Chapter 1
Historical Reflections on Current Issues in Tinnitus

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1 Introduction

Tinnitus research has acquired steady interest in the last six decades. A survey of PubMed under "tinnitus" listed a total of 7489 entries by May 6, 2011, covering clinical notes, management, and basic research. Figure 1.1 shows the number of annual entries. Before 1950, only 67 papers were listed, 2 of which dated back from 1880 (Hemming, 1880; Sexton, 1880). Since 1950, the number of tinnitus-related papers has been doubling every decade. In the 1950s, the average number of papers per year was 16; in the 1960s it increased to 34, and in the 1970s it was 50. The doubling trend followed in the 1980s, with 109 papers per year, 161 in the 1990s, and 311 in the first decade of the 21st century. The year 2010 produced 411 papers, and an extrapolation of the 155 papers for the first 4 months in 2011 suggests that the number of papers per year likely will exceed 500 for the first time. The number of basic research papers is about 15%, or about 1000 papers in the survey period.

What has this body of research contributed to our understanding of tinnitus mechanisms and treatment? This book is divided into two parts to address systematically the current issues in tinnitus research.

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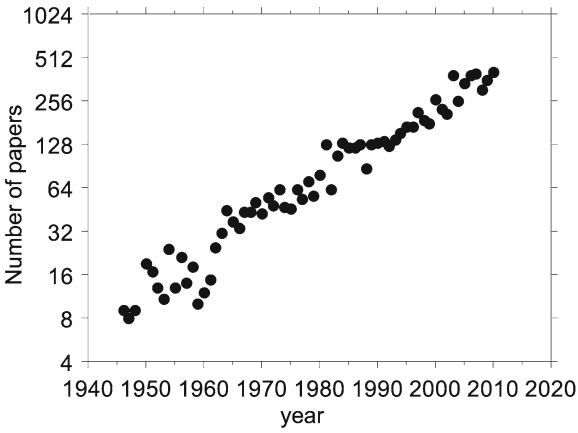

Fig. 1.1 Number of tinnitus papers cited in PubMed (as of May 6, 2011) shows an exponential increase with year published. Note vertical axis is a log scale. Exponential regression (line not plotted) shows a doubling time of 11.5 years (r^2=0.945)

The first part covers animal research. In Chapter 2, Heffner and Heffner evaluate the behavioral tests currently employed in detecting tinnitus. They describe the various conditioning procedures that are currently used, including the gap-startle reflex, and judge them against the following nine points: (1) Would the tinnitus-inducing agent used be expected to cause tinnitus in humans? (2) Would the procedure detect tinnitus in humans? (3) Has the procedure been tested by simulating tinnitus with physical sounds? (4) Would the test be affected by an accompanying hearing loss? (5) Would the test be affected by hyperacusis? (6) Can the procedure be used to determine the pitch of tinnitus? (7) Does the test give consistent results? (8) Does the procedure require group testing or can tinnitus be assessed in individual animals? (9) Can the procedure be used to follow an animal's tinnitus over time? They conclude that the startle reflex gap procedure shows the greatest promise.

In Chapter 3, Knipper, Müller, and Zimmermann discuss etiologies of tinnitus in the context of molecular changes in the peripheral auditory system, in subcortical areas, and in the auditory cortex. They frame their putative conclusions into six "hypotheses":(1) Outer hair cell (OHC) dysfunction is unlikely a primary cause of tinnitus. (2) Deafferentation of auditory fibers rather than OHC loss is a molecular correlate of tinnitus. (3) Two kinds of hyperactivity at the level of the dorsal cochlear nucleus (via sound-driven and somatosensory pathways) may differently influence higher brain areas after auditory trauma. (4) Tinnitus potentially correlates with an altered serotonergic and γ-aminobutyric-ergic (GABAergic) activity in limbic and paralimbic structures. (5) A decline in the immediate early gene *Arc/Arg3.1* could be responsible for synchronized network activity in the auditory cortex. (6) The efferent system is a likely candidate to influence hyperactivity responses in the central auditory pathways after auditory trauma.

In Chapter 4, Nouvian, Eybalin, and Puel advocate that the auditory nerve is a potential tinnitus generator through recruitment of *N*-methyl-D-aspartate (NMDA) receptors at the first auditory synapse. They discuss the salicylate and noise injury models of tinnitus from this perspective. They demonstrate that (1) cochlear NMDA

receptor activation contributes substantially to salicylate-induced tinnitus, and (2) primary auditory neuron hyperexcitability favors tinnitus occurrence. Some features resulting from the noise trauma can also be interpreted in the framework of the cochlear NMDA receptors hypothesis. Potentially, the delivery of NMDA antagonists into the cochlea constitutes a translational step to treat tinnitus resulting from sound overexposure. Although no direct proof has been reported for the involvement of transmitter release into tinnitus perception, the presynaptic active zone of inner hair cells (IHCs) would be the most appropriate structure to elicit changes in auditory fibers firing rate, thus favoring tinnitus.

