P.S., Shatz, C.J., 1999. Subplate neuron ablation alters neurotrophin expression and ocular dominance column formation. Proc. Natl. Acad. Sci. U. S. A. 96, 13491–13495.
Liberman, M.C., 1978. Auditory-nerve response from cats raised in a low-noise chamber. J. Acoust. Soc. Am. 63, 442–455.
Liberman, M.C., Dodds, L.W., 1984a. Single-neuron labeling and chronic cochlear pathology, II. Stereocilia damage and alterations of spontaneous discharge rates. Hear. Res. 16, 43–53.
Liberman, M.C., Dodds, L.W., 1984b. Single-neuron labeling and chronic cochlear pathology, III. Stereocilia damage and alterations of threshold tuning curves. Hear. Res. 16, 55–74.
Liberman, M.C., Kiang, N.Y., 1978. Acoustic trauma in cats. Cochlear pathology and auditory-nerve activity. Acta Otolaryngol. Suppl. 358, 1–63.
Liberman, M.C., Kiang, N.Y., 1984. Single-neuron labeling and chronic cochlear pathology, IV. Stereocilia damage and alterations in rate- and phase-level functions. Hear. Res. 16, 75–90.
Lin, H.W., Furman, A.C., Kujawa, S.G., Liberman, M.C., 2011. Primary neural degeneration in the Guinea pig cochlea after reversible noise-induced threshold shift. J. Assoc. Res. Otolaryngol. 12, 605–616.
Lindskog, M., Li, L., Groth, R.D., Poburko, D., Thiagarajan, T.C., Han, X., Tsien, R.W., 2010. Postsynaptic GluA1 enables acute retrograde enhancement of presynaptic function to coordinate adaptation to synaptic inactivity. Proc. Natl. Acad. Sci. U. S. A. 107, 21806–21811.
Lobarinas, E., Hayes, S.H., Allman, B.L., 2013. The gap-startle paradigm for tinnitus screening in animal models: limitations and optimization. Hear. Res. 295, 150–160.
Lockwood, A.H., Salvi, R.J., Coad, M.L., Towsley, M.L., Wack, D.S., Murphy, B.W., 1998. The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. Neurology 50, 114–120.
Lockwood, A.H., Salvi, R.J., Burkard, R.F., 2002. Tinnitus. N. Engl. J. Med. 347, 904–910.
Loeb, M., Smith, R.P., 1967. Relation of induced tinnitus to physical characteristics of the inducing stimuli. J. Acoust. Soc. Am. 42, 453–455.
Lowry, L.D., Eisenman, L.M., Saunders, J.C., 2004. An absence of tinnitus. Otol. Neurotol. 25, 474–478.
Lu, J., Cheng, X., Li, Y., Zeng, L., Zhao, Y., 2005. Evaluation of individual susceptibility to noise-induced hearing loss in textile workers in China. Arch. Environ. Occup. Health 60, 287–294.
Mahlke, C., Wallhäusser-Franke, E., 2004. Evidence for tinnitus-related plasticity in the auditory and limbic system, demonstrated by arg3.1 and c-fos immunocytochemistry. Hear. Res. 195, 17–34.
Maison, S.F., Usubuchi, H., Liberman, M.C., 2013. Efferent feedback minimizes cochlear neuropathy from moderate noise exposure. J. Neurosci. 33, 5542–5552.
Malmierca, M., Merchan, M., 2004. The auditory system. In: Paxinos, G. (Ed.), The Rat Nervous System. Academic Press, San Diego, pp. 997–1082.
Manzoor, N.F., Gao, Y., Licari, F., Kaltenbach, J.A., 2013. Comparison and contrast of noise-induced hyperactivity in the dorsal cochlear nucleus and inferior colliculus. Hear. Res. 295, 114–123.
Mazurek, B., Haupt, H., Gross, J., 2006. Pharmacotherapy in acute tinnitis. The special role of hypoxia and ischemia in the pathogenesis of tinnitis. HNO 54, 9–15.
