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Jos J. Eggermont
Fan-Gang Zeng
Arthur N. Popper
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Editors

Tinnitus

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Tinnitus

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Series Preface

November, 2011

The preface that follows is the one that we published in volume 1 of the Springer Handbook of Auditory Research (SHAR) back in 1992. Thus, 2012 marks the 20th year of SHAR. As anyone reading the original preface, or the many users of the series will note, we have far exceeded our original expectation of eight volumes. Indeed, with books published to date, and those in the pipeline, we are now set for more than 50 volumes in SHAR, and we are still open to new and exciting ideas for additional books.

We are very proud that there seems to be consensus, at least among our friends and colleagues, that SHAR has become an important and influential part of the auditory literature. While we have worked hard to develop and maintain the quality and value of SHAR, the real value of the books is very much attributable to the numerous authors who have given their time to write outstanding chapters and our many coeditors who have provided the intellectual leadership to the individual volumes. We have worked with a remarkable and wonderful group of people, many of whom have become great personal friends of both of us. We also continue to work with a spectacular group of editors at Springer - our current editor is Ann Avouris. Indeed, several of our past editors have moved on in the publishing world to become senior executives. To our delight, this includes the current president of Springer US, Dr. William Curtis.

But the truth is that the series would and could not be possible without the support of our families, and we want to take this opportunity to dedicate all of the SHAR books, past and future, to them. Our wives, Catherine Fay and Helen Popper, and our children, Michelle Popper Levit, Melissa Popper Levinsohn, Christian Fay, and Amanda Fay, have been immensely patient as we developed and worked on this series. We thank them and state, without doubt, that this series could not have happened without them.

1992

The Springer Handbook of Auditory Research presents a series of comprehensive and synthetic reviews of the fundamental topics in modern auditory research. The volumes are aimed at all individuals with interests in hearing research including advanced graduate students, post-doctoral researchers, and clinical investigators. The volumes are intended to introduce new investigators to important aspects of hearing science and to help established investigators to better understand the fundamental theories and data in fields of hearing that they may not normally follow closely.

Each volume presents a particular topic comprehensively, and each serves as a synthetic overview and guide to the literature. As such, the chapters present neither exhaustive data reviews nor original research that has not yet appeared in peer-reviewed journals. The volumes focus on topics that have developed a solid data and conceptual foundation rather than on those for which a literature is only beginning to develop. New research areas will be covered on a timely basis in the series as they begin to mature.

Each volume in the series consists of a few substantial chapters on a particular topic. In some cases, the topics will be ones of traditional interest for which there is a substantial body of data and theory, such as auditory neuroanatomy (Vol. 1) and neurophysiology (Vol. 2). Other volumes in the series deal with topics that have begun to mature more recently, such as development, plasticity, and computational models of neural processing. In many cases, the series editors are joined by a coeditor having special expertise in the topic of the volume.

Falmouth, MA, USA — Richard R. Fay
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Volume Preface

Tinnitus is a prevalent hearing disease in humans and affects 15% of the population, particularly the hearing impaired, veterans, and even young people who grow up with mp3 players and iPods. The mechanisms underlying tinnitus remain controversial. At present, there is no cure for tinnitus and treatment options are limited. Recognizing the significance of tinnitus to hearing, as well its being a window into the basic science of understanding of the hearing process, the present volume provides a broad overview of the topic. The volume focuses on neural mechanisms of tinnitus and its behavioral consequences. The book is divided into two parts to address systematically the current issues in tinnitus research.

After an opening chapter by Eggermont and Zeng that gives a historical prospective on tinnitus and its study, the first part of the book covers animal research that has led to increases in our understanding of the disease and its underlying mechanisms. In Chapter 2, Heffner and Heffner evaluate the behavioral tests for animals currently employed in understanding tinnitus. 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. This is followed by Chapter 4 by Nouvian, Eybalin, and Puel, who argue that the auditory nerve is a potential tinnitus generator through recruitment of *N*-methyl-D-aspartate receptors at the first auditory synapse. In Chapter 5, Dehmel, Koehler, and Shore discuss the role of the dorsal cochlear nucleus as an interaction node between auditory and somatosensory neural activity in inducing tinnitus. In Chapter 6, Robertson and Mulders address the role of the inferior colliculus in tinnitus. The last chapter of this section, Chapter 7, is a discussion by Eggermont of the role of the auditory cortex in sound perception in general and tinnitus in particular.

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. In Chapter 9, Moore dissects the psychophysics of tinnitus, particularly that of pitch, loudness, and masking, including residual inhibition. In Chapter 10, Noreña emphasizes the view that tinnitus results from central changes due to sensory deprivation, which result in

increased spontaneous activity and/or synchrony in auditory centers. Finally, in Chapter 11, Langguth, Ridder, Kleinjung, and Elgoyhen review the effects of transcranial magnetic stimulation, direct electrical brain stimulation, and pharmacological intervention in tinnitus patients.

As with all SHAR volumes, there are chapters in earlier volumes that relate to, and often provide background for, chapters in the current volume. The first SHAR volume, *The Auditory Pathway* (edited by Webster, Popper, and Fay, 1992) and *Integrative Functions in the Mammalian Auditory Pathway* (Vol. 15, edited by Oertel, Fay, and Popper, 2002) provide a background of auditory neuroanatomy and physiology that can help readers understand tinnitus origins and manifestations in various stages of the auditory pathway. Similarly, many of the chapters in *The Auditory Cortex* (Vol. 43, edited by Poeppel, Overath, Fay, and Popper, 2012) provide an extensive discussion of human brain imaging and function. Finally, *Auditory Prostheses: New Horizons* (Vol. 39, edited by Zeng, Popper, and Fay, 2011) shows that different sites and modes of stimulation can be explored to treat tinnitus. Specific discussions on tinnitus and related topics in SHAR include a chapter by Penner and Jastreboff in *Clinical Aspects of Hearing* (Vol. 7, edited by Van De Water, Popper, and Fay, 1996), by Bower and Brososki in *Auditory Trauma, Protection, and Repair* (Vol. 31, edited by Schacht, Popper, and Fay, 2007), and chapters by Grantham and by Kaltenbach and Manz in *Noise-Induced Hearing Loss: Scientific Advances* (Vol. 40, edited by Le Prell, Henderson, Fay, and Popper, 2011).