In Chapter 5, Dehmel, Koehler, and Shore discuss the role of the dorsal cochlear nucleus (DCN) as an interaction node between auditory and somatosensory neural activity in inducing tinnitus. They note that noise exposure and cisplatin, but not salicylate, induce hyperactivity in the DCN. Increased spontaneous firing rate (SFR) in the DCN is observed primarily in fusiform cells, the principal output neurons of the DCN, but may also be found in the inhibitory interneurons, cartwheel cells. DCN neurons are more responsive to trigeminal stimulation after noise trauma. This altered balance between auditory nerve and somatosensory inputs could produce tinnitus as a result of increased SFRs after noise exposure in the DCN fusiform cells that show an excitatory response to trigeminal stimulation.

In Chapter 6, Robertson and Mulders address the role of the inferior colliculus (IC) in tinnitus. A common feature is that the average change in neural activity across the entire sampled population after salicylate ingestion or noise trauma in the IC is significant, but rather modest. Within the first few weeks after a cochlear trauma, IC neurons become hyperexcitable but do not yet generate their own intrinsic spontaneous firing. With longer survival times, however, IC neurons generate their own intrinsic firing and hence hyperactivity in the IC may become "centralized" and independent of input from lower stages of the pathway. They also point out that, because reciprocal connections exist between most, or perhaps all, of the structures involved, it is possible, at least in theory, that hyperactivity and abnormal firing patterns at any point in these complex reciprocal pathways can set up interdependent patterns of activity in a number of auditory centers.

In Chapter 7, Eggermont discusses the role of the auditory cortex in sound perception in general and tinnitus in particular. After reviewing findings in SFR, neural synchrony, and tonotopic map changes after salicylate ingestion and after noise trauma, he emphasizes ways to prevent those changes by using either immediate post-trauma sound stimulation or pairing sound with vagus nerve stimulation after several weeks post trauma. Eggermont echoes the remarks of Robertson and Mulders in Chapter 6: The auditory cortex is most likely a way station in the subcortical and limbic pathways involved in the perception of tinnitus. As the auditory system is an interconnected network of afferent and efferent pathways, there is likely no single locus for igniting tinnitus in the auditory system either.

The second part of the book covers research and potential therapies in humans. In Chapter 8, Melcher describes the study of tinnitus in humans by means of brain imaging to measure human brain function and structure. After examining the various techniques, from electrophysiological methods to those based on glucose and

oxygen utilization, she critically reviews the current literature, from spontaneous and stimulus-evoked activities related to tinnitus and hyperacusis to somatosensory interactions with tinnitus. She also describes resting state correlations between brain regions, as well as structural changes, that may provide a network approach to the tinnitus percept. She finally suggests that many differences in the brain imaging results obtained between different studies may potentially reflect the type of tinnitus patients studied.

In Chapter 9, Moore dissects the psychophysics of tinnitus, particularly that of pitch, loudness, and masking, including residual inhibition. He notes that several problems arise when deciding the exact method to be used for obtaining a pitch match to tinnitus. The first is to decide the ear to which the matching tone is to be presented. A second problem is selection of the level of the matching sound. A third problem arises when the matching sound itself does not have a clear pitch. He suggests that the discrepancies in mean pitch matches for tinnitus related to the audiogram's edge frequency would be largely the result of octave errors. Training to reduce octave confusions may result in lower pitches, and may increase the reliability of the pitch matches. Applying a computational loudness model, he estimates that tinnitus typically has a loudness value between 0.15 and 2 sones (~20–50 dB SPL), with a few individuals reaching values as high as 20 sones (~83 dB SPL).

In Chapter 10, Noreña emphasizes the view that tinnitus results from central changes due to sensory deprivation, which result in increased spontaneous activity or synchrony in auditory centers, or both. These central changes involve modulation of central gain, homeostatic plasticity, structural plasticity, and multimodel plasticity. As a consequence of hearing loss, these adaptive central changes may come at a price: the overall increase of neural gain may amplify the neural background activity as well and thereby induce tinnitus. Auditory stimulation has been used as a kind of "distracter" in methods such as tinnitus retraining therapy that aim to reduce the consequences of tinnitus, and in addition to reverse tinnitus-related central changes in sound therapy. For existing tinnitus, acoustic stimulation results in only modest effects, while it more significantly suppresses hyperacusis. Electrical stimulation by cochlear implants appears far superior to acoustic stimulation in reducing tinnitus. This superiority may result from the fact that it bypasses the cochlea, which could have "dead regions" that may prevent acoustic stimulation from compensating for sensory deprivation and therefore from interfering with the central causes of tinnitus.

In Chapter 11, Langguth, De Ridder, Kleinjung, and Belén Elgoyhen review the effects of transcranial magnetic stimulation (TMS), direct electrical brain stimulation, and pharmacological intervention in tinnitus patients. Though encouraging, results of repetitive TMS (rTMS) must still be considered as preliminary owing to small sample sizes, methodological heterogeneity, and high interindividual variability. Data on the effect of the duration of treatment effect are still controversial. A search is needed into the subgroups of tinnitus patients who benefit most from rTMS and how their medical histories affect the outcome. Direct electrical brain stimulation for the treatment of tinnitus is at a very early stage of development. However, there is a subgroup of patients in whom the tinnitus is completely suppressed by electrical stimulation.

There is currently no specific pharmacological compound that has been approved for the treatment of tinnitus. However, a large variety of drugs that are approved for other indications are used for the treatment of tinnitus in clinical practice. Some of these compounds have also been investigated in clinical trials. Tinnitus-related comorbidities such as depression or anxiety can especially be addressed successfully with pharmacological treatment.