Mazurek, B., Stover, T., Haupt, H., Gross, J., Szczepek, A., 2008. Pathogenesis and treatment of presbyacusis, Current status and future perspectives. HNO 56 , 429–432, 425–434.
McFeely Jr., W.J., Bojrab, D.I., Davis, K.G., Hegyi, D.F., 1999. Otologic injuries caused by airbag deployment. Otolaryngol. Head Neck Surg. 121, 367–373.
Melcher, J.R., Kiang, N.Y., 1996. Generators of the brainstem auditory evoked potential in cat. III. Identified cell populations. Hear. Res. 93, 52–71.
Melcher, J.R., Levine, R.A., Bergevin, C., Norris, B., 2009. The auditory midbrain of people with tinnitus: abnormal sound-evoked activity revisited. Hear. Res. 257, 63–74.
Meltser, I., Tahera, Y., Canlon, B., 2009. Glucocorticoid receptor and mitogen-activated protein kinases activity after restraint stress and acoustic trauma. J. Neurotrauma 26, 1835–1845.
Merchan-Perez, A., Liberman, M.C., 1996. Ultrastructural differences among afferent synapses on cochlear hair cells: correlations with spontaneous discharge rate. J. Comp. Neurol. 371, 208–221.
Middleton, J.W., Kiritani, T., Pedersen, C., Turner, J.G., Shepherd, G.M., Tzounopoulos, T., 2011. Mice with behavioral evidence of tinnitus exhibit dorsal cochlear nucleus hyperactivity because of decreased GABAergic inhibition. Proc. Natl. Acad. Sci. U. S. A. 108, 7601–7606.
Milbrandt, J.C., Holder, T.M., Wilson, M.C., Salvi, R.J., Caspary, D.M., 2000. GAD levels and muscimol binding in rat inferior colliculus following acoustic trauma. Hear. Res. 147, 251–260.
Miller, J.D., Watson, C.S., Covell, W.P., 1963. Deafening effects of noise on the cat. Acta Oto-Laryngol. Suppl. 176.
Mirz, F., Gjedde, A., Sodkilde-Jrgensen, H., Pedersen, C.B., 2000. Functional brain imaging of tinnitus-like perception induced by aversive auditory stimuli. Neuroreport 11, 633–637.
Moffat, G., Adjout, K., Gallego, S., Thai-Van, H., Collet, L., Noreña, A.J., 2009. Effects of hearing aid fitting on the perceptual characteristics of tinnitus. Hear. Res. 254, 82–91.
Møller, A.R., 2003. Pathophysiology of tinnitus. Otolaryngol. Clin. North Am. 36 (249-266) v–vi.
Moore, B.C., Glasberg, B.R., Hess, R.F., Birchall, J.P., 1985. Effects of flanking noise bands on the rate of growth of loudness of tones in normal and recruiting ears. J. Acoust. Soc. Am. 77, 1505–1513.
Moore, B.C., Vinay, S.N., 2009. Enhanced discrimination of low-frequency sounds for subjects with high-frequency dead regions. Brain 132, 524–536.
Moore, B.C., Vinay, Sandhya, 2010. The relationship between tinnitus pitch and the edge frequency of the audiogram in individuals with hearing impairment and tonal tinnitus. Hear. Res. 261, 51–56.
Mossop, J.E., Wilson, M.J., Caspary, D.M., Moore, D.R., 2000. Down-regulation of inhibition following unilateral deafening. Hear. Res. 147, 183–187.
Mrena, R., Paakkonen, R., Back, L., Pirvola, U., Ylikoski, J., 2004. Otologic consequences of blast exposure: a Finnish case study of a shopping mall bomb explosion. Acta Otolaryngol. Suppl. 124, 946–952.
Mühlau, M., Rauschecker, J.P., Oestreicher, E., Gaser, C., Rottinger, M., Wohlschlager, A.M., Simon, F., Etgen, T., Conrad, B., Sander, D., 2006. Structural brain changes in tinnitus. Cereb. Cortex 16, 1283–1288.
Mulders, W.H., Robertson, D., 2011. Progressive centralization of midbrain hyperactivity after acoustic trauma. Neuroscience 192, 753–760.