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Chapter 1
Historical Reflections on Current Issues in Tinnitus

Jos J. Eggermont and Fan-Gang Zeng

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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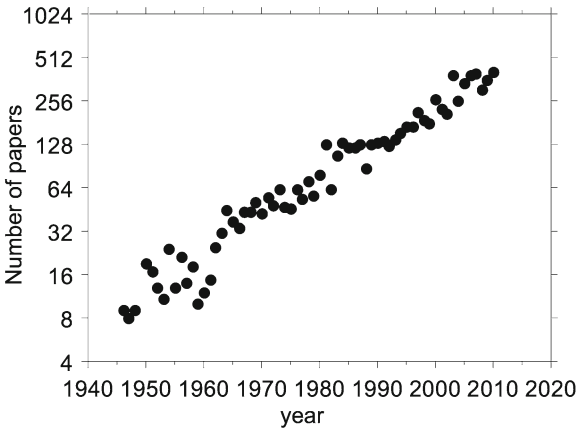

Fig. 1.1 Number of tinnitus papers cited in PubMed (as of May 6, 2011) shows an exponential increase with year published. Note vertical axis is a log scale. Exponential regression (line not plotted) shows a doubling time of 11.5 years (r^2=0.945)

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

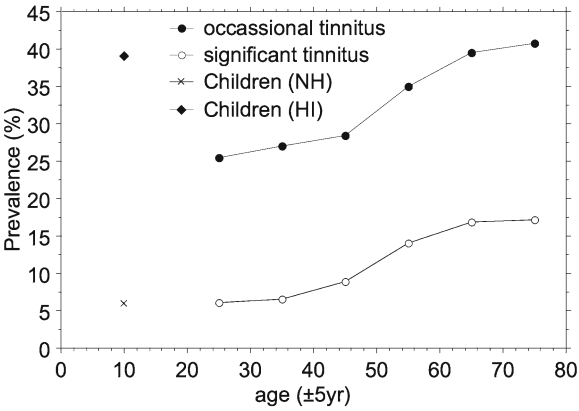

Fig. 1.2 Mean prevalence of occasional tinnitus (filled circles) and significant tinnitus (open circles) for adults. Two averages are shown for children; for those with normal hearing, NH (x) and those with hearing impairment, HI (diamonds). References are in the text

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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Chapter 2
Behavioral Tests for Tinnitus in Animals

Henry E. Heffner and Rickye S. Heffner

1 Introduction

Tinnitus refers to the perception of sound in the absence of external sound. Although this can include the perception of internal sounds, it is most often used to designate the perception of sound in the complete absence of acoustic stimulation, which is the way it is used here (e.g., McFadden, 1982; Penner & Jastreboff, 1996). Of the various causes of tinnitus, the best known are exposure to loud sound and the ingestion of large doses of ototoxic drugs, such as salicylate, which is the active ingredient of aspirin, or quinine, which is a former treatment for malaria and a current flavor component of tonic water. Interest in tinnitus has increased in recent years, aimed primarily at finding a treatment, but understanding this disorder may also give some insight into the neurological basis of the perception of sound. Because carefully controlled studies of neurological disorders are best conducted with animals, this has created a need for a way to determine if an animal has tinnitus.

Devising a behavioral test to determine whether an animal has tinnitus presents problems not encountered in routine animal psychophysics. Determining an animal's ability to detect or discriminate *physical* sounds involves training it to make a specific response in the presence of a particular sound and to make a different response, or no response at all, in the absence of that sound (e.g., Klump et al., 1995). For example, an animal can be trained to press a lever when a tone is presented and the intensity of the tone varied to determine the animal's detection threshold. Confidence that the resulting threshold is valid is obtained by demonstrating that the animal consistently presses the lever to suprathreshold intensities (has a high "hit" rate), rarely presses when no physical tone is present (has a low "false positive" rate), and that its ability to detect the tone declines sharply around

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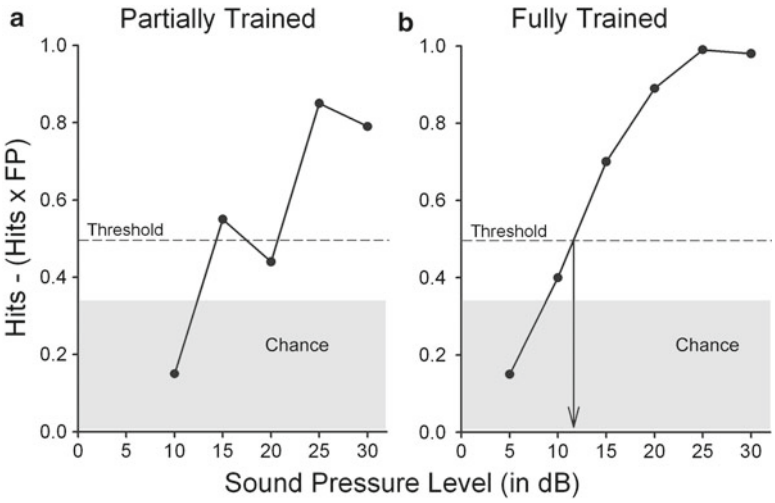