The remainder of this introductory chapter not only provides a historical perspective on current issues in tinnitus research, but also looks at future directions and important questions that remain to be solved. It also sets the stage for the book by focusing on the epidemiology and etiology, on the interaction between tinnitus and hyperacusis, and on the need for a typology of subjective tinnitus. "History is the best teacher," as many of the current issues on tinnitus were already recognized in the late 19th and early 20th centuries.

2 Objective versus Subjective Tinnitus

This book is about subjective tinnitus. The distinction between objective and subjective tinnitus can best be introduced with quotes from 19th-century medical practitioners that are still applicable. Sexton (1880, p. 963) wrote in the *British Medical Journal*:

> Although not a disease in itself, tinnitus aurium is frequently a most distressing symptom of some aural affections, and not unfrequently it is the only one of which the patient is cognisant. Those ringing or buzzing sounds, synonymous with tinnitus aurium, which are heard in the head or ears under certain circumstances, arise usually from the busy circulation in the immediate neighbourhood of the auditory conductive apparatus; and, in addition to these, but heard more rarely, are also the motions of the heart, the respiratory act, the throbbing of the carotid arteries in their bony canals, and the friction of the ossicula themselves in some anomalous conditions. Moreover, the phenomena which arise from these causes are subject to an increase by the existence of aural hypercemia, chronic and acate inflammations of the ear, flushings affecting this region, probably due to vaso-motor influences, the excitement of alcohol, quinine, and anesthetics, and straining at stool or labour. When tinnitus, however, arises from these subsidiary causes, it is never permanent until certain pathological changes, to be presently mentioned, have occurred in the conductive apparatus. I shall not include among the enumerated varieties of tinnitus aurium the phenomena of autophony, sounds arising from supposed contractions of the tensor tympani muscle, or from foreign bodies present in the external auditory meatus; although from these two latter causes the most distressing kind of tinnitus results.

Sexton clearly describes mostly what is today called "objective tinnitus" and its amplification by stress-related phenomena. Hemming (1880) further differentiated tinnitus from deafness and auditory illusions:

> Tinnitus may or may not accompany the deafness frequently produced by the diseases of infantile life, mumps, whooping-cough, and the exanthemata, especially scarlatina. Cerebral disease frequently accompanies, if it do not cause, tinnitus; but in the case of insane patients it is necessary to differentiate from tinnitus the hallucinations of hearing of which they are so often the victims.

These conditions form parts of the type that we now call "subjective tinnitus." The major etiology of subjective tinnitus was already clear to Fosbroke (1831), who stated in the *Lancet* (although overlooked by PubMed) that:

> Deafness varies from a diminution of hearing, to an almost extinction of the sense, A noise in the ears, resembling either the roar of the sea, the ebullition of boiling water, or the rustling of the wind among trees, accompanied sometimes with noise in the head, exists in almost every case of deafness, to whatever cause the deafness may be owing.

Hearing loss is the most common condition under which subjective tinnitus occurs (Davis & El-Rafaie, 2000). Hereafter, "tinnitus" refers to subjective tinnitus.

What makes tinnitus audible is the fundamental question in the search for mechanisms. In 1905, Zwaardemaker, a Dutch physiologist, was the first to demonstrate that, in an acoustic chamber of his own high-quality design, normal-hearing people nearly always experience tinnitus. He describes this tinnitus (Zwaardemaker, 1910, translated by J. J. E. from the German) as:

> It is a particularly soft sound resembling wind in a forest, but much softer, more likely high [pitched] than low, with a nearly unperceivable, weak, slowly rising and falling amplitude without a clear periodicity. Besides, one also can hear a high [pitched] chirping approximately in the 6th octave.

Zwaardemaker (1905) was also able to estimate the loudness of sounds needed to mask this percept and arrived at about 38 dB SPL (based on the conversion from the presented sound energy of 68×10^{-3} erg cm^2 s^{-1}). Much later, Heller and Bergman (1953) described the generality of this rediscovered phenomenon. Moore (Chapter 9) presents an overview of psychoacoustic aspects of tinnitus, remarkably arriving at a similar value for tinnitus loudness.

3 Tinnitus Across the Life Span

Tinnitus occurs in adults as well as in children, in war veterans and factory workers, and in classical musicians, rock stars, and disc jockeys. Figure 1.2 illustrates the prevalence across the life span, in which occasional tinnitus (<5 min) is distinguished from significant tinnitus (Davis, 1989). The adult data in the significant tinnitus group are based on data from Davis and El Refaie (2000), Nondahl et al. (2002), and Shargorodsky et al. (2010). The upper curve includes also occasional tinnitus and was based on two older studies by Hinchcliffe (1961) and Leske (1981).