Mulders, W.H., Robertson, D., 2013. Development of hyperactivity after acoustic trauma in the guinea pig inferior colliculus. Hear. Res. 298, 104–108.
Müller, M., Robertson, D., 1991. Shapes of rate-versus-level functions of primary auditory nerve fibres: test of the basilar membrane mechanical hypothesis. Hear. Res. 57, 71–78.
Neigh, G.N., Gillespie, C.F., Nemeroff, C.B., 2009. The neurobiological toll of child abuse and neglect. Trauma Violence Abuse 10, 389–410.
Nelson, J.J., Chen, K., 2004. The relationship of tinnitus, hyperacusis, and hearing loss. Ear Nose Throat J. 83, 472–476.
Nichols, J.A., Jakkamsetti, V.P., Salgado, H., Dinh, L., Kilgard, M.P., Atzori, M., 2007. Environmental enrichment selectively increases glutamatergic responses in layer II/III of the auditory cortex of the rat. Neuroscience 145, 832–840.
Nieschalk, M., Stoll, W., 1996. Direct loudness scaling in diagnosis of tinnitus. A contribution to loudness perception in tinnitus. HNO 44, 577–584.
Noreña, A., Micheyl, C., Chery-Croze, S., Collet, L., 2002. Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus. Audiol. Neurootol. 7, 358–369.
Noreña, A.J., Eggermont, J.J., 2003. Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. Hear. Res. 183, 137–153.
Noreña, A.J., Eggermont, J.J., 2005. Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. J. Neurosci. 25, 699–705.
Noreña, A.J., Tomita, M., Eggermont, J.J., 2003. Neural changes in cat auditory cortex after a transient pure-tone trauma. J. Neurophysiol. 90, 2387–2401.
Nottet, J.B., Moulin, A., Brossard, N., Suc, B., Job, A., 2006. Otoacoustic emissions and persistent tinnitus after acute acoustic trauma. Laryngoscope 116, 970–975.
Nowotny, M., Remus, M., Kossl, M., Gaese, B.H., 2011. Characterization of the perceived sound of trauma-induced tinnitus in gerbils. J. Acoust. Soc. Am. 130, 2827–2834.
Ochi, K., Eggermont, J.J., 1997. Effects of quinine on neural activity in cat primary auditory cortex. Hear. Res. 105, 105–118.
Ons, S., Rotllant, D., Marin-Blasco, I.J., Armario, A., 2010. Immediate-early gene response to repeated immobilization: Fos protein and arc mRNA levels appear to be less sensitive than c-fos mRNA to adaptation. Eur. J. Neurosci. 31, 2043–2052.
Ortmann, M., Müller, N., Schlee, W., Weisz, N., 2011. Rapid increases of gamma power in the auditory cortex following noise trauma in humans. Eur. J. Neurosci. 33, 568–575.
Packer, A.M., Yuste, R., 2011. Dense, unspecific connectivity of neocortical parvalbumin-positive interneurons: a canonical microcircuit for inhibition? J. Neurosci. 31, 13260–13271.
Peebles, C.L., Yoo, J., Thwin, M.T., Palop, J.J., Noebels, J.L., Finkbeiner, S., 2010. Arc regulates spine morphology and maintains network stability *in vivo*. Proc. Natl. Acad. Sci. U. S. A. 107, 18173–18178.
Penner, M.J., 1986a. Magnitude estimation and the "paradoxical" loudness of tinnitus. J. Speech Hear. Res. 29, 407–412.
Penner, M.J., 1986b. Tinnitus as a source of internal noise. J. Speech Hear. Res. 29, 400–406.
Phillips, S.L., Mace, S.T., 2008. Sound level measurements in music practice rooms. Music Performance Res. 2, 36–47.
Puel, J.L., Guitton, M.J., 2007. Salicylate-induced tinnitus: molecular mechanisms and modulation by anxiety. Prog. Brain Res. 166, 141–146.