Fig. 2.1 Illustration of how an animal's psychophysical function for the detection of a sound changes with training. A score of 1.0 indicates a 100% hit rate with a 0% false positive (FP) rate; a score of 0 indicates no hits. (**a**) Performance of a partially trained animal that has not yet learned to listen to low-level sounds; its performance does not consistently change with the sound level with the result that thresholds are ambiguous. In addition, failure to achieve near perfect performance at higher levels leads to low confidence in the results. (**b**) Performance of a fully trained animal with a monotonic relation between performance and sound level with a sharp decline in performance around threshold. Several weeks of training are usually necessary for an animal to become a reliable observer. The horizontal dashed line indicates the 50% definition of threshold; the shaded area indicates chance level of performance

threshold (Fig. 2.1); it can take several weeks of training for an animal to become a reliable observer. Moreover, by conducting the tests in an environment that is free of extraneous stimuli (i.e., a sound-proof room), it is possible to demonstrate that the animal is responding to the sound being presented and that its responding is not affected by other stimuli.

However, training an animal to respond to its tinnitus presents two problems not found when working with physical stimuli. The first is inducing the tinnitus; although it is well established that loud sound and salicylate cause tinnitus in humans, there is significant variability between subjects (McFadden, 1982). Specifically, humans differ in whether a particular treatment induces tinnitus, what the characteristics of the tinnitus will be (e.g., noise-like or tonal and, if tonal, what pitch), and how long it persists. Thus, unlike the situation with physical stimuli, one cannot be certain that a treatment will induce tinnitus in an animal and what the characteristics of the tinnitus will be. The second problem is that human studies indicate that treatments used to induce tinnitus may affect hearing in other ways; for example, loud sound and ototoxic drugs can cause a hearing loss and may also cause physical sounds to be perceived as distorted (e.g., Davis et al., 1950; Cazals, 2000).

Thus, it is necessary to rule out the possibility that an animal's responding is affected by changes to its hearing other than tinnitus.

This chapter reviews the procedures that have been devised to test animals for tinnitus. Because one of the first questions about tinnitus in animals is how well it matches what we know about tinnitus in humans, this chapter begins with a brief description of tinnitus in humans caused by exposure to loud sound and salicylate, as well as other auditory effects of these treatments.

2 Human Studies

The human literature consists primarily of studies of patients with preexisting tinnitus, with a much smaller number of studies in which tinnitus was experimentally induced, typically by loud sound or salicylate (McFadden, 1982; Cazals, 2000). The studies in which tinnitus was induced are important, not only because the relation between the tinnitus-inducing agent and the resulting tinnitus can be determined, but also because these studies often include additional measurements regarding the effects of the tinnitus-inducing agent on hearing. Studies of preexisting tinnitus have been particularly important in describing the general characteristics of tinnitus, such as how it interacts with physical sounds.

2.1 Exposure to Loud Sound

A small number of studies have exposed humans to loud sound and observed the resulting tinnitus. One early study, conducted by Hallowell Davis and his colleagues (1950), is worth describing in some detail because it is often overlooked. Using themselves and Harvard students as subjects, Davis and his colleagues would expose an ear to a loud sound and observe the resulting changes in sensitivity, loudness, and pitch perception. Subjects were tested once or twice a week, with time allowed for recovery between tests, thus providing multiple observations with replication on the same subjects. In commenting on the tinnitus that accompanied the hearing loss, they noted that tinnitus resulting from exposure to a loud tone was more likely to have a "definite and constant pitch" than that resulting from exposure to broadband noise. Moreover, the pitch of the tinnitus typically occurred at the high-frequency edge of a sharply localized hearing loss, an observation suggesting that tinnitus occurs when a section of the basilar membrane is rendered partly or completely unresponsive to sound, with the pitch of the tinnitus corresponding to the less affected portion of the basilar membrane at the high-frequency end of the damaged section (the idea that tinnitus can be an "edge" effect has been noted by others, e.g., Fowler, 1941; McFadden, 1982; Moore et al., 2010). Judging from the illustrations in their report, the pitch of the tinnitus was perceived to match a tone 1–1.5 octaves above the frequency of the exposing tone. It may be noteworthy that the tinnitus was

well above the frequency of maximum hearing loss, which was about 0.5 octave above the frequency of the exposing tone.

The hearing loss that resulted from exposure to loud sound was the main focus of the Davis et al. study, and several of their findings are pertinent to understanding tinnitus and evaluating animal models. First, an individual's preexposure audiogram did not vary much and could usually be replicated within 5 dB. Second, although exposing an ear to the same loud sound on more than one occasion tended to produce the same hearing loss each time, with the maximum hearing loss occurring at the same frequency, there could be significant variation. Third, exposing different subjects to the same loud sound could produce very different hearing losses, a result that has been observed in animals (e.g., Heffner & Harrington, 2002). Because the induced tinnitus may depend on the specific hearing loss, these results suggest that there is likely to be variation in the occurrence and pitch of tinnitus in subjects exposed to the same loud sound.