For normal-hearing children, the prevalence is generally based on large surveys at schools. Brunnberg et al. (2008) found the prevalence in normal-hearing children ($N = 2730$) to be 6%, similar to that for the 20- to 30-year-olds, and that for hearing impaired children ($N = 148$) at 39%. In another large study of 1100 children, normal hearing as well as hearing impaired, between 6 and 16 years (mean age 11.9 years), 34% reported tinnitus when asked while 6% spontaneously complained about it (Savastano, 2007; Savastano et al., 2009). A Brazilian study of 506 children between 5 and 12 years of age (Coelho et al., 2007) found that 37% experienced tinnitus and 19% suffered from their tinnitus. The first number corresponds with the average of

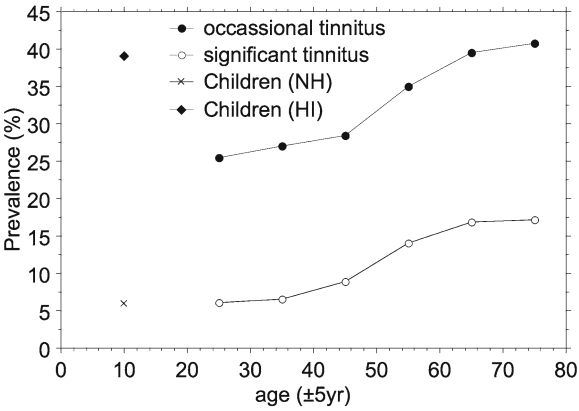

Fig. 1.2 Mean prevalence of occasional tinnitus (filled circles) and significant tinnitus (open circles) for adults. Two averages are shown for children; for those with normal hearing, NH (x) and those with hearing impairment, HI (diamonds). References are in the text

many other studies in children (e.g., Shetye & Kennedy, 2010), but the 19% of children who suffer from their tinnitus is about twice as high as the average from these other studies in children and in young adults with significant tinnitus. The percentage of children who experience tinnitus likely includes the occasional type (information not available in the references). Nonetheless the average prevalence in children with hearing impairment (39%) appears extremely high, likely reflecting a particular clinical subgroup. As these prevalence studies across the life span (Fig. 1.2) show, tinnitus is about twice as frequent in the elderly as in young adults. This increased tinnitus prevalence with age may be related to hearing loss and other age-related conditions (Hoffman & Reed, 2004).

In a discussion on the "Etiology of Tinnitus Aurium" at the annual meeting of the British Medical Association in Birmingham, July 1890, MacNaughton Jones (1890, pp.667–668) remarked that:

> Perchance as a personal sufferer in the past from two distinct varieties of tinnitus, I have taken special interest in this most troublesome symptom of affections of the ear and other organs. If for no other purpose than to elicit the views of my hearers as to the causation of tinnitus and its correlations with various morbid states of other organs founded on physiological, pathological, and clinical grounds, I am of opinion that such a discussion must be most interesting, not to the aural surgeon alone, but to every practitioner who is brought into daily contact with patients who complain of "noises in the head or ears." … I now submit to you a table of 260 cases of tinnitus aurium culled from my private casebook… The main symptoms complained of in 187 of the [260] cases were tinnitus and deafness alone; in 22 vertigo was present, and in 9 of these the typical symptoms of Ménière's affection occurred—nausea, vertigo, syncope, tinnitus, and deafness. …The following were the noises I have recorded as complained of by patients. The sound resembling buzzing; sea roaring; trees agitated; singing of kettle; bellows; bee humming; noise of shell; horse out of breath, puffing; thumping noise; continual beating; crackling sounds in the head; train; vibration of a metal; whistle of an engine; steam engine puffing; furnace blowing; constant hammering; rushing water; sea waves; drumming; rain falling; booming; railway whistling; distant thunder; chirping of birds; kettle boiling; waterfall; mill wheel; music; bells.

Unchanged since the 1800 s, hearing loss, resulting, for example, from exposure to loud noise, is considered an important risk factor for developing tinnitus.

Consequently, a history of recreational, occupational, and firearm noise exposure may all be associated with increased likelihood of acquiring tinnitus. The relation between noise exposure and significant tinnitus, however, differs depending on the presence or absence of hearing impairment. Occupational noise exposure was more likely to cause significant tinnitus in participants with hearing impairment, while leisure-time noise exposure was more associated with increased occurrence of significant tinnitus in participants without hearing impairment (Shargorodsky et al., 2010). Patients with traumatic brain injury form a new particular group with tinnitus complaints (Lew et al., 2007). Traumatic brain injury often results from blast-related injury caused by explosives that emit overpressurization shock waves or "blast waves." Because blast waves affect both gas- and fluid-filled structures (such as the middle and inner ear), they tend to be destructive to the auditory system. Tinnitus also frequently results from head and neck injury, including whiplash, and temporomandibular joint problems; all of these aberrant signals are conveyed to the dorsal cochlear nucleus by the trigeminal nerve (Dehmel et al., Chapter 5).

4 Do Animals Experience Tinnitus?

Tinnitus is generally considered to be a conscious percept (De Ridder et al., 2011), namely, people who have tinnitus are aware of it and can express to others how it sounds. Consciousness most likely has a solid neural correlate. One of the burning questions facing animal research into tinnitus must thus be: Are animals conscious of their tinnitus? According to Ward (2011) conscious percepts are thalamocortical based, thereby putting mammals firmly in possession of the putative neural substrate. But can they express the presence of their tinnitus? Behavioral test in animals generally do not rely heavily on thalamocortical activity; however, they may reflect subthalamic changes in spontaneous activity or in synaptic gain, or both. For instance, cortical ablation generally allows relearning of conditioned response and hardly affects pre-pulse (or gap) startle reflexes (Heffner and Heffner, Chapter 2; Eggermont, Chapter 7). Understandably, tests that can unambiguously indicate whether an animal perceives tinnitus are essential to advance tinnitus research.