Puel, J.L., Ruel, J., Guitton, M., Pujol, R., 2002. The inner hair cell afferent/efferent synapses revisited: a basis for new therapeutic strategies. Adv. Otorhinolaryngol. 59, 124–130.

Qiu, C., Salvi, R., Ding, D., Burkard, R., 2000. Inner hair cell loss leads to enhanced response amplitudes in auditory cortex of unanesthetized chinchillas: evidence for increased system gain. Hear. Res. 139, 153–171.

Rajan, R., 1998. Receptor organ damage causes loss of cortical surround inhibition without topographic map plasticity. Nat. Neurosci. 1, 138–143.

Rajan, R., Irvine, D.R., Wise, L.Z., Heil, P., 1993. Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex. J. Comp. Neurol. 338, 17–49.

Rauschecker, J.P., Leaver, A.M., Mühlau, M., 2010. Tuning out the noise: limbic–auditory interactions in tinnitus. Neuron 66, 819–826.

Roberts, L.E., Moffat, G., Bosnyak, D.J., 2006. Residual inhibition functions in relation to tinnitus spectra and auditory threshold shift. Acta Otolaryngol. Suppl. 27–33.

Roberts, L.E., Moffat, G., Baumann, M., Ward, L.M., Bosnyak, D.J., 2008. Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. J. Assoc. Res. Otolaryngol. 9, 417–435.

Roberts, L.E., Eggermont, J.J., Caspary, D.M., Shore, S.E., Melcher, J.R., Kaltenbach, J.A., 2010. Ringing ears: the neuroscience of tinnitus. J. Neurosci. 30, 14972–14979.

Robertson, D., Irvine, D.R., 1989. Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. J. Comp. Neurol. 282, 456–471.

Robertson, D., Bester, C., Vogler, D., Mulders, W.H., 2013. Spontaneous hyperactivity in the auditory midbrain: relationship to afferent input. Hear. Res. 295, 124–129.

Robles, L., Ruggero, M.A., 2001. Mechanics of the mammalian cochlea. Physiol. Rev. 81, 1305–1352.

Rossiter, S., Stevens, C., Walker, G., 2006. Tinnitus and its effect on working memory and attention. J. Speech Lang. Hear. Res. 49, 150–160.

Roux, I., Safieddine, S., Nouvian, R., Grati, M., Simmler, M.C., Bahloul, A., Perfettini, I., Le Gall, M., Rostaing, P., Hamard, G., Triller, A., Avan, P., Moser, T., Petit, C., 2006. Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. Cell 127, 277–289.

Ruel, J., Chabbert, C., Nouvian, R., Bendris, R., Eybalin, M., Leger, C.L., Bourien, J., Mersel, M., Puel, J.L., 2008. Salicylate enables cochlear arachidonic-acid-sensitive NMDA receptor responses. J. Neurosci. 28, 7313–7323.

Rüttiger, L., Ciuffani, J., Zenner, H.P., Knipper, M., 2003. A behavioral paradigm to judge acute sodium salicylate-induced sound experience in rats: a new approach for an animal model on tinnitus. Hear. Res. 180, 39–50.

Rüttiger, L., Singer, W., Panford-Walsh, R., Matsumoto, M., Lee, S.C., Zuccotti, A., Zimmermann, U., Jaumann, M., Rohbock, K., Xiong, H., Knipper, M., 2013. The reduced cochlear output and the failure to adapt the central auditory response causes tinnitus in noise exposed rats. PLoS One 8, e57247.

Sachs, M.B., Abbas, P.J., 1974. Rate versus level functions for auditory-nerve fibers in cats: tone-burst stimuli. J. Acoust. Soc. Am. 56, 1835–1847.

Salvi, R.J., Wang, J., Ding, D., 2000. Auditory plasticity and hyperactivity following cochlear damage. Hear. Res. 147, 261–274.

Saunders, J.C., 2007. The role of central nervous system plasticity in tinnitus. J. Commun. Disord. 40, 313–334.