Finally, Davis and his colleagues noted that exposure to loud sound produced more than a hearing loss; it also distorted the perception of physical sounds. For example, the exposure could cause a pure tone to sound "rough," "noisy," or "buzzing"; it could also cause a single tone to sound like two tones presented in combination, which they referred to as "doubles." In addition, the pitch of a tone in the exposed ear might be shifted in comparison with its pitch in the unexposed ear, a phenomenon referred to as "diplacusis." It should be noted that Davis and his colleagues reported that the hearing loss, and presumably the accompanying effects, disappeared within a few days or at most a week. Thus, they observed no permanent effects for the exposures they used, which consisted of tones of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz, as well as noise resembling aircraft noise, at intensities ranging from 110 to 130 dB sound pressure level (SPL) and durations ranging from 1 to 64 minutes (with the higher intensities presented for shorter times).

Since 1950, there have been two studies of tinnitus induced by exposure to loud sound that systematically looked at the relationship between the pitch of the resulting tinnitus, the exposing stimulus, and the hearing loss (Loeb & Smith, 1967; Atherley et al., 1968); interestingly, the authors of these studies were apparently unaware that Davis and colleagues (1950) had previously reported on tinnitus. The study by Loeb and Smith found, as had Davis et al, that the median pitch of tone-induced tinnitus was higher than both the exposing tone and the frequency of maximum hearing loss. On the other hand, Loeb and Smith found that the median pitch of tinnitus induced by exposure to octave-band noise (which was not investigated by Davis et al.) was only slightly higher than the center frequency of the stimulating noise and *below* the frequency of the maximum hearing loss (Table 2.1). All but 3 of the 86 cases studied by Loeb and Smith reported tonal tinnitus (the authors did not say which stimuli produced noise-like tinnitus).

The study by Atherley et al. exposed 57 subjects to 1/3-octave filtered noise, 51 of whom developed transient tinnitus. They found the median pitch of the tinnitus to be slightly higher than the center frequency of the exposing noise band in 43 of the 50 cases for which pitch matches were obtained, results similar to those found by Loeb and Smith for octave-band noise (Table 2.1). Again, like Loeb and Smith,

Table 2.1 Relations between frequency of the exposing sound, frequency of maximum hearing loss, and pitch of tinnitus in humans

Exposing sound	Maximum hearing loss relative to exposing sound	Pitch of tinnitus relative to	
		Exposing sound	Maximum hearing loss
Tone[a]	0.5 oct. above	1–1.5 oct. above	Not specified
Tone[b]	0.35–0.96 oct. above	1.04–1.76 oct. above	0.08–1.41 oct. above
1/3–oct. noise[c,d]	0.42–0.81 oct. above	0.12–0.58 oct. above	0.19–0.22 oct. below
1–oct. noise[b,d]	0.60–1.91 oct. above	0.04–0.61 oct. above	0.48–1.87 oct. below

[a] Davis et al., 1950.
[b] Loeb & Smith, 1967.
[c] Atherley et al., 1968.
[d] Center frequency of the noise bands used in the calculations. oct, octaves. The values are averages; there was notable individual variation in hearing loss and pitch of tinnitus

Atherley et al. found that the median pitch of the narrowband noise-induced tinnitus was below the frequency of the maximum hearing loss.

One important question on which there is conflicting evidence is whether exposing one ear to a loud sound results in tinnitus that is lateralized to that ear, to the other ear, or to both, a point not addressed in the three previously mentioned studies. Specifically, two studies reported that tinnitus is not always lateralized to the exposed ear. Theilgaard (1951) reported that of 189 exposures, tinnitus was lateralized to the unexposed ear in 33 exposures, with the remaining 156 exposures lateralized to the exposed ear. However, Thompson and Gales (1961), who exposed the ears of their 4 subjects multiple times, reported that 3 of the 4 subjects typically reported tinnitus lateralized, not to the exposed ear, but to the unexposed ear, with the remaining subject lateralizing tinnitus to one or the other ear or to both. Although the earlier report by Davis et al. (1950) did not comment on the perceived location of the tinnitus, one of the authors later stated that the tinnitus was always lateralized to the exposed ear (J. E. Hawkins, Jr., personal communication to H. Heffner, February 25, 2003). A possible explanation for these disparate results may lie in the time allowed between exposures. All three studies (Davis et al., 1950; Theilgaard, 1951; Thompson & Gales, 1961) involved exposing each ear on multiple occasions. The procedure used by Thompson and Gales involved exposing the left ear first and the right ear 1–2 hours later. In contrast, Davis and his colleagues waited at least several days between exposures (Theilgaard did not report the time between exposures). Thus, it is possible that the perception of tinnitus in the ear contralateral to the exposure might be due to the exposure reinstating tinnitus in the previously exposed ear (that tinnitus can be reinstated by a stimulus that in itself would not cause tinnitus has been suggested by Heffner [2011]).

In summary, human studies indicate that exposure to a loud sound sufficient to induce tinnitus would be expected to have the following results:

1. The exposure will produce an immediate hearing loss; if the exposure does not cause permanent damage, both the hearing loss and tinnitus will subside in a few days.

2. The tinnitus is more likely to have a definite and constant pitch if it is produced by exposure to tones or narrowband noise rather than broadband noise.
3. The exposure may affect the perception of physical stimuli, causing them to sound distorted, at least during recovery from the temporary portion of the hearing loss.
4. The median pitch of tone-induced tinnitus is higher than the frequency of the exposing tone; the median pitch of noise-induced tinnitus is usually near or slightly higher than the center frequency of the exposing noise band.
5. The median pitch of tone-induced tinnitus is higher than the frequency of the maximum hearing loss; on the other hand, the median pitch of noise-induced tinnitus is lower than the frequency of maximum hearing loss.
6. There is considerable individual variation in both the hearing loss and the pitch of the tinnitus induced by a loud sound.
7. It is likely that exposing one ear to loud sound will cause any resulting tinnitus to be lateralized to that ear, given that tinnitus has not been recently induced in the other ear.