5 The Plurality of Tinnitus

Very short (<10 s) tonal tinnitus, accompanied by fullness in the ear and transient mild hearing loss, has been experienced by nearly everyone. The underlying mechanism is not clear, but it combines three of the four symptoms that define Ménière's disease: tinnitus, fullness in the ear, and (conductive) hearing loss (the fourth one being vertigo). Transient (less than a few days) tinnitus may follow exposure to loud recreational environments such as (ice) hockey play-off games (Hodgetts & Liu, 2006), rock concerts, and the like (Saunders & Griest, 2009). The duration of this

tinnitus may reflect the temporary threshold shifts induced by the noise environment. Do these forms of reversible tinnitus result from the same mechanisms as sustained tinnitus (Eggermont, Chapter 7; Moore, Chapter 9)? Are they conditioning the increased prevalence of tinnitus in old age (Kujawa & Liberman, 2006)?

The plurality of tinnitus can also be reflected by the following questions. Is salicylate-induced tinnitus the same as noise-induced? Is pure somatic (trigeminal) tinnitus qualitatively the same as "cochlear" tinnitus? Does somatic tinnitus depend on modulation of spontaneous "normal" cochlear output? Does somatic tinnitus exist in deaf ears (Dehmel et al., Chapter 5)? Conductive hearing loss (CHL) likely induces a mild form of hyperacusis, or a gain change (Formby et al., 2003), which typically leads to increased spontaneous firing rate (SFR) in the ventral cochlear nucleus and potentially tinnitus (Sumner et al., 2005).

Because tinnitus and hyperacusis frequently co-occur in humans, one could assume that this also happens in animals. This relationship opens the possibility that behavioral tests may reflect hyperacusis (Heffner and Heffner, Chapter 2). Based on so many different etiologies (Davis & El-Rafaie, 2000; Hoffman & Reed, 2004), even for sustained tinnitus, one would expect different outcomes of clinical trials for each of the etiologies. Yet, in general, patients are grouped only on severity of tinnitus, based on one of the many tinnitus questionnaires (Newman & Sandridge, 2004). Should one be surprised that hardly any clinical trial that tests drug effects is considered significant (Langguth et al., Chapter 11)? It is noteworthy that tinnitus retraining therapy (TRT; Jastreboff, 1990) and cognitive–behavioral therapy (CBT; Hallam et al., 1984), which ameliorate the tinnitus percept and its psychological impact, are considerably more effective in handling the annoyance aspects of tinnitus than the tinnitus itself (Martinez-Devesa et al., 2010; Bauer & Brozoski, 2011).

6 Tinnitus and Hyperacusis Are Comorbid

Although tinnitus is a percept of sound in the absence of external stimulation and hyperacusis is an increased response to external stimulation, they are often comorbid. The prevalence of hyperacusis in tinnitus patients can be as high as 79% (Dauman & Bouscau-Faure, 2005). Hyperacusis occurs among others in migraine, with a prevalence between 70% and 83% during attacks and 76% between attacks (Marriage & Barnes, 1995). Jastreboff and Hazell (1993) described hyperacusis as a "manifestation of increased central gain," which may cause enhanced perception of peripheral signals. Many people with hyperacusis have "normal" audiograms, thereby excluding hyperacute thresholds as well as hearing impairment (Anari et al., 1999). Threshold measures are not sensitive, as Kujawa and Liberman (2009) demonstrated that cochlear and nervous damages can occur in the presence of normal audiometry. Hyperacusis may be accompanied by increased amplitude of distortion product otoacoustic emissions (DPOAEs) in tinnitus patients with normal hearing (Sztuka et al., 2010). Clinical conditions other than peripheral lesions also can have hyperacusis as one of the symptoms and generally share a serotonin deficiency

(Marriage & Barnes, 1995). Zimmerman et al. (Chapter 3) demonstrate an altered serotonergic and GABAergic activity in limbic and paralimbic structures.

Hyperacusis may confound imaging studies of tinnitus as the BOLD response corresponds closely to loudness (Langers et al., 2007; Melcher, Chapter 8). Sound therapy can temporarily alleviate the effects of hyperacusis (Noreña, Chapter 10). In particular, Noreña (2011) distinguished two major types of tinnitus and their interactions with hyperacusis. The first type is "ventral cochlear nucleus (VCN) tinnitus," which results from near normal SFR in the auditory nerve fibers that is enhanced by an increase in central synaptic gain, potentially already occurring in the VCN itself (Vogler et al., 2011). The gain change results from a hearing loss caused by damage of the OHCs, the normal SFR requires that the IHCs are intact. In VCN tinnitus, the cochlear output thus feeds the increased central gain mechanism (Nouvian et al., Chapter 4; Robertson & Mulders, Chapter 6). In contrast, "DCN tinnitus" results when the SFR output of the auditory nerve has been considerably reduced, likely as a result of IHC loss. The driving forces for the putative increase of SFR in DCN tinnitus potentially are the somatosensory system (trigeminal tinnitus; Dehmel et al., Chapter 5) or corticofugal activity (Luo et al., 2008). Increased gain after noise trauma likely occurs in the DCN as well (Middleton et al., 2011). Getting back to the plurality issue, is VCN tinnitus (with hyperacusis) of the same quality as tinnitus in deaf ears ("DCN tinnitus")? Hyperacusis likely does not occur in deaf ears; hence "pure" DCN tinnitus would not be comorbid with hyperacusis (Noreña, Chapter 10). It is most probable that real-life tinnitus is a mix of VCN- and DCN-driven changes in spontaneous firing rates and neural synchrony (Eggermont, Chapter 7).