Schaette, R., Kempter, R., 2009. Predicting tinnitus pitch from patients' audiograms with a computational model for the development of neuronal hyperactivity. J. Neurophysiol. 101, 3042–3052.

Schaette, R., Kempter, R., 2012. Computational models of neurophysiological correlates of tinnitus. Front. Syst. Neurosci. 6, 34.

Schaette, R., McAlpine, D., 2011. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. J. Neurosci. 31, 13452–13457.

Schecklmann, M., Landgrebe, M., Poeppl, T.B., Kreuzer, P., Manner, P., Marienhagen, J., Wack, D.S., Kleinjung, T., Hajak, G., Langguth, B., 2013. Neural correlates of tinnitus duration and distress: a positron emission tomography study. Hum. Brain Mapp. 34, 233–240.

Schneider, M.E., Belyantseva, I.A., Azevedo, R.B., Kachar, B., 2002. Rapid renewal of auditory hair bundles. Nature 418, 837–838.

Schreiber, B.E., Agrup, C., Haskard, D.O., Luxon, L.M., 2010. Sudden sensorineural hearing loss. Lancet 375, 1203–1211.

Schroeder, C.E., Lindsley, R.W., Specht, C., Marcovici, A., Smiley, J.F., Javitt, D.C., 2001. Somatosensory input to auditory association cortex in the macaque monkey. J. Neurophysiol. 85, 1322–1327.

Schwaber, M.K., Garraghty, P.E., Kaas, J.H., 1993. Neuroplasticity of the adult primate auditory cortex following cochlear hearing loss. Am. J. Otol. 14, 252–258.

Seki, S., Eggermont, J.J., 2003. Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. Hear. Res. 180, 28–38.

Sereda, M., Hall, D.A., Bosnyak, D.J., Edmondson-Jones, M., Roberts, L.E., Adjamian, P., Palmer, A.R., 2011. Re-examining the relationship between audiometric profile and tinnitus pitch. Int. J. Audiol. 50, 303–312.

Sewell, W.F., 1984. Furosemide selectively reduces one component in rate-level functions from auditory-nerve fibers. Hear. Res. 15, 69–72.

Shargorodsky, J., Curhan, G.C., Farwell, W.R., 2010. Prevalence and characteristics of tinnitus among US adults. Am. J. Med. 123, 711–718.

Sheets, L., Trapani, J.G., Mo, W., Obholzer, N., Nicolson, T., 2011. Ribeye is required for presynaptic $Ca_V1.3a$ channel localization and afferent innervation of sensory hair cells. Development 138, 1309–1319.

Shetye, A., Kennedy, V., 2010. Tinnitus in children: an uncommon symptom? Arch. Dis. Child. 95, 645–648.

Shiomi, Y., Tsuji, J., Naito, Y., Fujiki, N., Yamamoto, N., 1997. Characteristics of DPOAE audiogram in tinnitus patients. Hear. Res. 108, 83–88.

Shore, S.E., 2011. Plasticity of somatosensory inputs to the cochlear nucleus – implications for tinnitus. Hear. Res. 281, 38–46.

Shore, S.E., Koehler, S., Oldakowski, M., Hughes, L.F., Syed, S., 2008. Dorsal cochlear nucleus responses to somatosensory stimulation are enhanced after noise-induced hearing loss. Eur. J. Neurosci. 27, 155–168.

Shulman, A., Strashun, A.M., 2009. Fluid dynamics vascular theory of brain and inner-ear function in traumatic brain injury: a translational hypothesis for diagnosis and treatment. Int. Tinnitus J. 15, 119–129.

Shulman, A., Strashun, A.M., Afriyie, M., Aronson, F., Abel, W., Goldstein, B., 1995. SPECT imaging of brain and tinnitus-neurotologic/neurologic implications. Int. Tinnitus J. 1, 13–29.

Simoens, V.L., Hébert, S., 2012. Cortisol suppression and hearing thresholds in tinnitus after low-dose dexamethasone challenge. BMC Ear Nose Throat Disord. 12, 4.