2.2 Effect of Salicylate

In contrast to exposure to loud sound, a number of studies have examined the effect of salicylate on hearing and the auditory system (McFadden, 1982; Cazals, 2000) because salicylate, in the form of aspirin, is widely used as an analgesic and because its effects on hearing are believed to be temporary. The most noticeable effects of high doses of salicylate, usually administered orally, are tinnitus and hearing loss, both of which increase during the initial days of treatment and then level off, fluctuate, or decrease; the effects are reversible and typically disappear a few days after treatment is stopped (Cazals, 2000). The pitch of the tinnitus is usually described as a high-frequency tone or noise, although it is occasionally lower; one study found pitch matches ranging from 14.5 kHz down to 900 Hz, with the loudness of the tinnitus matched to external tones of greater than 60 dB (Day et al., 1989). The degree of hearing loss varies with the amount of salicylate, but the relationship between plasma salicylate levels and hearing loss is not perfect and there is much individual variation (Cazals, 2000). Some studies indicate that the hearing loss is equal at all frequencies whereas others have found that the loss is greater at high frequencies (cf. McCabe & Dey, 1965; Myers & Bernstein, 1965). No relationship between the pitch of the tinnitus and the hearing loss has been observed, possibly because the audiograms have not been sufficiently detailed, as they are typically conducted in octave steps, or because they did not extend into the high-frequency range above 8 kHz (McFadden, 1982). As previously mentioned, both effects are typically reversible, with the tinnitus subsiding and hearing returning to preexposure levels in 1–3 days after salicylate has been discontinued.

Besides inducing tinnitus and hearing loss, salicylate has been found to affect the perception of sound; the most prominent example is a hypersensitivity that

causes some sounds to be especially irritating, a phenomenon also referred to as hyperacusis (more on this later). Salicylate also affects other auditory functions such as frequency selectivity, temporal integration, and gap detection (Cazals, 2000).

Two final points are especially noteworthy. First, the effect of salicylate is highly variable; not only do the hearing loss and tinnitus vary between individuals with the same blood levels of salicylate, but the blood levels of salicylate among individuals given the same dosage may also differ noticeably (Cazals, 2000). Thus, animals given the same dose of salicylate would be expected to vary in their tinnitus. Second, salicylate crosses the blood–brain barrier, giving it the potential to cause tinnitus by acting directly on the central auditory system. However, elderly people with hearing loss resulting from loss of hair cells in the cochlea that encode high frequencies (presbycusis) do not develop tinnitus when given salicylate (Mongan et al., 1973; Schuknecht & Gacek, 1993). This suggests that it is the effect of salicylate on hair cells that causes tinnitus and any direct central effect of salicylate is not sufficient, although it may still play a role.

2.3 Interaction Between Tinnitus and Physical Sounds

An important question is whether tinnitus interacts with physical sounds. Over the years, there have been several reports of interactions between tinnitus and external sounds; one of the earliest and most detailed is that of R. L. Wegel (1931). Studying his own tinnitus, Wegel observed that his tinnitus interacted with external tones that were close in pitch to his tinnitus to make the sound "impure and discordant," although only at intensities close to threshold. He also observed that tones close in pitch to his tinnitus not only rendered the tinnitus inaudible, but were themselves inaudible—in other words, the tinnitus and the external tones cancelled each other out. Finally, Wegel stated that external tones could interact with his tinnitus to produce "mushy" beats.

Although other researchers have also found similar interactions between tinnitus and external tones, it is now believed that these occur only in cases in which the ear itself is generating a physical sound (McFadden, 1982; Penner & Jastreboff, 1996; Penner, 2000). Specifically, it is well established that the ear is not just a passive receiver, but that it can spontaneously generate sounds, referred to as spontaneous otoacoustic emissions (SOAEs). However, most tinnitus is not associated with SOAEs, which may account for why other researchers were unable to replicate Wegel's findings (e.g., Davis et al., 1950). Indeed, it has been emphasized that in some ways tinnitus is not like an external sound, especially when it comes to masking (McFadden, 1982; Penner & Jastreboff, 1996). For example, tinnitus can sometimes be masked by sounds that would not mask an external tone of similar pitch, and the intensity necessary to mask the tinnitus does not always relate to the tinnitus in the same way it relates to the masking of external tones.

There are, however, two well-established ways that tinnitus and external sounds do interact, although it should be noted that in both cases the external sound affects

the perception of tinnitus and not the other way around. One effect is that tones close in pitch to one's tinnitus will temporarily suppress the tinnitus, an effect that can make it difficult to match an external tone to the pitch of one's tinnitus; this is referred to as "residual inhibition" (e.g., McFadden, 1982). The other is that the intensity of a broadband noise used to mask tinnitus must be continuously increased over time to maintain the masking; this is in contrast to masking an external tone in which the level of the broadband noise remains relatively constant, and is an example of how tinnitus does not behave as does an external sound of equivalent loudness (Penner & Jastreboff, 1996).

3 Determining Auditory Sensitivity in Animals

Because the procedures for inducing tinnitus also cause a hearing loss, it is often necessary to obtain a measure of auditory sensitivity to rule out the possibility that changes in the performance of an animal after exposure to a tinnitus-inducing agent are the result of the hearing loss rather than the tinnitus. Because behavioral measures are time consuming, the threshold shifts are usually measured electrophysiologically. Thus, before describing the procedures for detecting tinnitus, it is helpful to review the correspondence between electrophysiological and behavioral measures of hearing loss.