7 A Common Mechanism for Tinnitus and Hyperacusis?

Tinnitus is aberrant spontaneous activity, reflected in changes in SFR, in firing pattern (bursting), or in firing synchrony. Changes therein are generally considered to be the result of a less effective inhibitory system and its main transmitters, glycine and GABA. Hyperacusis is the result of a gain change affecting stimulus-driven neural activity. Increased gain may also result from a decreased inhibition (Middleton et al., 2011; Wang et al., 2011; Zimmermann et al., Chapter 3). The main question now is how decreased inhibition sometimes causes only tinnitus or only hyperacusis, and much more often both.

It has been generally accepted that in the absence of mechanical stimulation of the hair cells, a resting depolarizing current exists in the hair cells, which is responsible for the spontaneous release of neurotransmitter. Movement of the stereocilia modulates this resting current, causing Ca^{2+} influx through voltage-gated Ca^{2+} channels and thereby evoked neurotransmitter release. However, perfusions of glutamate in the cochlea caused a reduction in tone-evoked activity without a change in spontaneous rate (Gleich et al., 1990). Thus, spontaneous and driven transmitter release in hair cells is different. α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors are activated by both normal spontaneous and driven activity, but

NMDA receptors cause the increase in SFR, such as following salicylate application (Nouvian et al., Chapter 4). Action potential–evoked neurotransmitter release from central neuron synapses also requires Ca^{2+} influx. Spontaneous vesicle fusion occurs both in the absence of action potentials and without any apparent stimulus and is hence thought to be Ca^{2+}independent. In contrast, Fredj and Burrone (2009) suggested that spontaneous release originates from a resting pool of synaptic vesicles that is normally not mobilized by neuronal activity.

GABA is the main inhibitory neurotransmitter in the adult mammalian central nervous system (CNS). Its principal action, mediated by ionotropic $GABA_A$ receptors, is to increase membrane permeability to chloride ions. This leads to a net inward flow of anions resulting in an inhibitory postsynaptic potential. This event occurs when postsynaptic $GABA_A$ receptors are activated after brief exposure to a high concentration of GABA, which is released from presynaptic vesicles. The resultant increase in membrane conductance underlies what is known as "phasic" inhibition. Low GABA concentration in the extracellular space can result in the persistent or "tonic" activation of $GABA_A$ receptors, in a manner that is temporally dissociated from phasic synaptic events. Tonic activation of $GABA_A$ receptors, which are typically located extrasynaptically, results in a persistent increase in the cell's input conductance. Thus, for a given excitatory postsynaptic current, the size and duration of the excitatory postsynaptic potential will be reduced, and the temporal and spatial window over which signal integration can occur will be narrowed, making it less likely that an action potential will be generated (Farrant & Nusser, 2005). It is thus highly likely that changes in spontaneous activity result from changes in tonic inhibition and can be independent from the stimulus-driven changes in phasic inhibition that likely determines the presence of hyperacusis. The fact that both tonic and phasic inhibition ultimately depend on the Ca^{2+} concentration in the nerve ending may couple increased SFR and hyperacusis.

8 Tinnitus as Maladaptive Plasticity in the CNS

Homeostatic mechanisms stabilize the mean firing activity of a neuron over a time period of a few days, and typically do so by scaling the efficacy of the neuron's synapses (Turrigiano, 1999). An important aspect of synaptic scaling is that the direction of change in the synaptic strength depends on both the nature of the synapse and the nature of the postsynaptic neuron. Cortical pyramidal neurons are embedded in networks with extensive recurrent excitatory and inhibitory feedback. Pyramidal-neuron firing rates reflect not only their excitatory drive, but also the balance between excitatory inputs from other pyramidal neurons and inhibitory inputs from GABAergic interneurons.

In the healthy auditory system, homeostatic plasticity could help to ensure that the working point of auditory neurons is within the right range of firing rates independent of the prevailing acoustic environment. Homeostatic plasticity in auditory

neurons might also prevent us from perceiving normal spontaneous neuronal activity as sound. Schaette and Kempter (2006, 2009) modeled the effects of homeostatic plasticity by a change in a gain factor proportional to the deviation of the mean activity from a certain target rate. In their model, homeostatic plasticity restores the mean firing rate of neurons in the DCN after hearing loss. Thus, both stimulus-driven and spontaneous mean firing rates are scaled upward to the pre-noise exposure target level. This applies to all affected neurons along the auditory pathway. Restoring the mean rate therefore likely increases the spontaneous rate throughout the auditory system. For example, Dehmel et al. (Chapter 5) show that increased efficacy of somatosensory inputs to DCN granule cells after hearing loss is potentially part of this upregulation of SFR.

Do homeostatic mechanisms as described regulate both the effects of the phasic and tonic inhibition, and thereby link them? This would then again assume comorbidity between tinnitus (spontaneous activity) and hyperacusis (stimulus-driven activity). Zimmermann et al. (Chapter 3) discuss homeostatic scaling and neural hyperactivity as well as their potential interactions with tinnitus and hyperacusis.