Singer, W., Zuccotti, A., Jaumann, M., Lee, S.C., Panford-Walsh, R., Xiong, H., Zimmermann, U., Franz, C., Geisler, H.S., Köpschall, I., Rohbock, K., Varakina, K., Verpoorten, S., Reinbothe, T., Schimmang, T., Rüttiger, L., Knipper, M., 2013. Noise-induced inner hair cell ribbon loss disturbs central arc mobilization: a novel molecular paradigm for understanding tinnitus. Mol. Neurobiol. 47, 261–279.

Sirimanna, T., Stephens, D., Board, T., 1996. Tinnitus and audioscan notches. J. Audiol. Med. 5, 38–48.

Sliwinska-Kowalska, M., Pawelczyk, M., 2013. Contribution of genetic factors to noise-induced hearing loss: a human studies review. Mutat. Res. 752, 61–65.

Sliwinska-Kowalska, M., Noben-Trauth, K., Pawelczyk, M., Kowalski, T.J., 2008. Single nucleotide polymorphisms in the cadherin 23 (CDH23) gene in Polish workers exposed to industrial noise. Am. J. Hum. Biol. 20, 481–483.

Smith, R.J.H., Gurrola, J.G., Kelley, P.M., 1993. OTOF-related deafness. In: Pagon, R.A., Bird, T.D., Dolan, C.R., Stephens, K., Adam, M.P. (Eds.), GeneReviews. , Seattle, WA.

Snyder, R.L., Sinex, D.G., 2002. Immediate changes in tuning of inferior colliculus neurons following acute lesions of cat spiral ganglion. J. Neurophysiol. 87, 434–452.

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. Hear. Res. 147, 200–220.

Snyder, R.L., Bonham, B.H., Sinex, D.G., 2008. Acute changes in frequency responses of inferior colliculus central nucleus (ICC) neurons following progressively enlarged restricted spiral ganglion lesions. Hear. Res. 246, 59–78.

Spoendlin, H., 1985. Histopathology of noise deafness. J. Otolaryngol. 14, 282–286.

Spoendlin, H., Schrott, A., 1989. Analysis of the human auditory nerve. Hear. Res. 43, 25–38.

Stanbury, M., Rafferty, A.P., Rosenman, K., 2008. Prevalence of hearing loss and work-related noise-induced hearing loss in Michigan. J. Occup. Environ. Med. 50, 72–79.

Stevens, G., Flaxman, S., Brunskill, E., Mascarenhas, M., Mathers, C.D., Finucane, M., 2013. Global and regional hearing impairment prevalence: an analysis of 42 studies in 29 countries. Eur. J. Public. Health 23, 146–152.

Sun, W., Manohar, S., Jayaram, A., Kumaraguru, A., Fu, Q., Li, J., Allman, B., 2011. Early age conductive hearing loss causes audiogenic seizure and hyperacusis behavior. Hear. Res. 282, 178–183.

Syka, J., 2002. Plastic changes in the central auditory system after hearing loss, restoration of function, and during learning. Physiol. Rev. 82, 601–636.

Szczepaniak, W.S., Møller, A.R., 1996. Evidence of neuronal plasticity within the inferior colliculus after noise exposure: a study of evoked potentials in the rat. Electroencephalogr. Clin. Neurophysiol. 100, 158–164.

Tan, C.M., Lecluyse, W., McFerran, D., Meddis, R., 2013. Tinnitus and patterns of hearing loss. J. Assoc. Res. Otolaryngol. 14, 275–282.

Terakado, M., Kumagami, H., Takahashi, H., 2011. Distribution of glucocorticoid receptors and 11 beta-hydroxysteroid dehydrogenase isoforms in the rat inner ear. Hear. Res. 280, 148–156.

Thai-Van, H., Micheyl, C., Noreña, A., Collet, L., 2002. Local improvement in auditory frequency discrimination is associated with hearing-loss slope in subjects with cochlear damage. Brain 125, 524–537.