3.1 Electrophysiological Measures of Auditory Sensitivity

The most commonly used electrophysiological measure of auditory sensitivity is the auditory brain stem response (ABR) because it is a relatively simple procedure to use. Unlike a behavioral assessment, which can take weeks or months to complete, the ABR allows an estimate of auditory sensitivity to be made on a sedated animal in a few hours. Although speed is a real advantage, it is necessary to determine if the results are sufficiently accurate for the purposes of the study.

A recent study comparing behavioral and ABR measures of threshold shift in rats exposed to loud sound found that the correspondence between the two measures depended on two factors: first, whether it was the initial threshold shift (the temporary plus permanent), or just the permanent threshold shift that was being measured; second, whether the stimulus to be detected was a tone or an octave-noise band (Heffner et al., 2008). Specifically, the tone-evoked ABR estimated the initial pure-tone threshold shifts to within ±5 dB only 11% of the time and the permanent threshold shifts 55% of the time, with large errors being common for both. Better correspondence between the ABR estimates and behavioral threshold shifts was found an octave (20- to 40-kHz) noise band, with the ABR estimating the initial threshold shifts to within ±5 dB 25% of the time and the permanent threshold shifts 89% of the time, with much smaller errors.

The finding that the ABR estimates the permanent pure-tone threshold shift to within ±5 dB about 60% of the time is not unusual, as comparisons of behavioral and evoked-potential thresholds recorded from the inferior colliculus after sensorineural damage found a similar degree of correspondence (Henderson et al., 1983; Davis & Ferraro, 1984; for a review, see Heffner et al., 2008). Although tone-evoked measurements of hearing do not give an accurate estimate of threshold shift, it may be possible to improve their accuracy by using octave noise rather than tones to evoke the ABR (Heffner et al., 2008).

4 Behavioral Procedures for Determining if Animals Have Tinnitus

There are currently eight behavioral procedures that have been used to test animals for tinnitus; they are discussed in the approximate order in which they were developed. In addition to describing the procedures, they are evaluated on the following points:

1. Would the tinnitus-inducing agent used 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. Has the procedure been used to determine the pitch of tinnitus?
7. Are the results of the procedure consistent?
8. Does the procedure require group testing or can tinnitus be assessed in individual animals?
9. Can the procedure follow an animal's tinnitus over time?

Before beginning, it should be noted that interpreting these studies is complicated by the fact that there is no standard way in which the results are presented. In some studies, a high score indicates a negative response, that is, the animal is not responding to the stimulus, which could be either an external sound or its tinnitus; in others, it means the opposite. Adding to the confusion is that a positive sign of tinnitus could be either a high or a low score, depending on whether tinnitus was induced before or after training. These factors must be kept in mind when viewing the graphical presentations of the results.

4.1 Conditioned Suppression Procedure of Jastreboff

The first behavioral test of tinnitus in animals, developed by Jastreboff and his colleagues, uses the conditioned suppression procedure (Jastreboff et al., 1988). This consists of allowing a thirsty animal to drink from a water spout in the presence of

a background sound and then suppressing its drinking when the background sound is turned off by following the "silent" interval with electric shock.The effect of tinnitus on this task depends on when the tinnitus was induced. Animals in which tinnitus is induced *after* training are expected to continue perceiving a sound (their tinnitus) when the background sound is turned off and thus be less likely to suppress their drinking during testing (when the shock is discontinued). On the other hand, animals in which tinnitus is induced *before* training come to associate their tinnitus that they hear during the silent intervals with shock and are more likely to suppress their drinking when the shock is discontinued. This basic approach has been used by several laboratories, as described in the text that follows.

4.1.1 Jastreboff and Colleagues

The behavioral procedure used by Jastreboff and his colleagues was developed to test for tinnitus in rats given salicylate (e.g., Jastreboff et al., 1988; Jastreboff & Brennan, 1994). Although the details of their method have varied somewhat, the basic procedure is as follows. A thirsty rat is placed in a test cage for two or more daily sessions and accustomed to licking a water spout to obtain water in the presence of a broadband noise. Next, it is trained to stop licking whenever the broadband noise is turned off for 60 s by presenting a brief foot shock at the end of the "noise off" or silent interval. Training consists of one or more daily sessions in which the rat is presented with five silent intervals in each session. The number of licks the animal makes during the 60 s when the background noise is turned off is compared to the number it made during the preceding 60-s sound-on interval and the animal is trained until the number of licks during the silent interval is less than 25% of the number of licks in the preceding interval. The entire training procedure requires as few as seven daily sessions, by which time the animal is reliably discriminating silence from sound (e.g., Jastreboff & Brennan, 1994). For testing, the animals are exposed to a tinnitus-inducing agent and tested for five or more sessions with each session containing five silent intervals. Note that the animals are tested "in extinction" (the shock is turned off), which means that they eventually learn to continue licking when the background noise is turned off, at which point they can no longer be tested.

The results have shown that rats given salicylate after training are more likely to continue drinking during silent intervals than control animals given saline, suggesting that the animals given salicylate develop tinnitus and thus no longer experience silence, which was associated with shock, during the noise-off intervals (Fig. 2.2). Indeed, there is a dose–response relationship such that the effect of salicylate on behavior increases as a function of dosage, suggesting that the more salicylate the more salient the tinnitus and the less likely an animal is to stop drinking when the background sound is off (Jastreboff & Brennan, 1994). On the other hand, rats given salicylate before training are less likely than control animals to continue drinking during silent intervals, suggesting that they develop tinnitus during training and came to associate it with the shock (Fig. 2.2); this would work if the background