9 The Limbic Connection: Fear of Tinnitus?

The amygdala, the fear center of the brain, receives two inputs from the auditory system, a fast one via the auditory extralemniscal or nontonotopic pathways involve the dorsal and medial geniculate body (MGB) and a slower one via the secondary auditory cortex (LeDoux, 1991; Farb & Ledoux, 1999). The amygdala also constitutes a feedback loop via its connection to the auditory cortex. This integration of the limbic system and the thalamocortical complex is involved in the emotional aspects of tinnitus. The findings that limbic structures are more active in response to sound stimulation in some patients with tinnitus (Lockwood et al., 1998) support the involvement of the extralemniscal auditory system in tinnitus (Melcher, Chapter 8). A potentially important loop from MGB to amygdala, via the nucleus acumbens (NAc), the thalamic reticular nucleus and back to the thalamus, may function as a gate to filter out unwanted sound such as tinnitus (Rauschecker et al., 2010). This “gating” mechanism would explain why not everyone with hearing loss experiences tinnitus.

10 Are Tinnitus and Neuropathic Pain Homologues?

Early studies had already pointed to the similarity of severe tinnitus and central neuropathic pain that occurs without stimulation of pain receptors (Tonndorf, 1987; Møller, 1997). For instance, perception of auditory stimuli is often abnormal in tinnitus patients, and perception of nociceptive stimuli is often abnormal in people with central pain. Many individuals with severe tinnitus often have hyperacusis and individuals with

central pain often have hyperalgesia. The similarity between these two forms of enhanced sensitivity and excessive reaction to normal sound (hyperacusis) and normal touch (hyperalgesia) is striking. Hyperalgesia is dependent on NMDA receptor–mediated activity and the loss of inhibitory control (Dickenson, 1996). It is likely, but so far not demonstrated, that hyperacusis has the same neural correlates. Chronic pain is in part an emotion (Chapman, 1996) and tinnitus is also, in part, an emotion.

Neuropathic pain likely arises as a result of changes in the properties of neurons in the CNS or central sensitization. Several mechanisms that may cause the central sensitization of pain have been described (Milligan & Watkins, 2009). The best-characterized mechanism involves a change in the function of NMDA receptors in the spinal cord dorsal horn neurons. Activation of sensory neurons by painful stimuli leads to activation of pain-projection neurons in the spinal cord. During strong or persistent nociceptive stimulation or both, sufficient amounts of substance P and glutamate are released to sustain the depolarization of the spinal cord neurons. When this happens, Mg^{2+} ions that normally block the NMDA channel are removed, allowing Ca^{2+} to flow through the channel into the neuron. This results in the amplification of pain messages being relayed to higher brain centers. Similar changes in NMDA activation in the cochlea after salicylate application and noise trauma have been described (Nouvian et al., Chapter 4), demonstrating yet another aspect in the analogy between tinnitus and pain.

It is now generally accepted that there are specific nociceptive pathways and that these are subject to complex facilitatory and inhibitory "gate" controls. Pain is thus a reflection not simply of peripheral inputs or pathology but also of central neuronal plasticity, in which deafferentation or prior experience leads persisting changes in neuron response properties that affect perception and behavior (Latremoliere & Woolf, 2009). Central auditory system plasticity is similarly invoked as a major factor in severe tinnitus (Salvi et al., 2000; Eggermont & Roberts, 2004), as is "gate control" (Rauschecker et al., 2010; Eggermont, Chapter 7).

Phantom pain belongs to the complex group of phantom phenomena that often develop after amputations. Milder phantom phenomena involve feeling the presence of the previously amputated extremity. Pain in a nonexisting body part develops in 50%–80% of all amputees (Flor et al., 2006). Similarly, partial deafferentation of the auditory system gives rise to tinnitus with a pitch reflecting the missing inputs (tinnitus spectrum), and may therefore be termed a phantom sound (Jastreboff, 1990; Moore, Chapter 9). The concept of phantom pain fits with tinnitus resulting from noise-induced hearing loss but not easily with somatic tinnitus and normal hearing.

11 Neuroscience-Inspired Management of Tinnitus

The neural substrates of tinnitus suggest various approaches to modify neural processing and thereby change the properties of tinnitus and so obtain some alleviation of it. These approaches include neurophysiological, psychological, and pharmacological

ones. The neurophysiological-based interventions for tinnitus include substitution methods to compensate missing activity in the output of the cochlea via specially tailored acoustic environments, and via amplification of environmental sounds in the hearing frequency range, such as by hearing aids. In deaf persons the missing sounds can be applied by a cochlear implant (Noreña, Chapter 10). Other approaches in this area comprise masking or suppression of the tinnitus (Moore, Chapter 9). New approaches require direct stimulation of the auditory cortex or other brain areas. A noninvasive method that may be useful to suppress tinnitus is based on transcranial magnetic stimulation (Langguth et al., Chapter 11).

Psychological and counseling approaches may be based on neurophysiological models of tinnitus or derived from treatment paradigms for people with depression, and are not included in this book. Readers interested in this topic may reference Henry et al. (2005) and Bauer and Brozoski (2011).

Potential tinnitus-alleviating drugs are often selected from those used in treating putative transmitter imbalances in the CNS, as occurring in epilepsy, neuropathic pain, and depression. For instance, there are similarities in animal models regarding the neural mechanisms underlying epilepsy and central tinnitus (Eggermont, 2005). Anticonvulsants therefore have the potential for relieving tinnitus distress, as their mode of action is to reduce central excitation or increase inhibition or both, but so far this has not been conclusively been demonstrated (Davies, 2004; Dobie, 2004; Langguth et al., Chapter 11).