Thai-Van, H., Micheyl, C., Moore, B.C., Collet, L., 2003. Enhanced frequency discrimination near the hearing loss cut-off: a consequence of central auditory plasticity induced by cochlear damage? Brain 126, 2235–2245.

Turner, B.B., 1986. Tissue differences in the up-regulation of glucocorticoid-binding proteins in the rat. Endocrinology 118, 1211–1216.

Turner, J.G., 2007. Behavioral measures of tinnitus in laboratory animals. Prog. Brain Res. 166, 147–156.

Turner, J.G., Parrish, J., 2008. Gap detection methods for assessing salicylate-induced tinnitus and hyperacusis in rats. Am. J. Audiol. 17, S185–S192.

Turner, J.G., Brozoski, T.J., Bauer, C.A., Parrish, J.L., Myers, K., Hughes, L.F., Caspary, D.M., 2006. Gap detection deficits in rats with tinnitus: a potential novel screening tool. Behav. Neurosci. 120, 188–195.

Turrigiano, G.G., 1999. Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. Trends Neurosci. 22, 221–227.

Tyagarajan, S.K., Fritschy, J.M., 2010. $GABA_A$ receptors, gephyrin and homeostatic synaptic plasticity. J. Physiol. 588, 101–106.

Tyler, R.S., Conrad-Armes, D., 1983. The determination of tinnitus loudness considering the effects of recruitment. J. Speech Hear. Res. 26, 59–72.