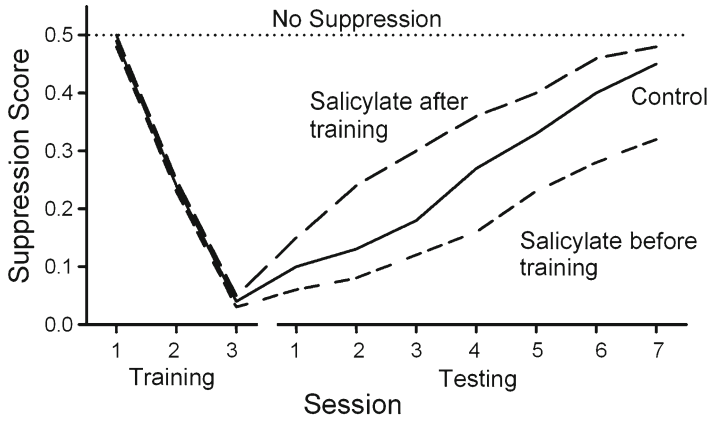

Fig. 2.2 Hypothetical example of the results using Jastreboff's conditioned suppression procedure. Rats are trained to stop drinking when a background sound is turned off by following the silent intervals with shock. The suppression score is the number of licks during the silent interval divided by the number of licks in the preceding sound interval plus the number of licks in the silent intervals, that is, During/(Pre + During). A score of 0.5 indicates no suppression whereas a score of 0.0 indicates complete suppression. During testing, the shock is turned off and the animals eventually stop suppressing. Animals given salicylate *before* training have learned to associate their tinnitus with shock and take longer than control animals to stop suppressing. Animals given salicylate *after* training generalize to their tinnitus from the background sound and take less time than control animals to stop suppressing. (After Penner & Jastreboff, 1996.)

noise masked the animals' tinnitus so that it was more apparent during the silent intervals.

To demonstrate that animals have developed tinnitus, it is necessary to rule out alternative explanations of their behavior. One of the first is the possibility that the salicylate has some general effect on behavior, such as a change in thirst, motivation, or an analgesic effect that reduced sensation of the foot shock However, these explanations are easily ruled out because giving salicylate before training has the opposite effect of giving salicylate after training; the first causes the animals to be less likely to drink whereas the second causes them to be more likely to drink when the background sound is turned off (Jastreboff et al., 1988). Thus, the results do not seem to be due to any general motivational effect of salicylate on the tendency of animals to drink or to avoid foot shock. One point that may be noted is that the animals given salicylate before training suppress more than the untreated control animals, suggesting that their tinnitus was a more effective signal for shock than was silence (Fig. 2.2); that a sound can make a more effective signal for shock than silence was supported by a test in which a 7-kHz tone was also found to be more effective than silence in causing rats to suppress their licking (Jastreboff et al., 1988).

Jastreboff and his colleagues have addressed three other questions regarding their procedure: What might be the effect of hearing loss? Would the animals be expected to generalize from the background sound to their tinnitus? Is the effect of

salicylate restricted to auditory stimuli? The impact of hearing loss was addressed by showing that reducing the SPL of the background sound by 20 dB did not cause the animals to test positive for tinnitus (Jastreboff, 1990); thus a hearing loss of up to at least 20 dB would not be expected to affect the results. That animals trained with broadband noise as a safe signal would generalize to tonal tinnitus was addressed by showing that presenting a tone when the broadband sound was turned off (i.e., simulating tinnitus) caused untreated animals to respond much as did the salicylate-treated animals (Brennan & Jastreboff, 1991: Jastreboff et al., 1988). Finally, salicylate had no effect on rats that had been trained to stop licking when a light (instead of noise) was turned off (Jastreboff et al., 1988); thus, salicylate does not have a general effect on an animal's performance, but, instead, its effect is specific to auditory tasks.

Jastreboff's procedure has also been used to estimate both the apparent loudness and the pitch of tinnitus resulting from salicylate. Apparent loudness is estimated by comparing the responses of animals given different doses of salicylate with the responses of animals given different intensities of a tone simulating tinnitus. The expectation is that the perceived loudness of tinnitus in salicylate-treated animals can be determined by matching their score (i.e., the amount they differ from the control group) to the score of the animals in the simulated tinnitus test (Jastreboff & Brennan, 1994). Thus, for example, the perceived loudness (or salience) of tinnitus in a group of animals given salicylate was considered to be 60 dB because their average score matched that of a group of untreated animals for whom a 60-dB, 10-kHz tone was turned on during the silent intervals.

The pitch of the animals' tinnitus was determined by administering salicylate to them before training so that any tinnitus they developed would be paired with shock; they were then presented with tones of different frequencies in the expectation that tones similar in pitch to their tinnitus would cause greater suppression of licking (Brennan & Jastreboff, 1991). The results showed that the suppressing effect of tones increased as their frequency was increased from 7 to 11 kHz, leading the authors to suggest that the tinnitus in rats caused by salicylate was 10 kHz or higher (Fig. 2.3). However, because the animals were not tested above 11 kHz, to determine if higher frequencies caused even less suppression, it is possible that the pitch of the tinnitus may actually be higher. The possibility that these results were affected by the hearing loss caused by salicylate, which increases with frequency (Brennan et al., 1996), was ruled out by showing that rats given salicylate after training, which would have had the same hearing loss, differed in their response to the tones from those animals given salicylate before training (Fig. 2.3).