12 Future Directions

Tinnitus research is making tremendous progress in both understanding of mechanisms and development of treatment. Discussed below are some of the important questions that will likely be solved or need to be addressed.

12.1 Theoretical Modeling of Tinnitus

Modeling has already shown a quantitative role of brain plasticity in tinnitus generation. Specifically, a computational model incorporating homeostatic mechanisms can explain the increased spontaneous firing rate after hearing loss in the dorsal cochlear nucleus (Schaette & Kempter, 2006, 2008). Gain adaptation (Parra & Pearlmutter, 2007) is another model that predicts a direct link, which has now been experimentally verified, between the percept of a Zwicker tone, an auditory after image, and tinnitus (Noreña & Eggermont, 2003). Finally, Trenado et al. (2009) proposed a multiscale model of neural correlates of auditory selective attention and its role in the tinnitus decompensation. The quantitative modeling of tinnitus is likely to expand quickly in the near future.

12.2 Molecular and Cellular Mechanisms

Knipper et al. (Chapter 4) provide an excellent introduction on molecular and cellular mechanisms of tinnitus, but much needs to be learned as this aspect of tinnitus research is still in its infancy. Although many genes have been identified to cause deafness, there appears to be no clear heritability of tinnitus (Kvestad et al., 2010). Addressing molecular issues and even identifying genetic components in human tinnitus will be difficult but definitely needed.

12.3 Physiological Mechanisms

Physiological study has been the mainstay of animal tinnitus research, but its link to the noninvasive imaging and scalp-recording data in humans is still limited. For instance, the human equivalent of the triad of proposed tinnitus substrates has not been established. Magnetoencephalography (MEG) recordings only infer cortical reorganization in humans with tinnitus, while positron emission tomography (PET) scans can detect increased baseline activity in the auditory system. However, the low spatial resolution of both techniques makes determination of the affected auditory cortical areas difficult, if not impossible. High-resolution functional magnetic resonance imaging (fMRI) has the potential to define the tonotopic map and delineate the affected areas in humans with tinnitus (Formisano et al., 2003). The same linkage also needs to be established in the time domain. For instance, animal research shows clearly local neural synchrony changes associated with tinnitus. Synchrony changes in spontaneous activity in humans with tinnitus depend on the frequency bands of the electroencephalogram (EEG): Temporal cortex alpha band activity is reduced while gamma band activity is enhanced.

12.4 Psychophysical and Functional Consequences

Humans can indicate if they have hyperacusis or tinnitus or both, whereas in animals it has to be deduced from the startle reflex test, which is sensitive to both hyperacusis and tinnitus, but in an opposite way (Sun et al., 2009). Many questions remain unclear in this important area of research. How does one delineate brain changes due to tinnitus from those caused by hyperacusis and by hearing loss? Is tinnitus without hearing loss different from that accompanied by hearing loss? Does hyperacusis affect tinnitus loudness as well as annoyance? An enhanced acoustic environment can modulate hyperacusis (Noreña & Chery-Croze, 2007), but will it change the co-occurring tinnitus loudness? Recording of electrical activities from the cochlear promontory in humans is possible and may provide insight into tinnitus spectrum in terms of spontaneous activity, burst firing, and neural synchrony.

Perhaps the spectral power is related to tinnitus loudness. Finally, it is possible to observe whether promontory recording can be modulated by attention or other cortical activity.

12.5 Classification of Tinnitus

About half of tinnitus patients cannot identify a cause for their tinnitus. Tyler et al. (2008) used cluster analysis to identify four subgroups among tinnitus patients based on their symptoms: (1) constant distressing tinnitus, (2) varying tinnitus that is worse in noise, (3) tinnitus patients who can cope and whose tinnitus is not influenced by touch (somatic modulation), and (4) tinnitus patients who can cope but whose tinnitus is worse in quiet environments. For people with tinnitus, their etiologies and underlying biological substrates may be very different. At present we do not know whether there is a connection of these clusters to the etiology, nor do we know what differentiates the brains of these four classes of tinnitus. Involvement of the limbic system is likely but a definitive answer is lacking. In addition to the current use of questionnaires, it is critical to develop objective diagnostics such as the resting state brain imaging to classify tinnitus and to evaluate its treatment outcomes, without which it would be difficult to conduct meaningful clinical trials.

12.6 Treatment Options

The last two chapters in this book (Noreña, Chapter 10; Langguth et al., Chapter 11) provide short-term solutions from sound therapy to magnetic and electric stimulation and pharmaceutical treatment. A middle-term solution can be improved sound therapy that has a solid neuroscience underpinning, and may be combined with novel drug delivery and electrical stimulation techniques (e.g., Engineer et al., 2011; Zeng et al. 2011). The ultimate treatment for tinnitus caused by hearing loss will be regenerating cochlear hair cells and establishing a successful innervation with the remaining auditory nerve fibers (Brigande & Heller, 2009). It is also possible that these new hair cells release transmitter at rates different from standard IHCs, causing tinnitus as a result. Many obstacles need to be overcome before a biological means of tinnitus treatment becomes reality.

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