Tzingounis, A.V., Nicoll, R.A., 2006. Arc/Arg3.1: linking gene expression to synaptic plasticity and memory. Neuron 52, 403–407.
Van Gendt, M.J., Boyen, K., de Kleine, E., Langers, D.R., Van Dijk, P., 2012. The relation between perception and brain activity in gaze-evoked tinnitus. J. Neurosci. 32, 17528–17539.
Van Laer, L., Carlsson, P.I., Ottschytsch, N., Bondeson, M.L., Konings, A., Vandevelde, A., Dieltjens, N., Fransen, E., Snyders, D., Borg, E., Raes, A., Van Camp, G., 2006. The contribution of genes involved in potassium-recycling in the inner ear to noise-induced hearing loss. Hum. Mutat. 27, 786–795.
Vogler, D.P., Robertson, D., Mulders, W.H., 2011. Hyperactivity in the ventral cochlear nucleus after cochlear trauma. J. Neurosci. 31, 6639–6645.
Wagenaar, O., Wieringa, M., Verschuure, H., 2010. A cognitive model of tinnitus and hyperacusis; a clinical tool for patient information, appeasement and assessment. Int. Tinnitus J. 16, 66–72.
Wallén, M.B., Hasson, D., Theorell, T., Canlon, B., 2012. The correlation between the hyperacusis questionnaire and uncomfortable loudness levels is dependent on emotional exhaustion. Int. J. Audiol. 51, 722–729.
Wang, H., Brozoski, T.J., Turner, J.G., Ling, L., Parrish, J.L., Hughes, L.F., Caspary, D.M., 2009. Plasticity at glycinergic synapses in dorsal cochlear nucleus of rats with behavioral evidence of tinnitus. Neuroscience 164, 747–759.
Wang, J., Ding, D., Salvi, R.J., 2002. Functional reorganization in chinchilla inferior colliculus associated with chronic and acute cochlear damage. Hear. Res. 168, 238–249.
Wang, Q., Green, S.H., 2011. Functional role of neurotrophin-3 in synapse regeneration by spiral ganglion neurons on inner hair cells after excitotoxic trauma in vitro. J. Neurosci. 31, 7938–7949.
Wang, Y., Liberman, M.C., 2002. Restraint stress and protection from acoustic injury in mice. Hear. Res. 165, 96–102.
Ward, L.M., Baumann, M., 2009. Measuring tinnitus loudness using constrained psychophysical scaling. Am. J. Audiol. 18, 119–128.
Weisz, C.J., Lehar, M., Hiel, H., Glowatzki, E., Fuchs, P.A., 2012. Synaptic transfer from outer hair cells to type II afferent fibers in the rat cochlea. J. Neurosci. 32, 9528–9536.
Weisz, N., Hartmann, T., Dohrmann, K., Schlee, W., Noreña, A., 2006. High-frequency tinnitus without hearing loss does not mean absence of deafferentation. Hear. Res. 222, 108–114.
Whiting, B., Moiseff, A., Rubio, M.E., 2009. Cochlear nucleus neurons redistribute synaptic AMPA and glycine receptors in response to monaural conductive hearing loss. Neuroscience 163, 1264–1276.
WHO, 2008. The Global Burden of Disease. World Health Organization.
Wolf, O.T., 2009. Stress and memory in humans: twelve years of progress? Brain Res. Mol. Brain Res. 1293, 142–154.
Xu, H., Kotak, V.C., Sanes, D.H., 2010. Normal hearing is required for the emergence of long-lasting inhibitory potentiation in cortex. J. Neurosci. 30, 331–341.
Yang, M., Tan, H., Yang, Q., Wang, F., Yao, H., Wei, Q., Tanguay, R.M., Wu, T., 2006. Association of hsp70 polymorphisms with risk of noise-induced hearing loss in Chinese automobile workers. Cell Stress Chaperones 11, 233–239.
Yang, S., Weiner, B.D., Zhang, L.S., Cho, S.J., Bao, S., 2011. Homeostatic plasticity drives tinnitus perception in an animal model. Proc. Natl. Acad. Sci. U. S. A. 108, 14974–14979.
Yao, X., Rarey, K.E., 1996. Localization of the mineralocorticoid receptor in rat cochlear tissue. Acta Otolaryngol. 116, 493–496.
Yates, G.K., 1991. Auditory-nerve spontaneous rates vary predictably with threshold. Hear. Res. 57, 57–62.
Yilmaz-Rastoder, E., Miyamae, T., Braun, A.E., Thiels, E., 2011. LTP- and LTD-inducing stimulations cause opposite changes in arc/arg3.1 mRNA level in hippocampal area CA1 *in vivo*. Hippocampus 21, 1290–1301.
Zacharek, M.A., Kaltenbach, J.A., Mathog, T.A., Zhang, J., 2002. Effects of cochlear ablation on noise induced hyperactivity in the hamster dorsal cochlear nucleus: implications for the origin of noise induced tinnitus. Hear. Res. 172, 137–143.
Zeng, F.G., 2013. An active loudness model suggesting tinnitus as increased central noise and hyperacusis as increased nonlinear gain. Hear. Res. 295, 172–179.
Zeng, F.G., Turner, C.W., 1991. Binaural loudness matches in unilaterally impaired listeners. Q. J. Exp. Psychol. A 43, 565–583.
Zenner, H.P., Pfister, M., Birbaumer, N., 2006. Tinnitus sensitization: sensory and psychophysiological aspects of a new pathway of acquired centralization of chronic tinnitus. Otol. Neurotol. 27, 1054–1063.
Zilberstein, Y., Liberman, M.C., Corfas, G., 2012. Inner hair cells are not required for survival of spiral ganglion neurons in the adult cochlea. J. Neurosci. 32, 405–410.
Zirke, N., Seydel, C., Arsoy, D., Klapp, B.F., Haupt, H., Szczepek, A.J., Olze, H., Goebel, G., Mazurek, B., 2013. Analysis of mental disorders in tinnitus patients performed with Composite International Diagnostic Interview. Qual. Life Res. (Epub ahead of print).
Zuccotti, A., Kuhn, S., Johnson, S.L., Franz, C., Singer, W., Hecker, D., Geisler, H.S., Köpschall, I., Rohbock, K., Gutsche, K., Dlugaiczyk, J., Schick, B., Marcotti, W., Rüttiger, L., Schimmang, T., Knipper, M., 2012. Lack of brain-derived neurotrophic factor hampers inner hair cell synapse physiology, but protects against noise-induced hearing loss. J. Neurosci. 32, 8545–8553.