4.1.2 Other Investigators Using Jastreboff's Procedure

Jastreboff's conditioned suppression procedure has been modified and used by other researchers, two examples of which are presented here. First, the procedure has been used with two modifications to detect tinnitus in hamsters exposed in one ear to a loud sound: avoidable shock was used, which would make it more difficult for

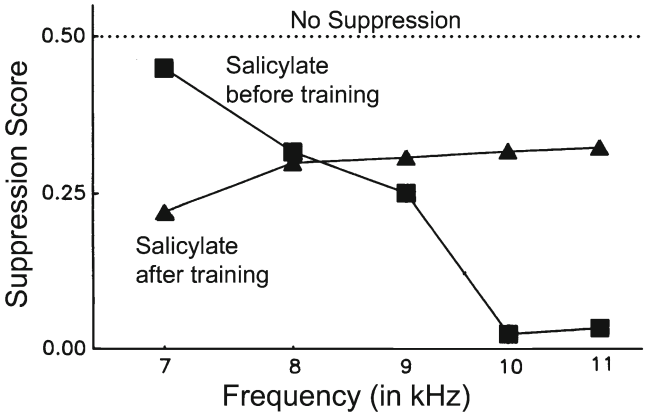

Fig. 2.3 Estimation of the pitch of tinnitus in rats given salicylate using the Jastreboff conditioned suppression procedure. Rats trained to suppress licking when a background noise was turned off were then tested by presenting a tone when the noise was turned off. Rats given salicylate before training learn to associate their tinnitus (audible during silent periods) with shock. Their suppression to 10- and 11-kHz tones suggests that those frequencies are similar in pitch to their tinnitus. Rats given salicylate after training (at the beginning of testing) associated neither their tinnitus nor the tones with shock and suppressed less to the tones. Because the animals were not tested at higher frequencies, beyond the range in which the tones had a suppressing effect, it is not known if the pitch of the tinnitus is higher than 11 kHz. See Figure 2.2 for a description of the suppression score. (Modified from Brennan & Jastreboff, 1991.)

the hamsters to learn that the shock was turned off during testing as they usually avoided the shock during training, and the hamsters were given extensive training to increase the possibility that they would respond to any tinnitus they might develop (Heffner & Harrington, 2002). The test consisted of training hamsters to discriminate silence from broadband noise and tones ranging in frequency from 8 to 24 kHz, the pitch range over which they might be expected to develop tinnitus after being exposed to the loud sound (a 124-dB, 10-kHz tone). In addition, the location of the loudspeakers through which the sounds were presented was varied because preliminary testing indicated that changing the location of the sound source would otherwise affect the animals' response—an important consideration as the animals would likely develop tinnitus only in one ear. The results of this study showed that exposure to the 10-kHz tone made the hamsters more likely to drink during silent intervals, as compared to control animals, indicating that they were hearing a sound, that is, their tinnitus. In addition, the longer the duration of the exposure to the 10-kHz tone, the higher the tinnitus score, suggesting that longer exposures made the tinnitus more salient. The hearing loss resulting from the tone exposure was not considered a factor because only one ear was exposed, leaving the other ear with normal hearing.

The conditioned suppression procedure has also been used by Zheng and his colleagues to look at the effect of various drugs on salicylate-induced tinnitus in rats (e.g., Zheng et al., 2010). They modified the procedure developed by Jastreboff in

two ways. First, because Jastreboff's results suggest that salicylate produces tinnitus similar in pitch to 10- to 11-kHz tones, they use background tones of 8–11 kHz, instead of noise, on the assumption that the animals will be more likely to generalize from the tones to their tinnitus. Second, they screen each animal by testing its response to salicylate to one or more background tones. If an animal tests negative to one tone, they try a tone of a different frequency or intensity; if no tone can be found that causes the animal to test positive for tinnitus, it is assumed not to develop tinnitus and is dropped from the study. Thus, in testing the effects of various drugs on salicylate-induced tinnitus, only animals that have previously tested positive are included in the study.

4.1.3 Conditioned Suppression Summary

In summary, Jastreboff's conditioned suppression procedure is based on training animals to discriminate the presence of a physical sound from its absence by training them to cease drinking when the sound is turned off, an event that signals impending shock (which may or may not be avoidable). The procedure can work two ways: if tinnitus is induced after training, the animals are expected to generalize to it as a safe signal and be more likely to continue drinking when the sound is turned off; if tinnitus is induced before training, the animals will associate it with shock and be less likely to drink when the sound is turned off.

Evaluating Jastreboff's conditioned suppression procedure on the nine points:

1. The tinnitus-inducing agents used with this procedure (salicylate, quinine, exposure to loud sound) would be expected to cause tinnitus in humans.
2. The procedure of having subjects report the presence or absence of sound as a way of determining if they have tinnitus would reveal tinnitus in humans.
3. The procedure has been tested by simulating tinnitus with physical sounds, showing that animals trained to respond to broadband noise will generalize to tones.
4. Hearing loss as a factor has been ruled out by showing that reducing the background sound, to similate a hearing loss, does not cause animals to test positive for tinnitus and by testing animals that have been exposed to loud sound in only one ear, which leaves them with normal hearing in the other ear.
5. Because the animals are trained to discriminate sound from silence, as opposed to responding to the quality of the sound, hyperacusis would not be expected to affect the results.
6. The procedure has been used to determine the pitch of tinnitus induced by salicylate.
7. The results are generally consistent with higher doses of salicylate and increased exposure to loud sound resulting in higher tinnitus scores.
8. Animals are tested in groups, with an untreated control group for comparison; this reduces the statistical power of such studies and requires large numbers of animals.

9. The procedure cannot be used to follow the animals' tinnitus over time because the shock is turned off (they are tested in extinction), which soon causes them to stop responding to their tinnitus.

4.2 Conditioned Avoidance Procedure of Bauer and Brozoski

The behavioral procedure devised by Bauer and Brozoski is derived from that of Brennan and Jastreboff (1991). It involves training animals to discriminate sound from silence and then presenting tones during the silent intervals with the expectation that the animals will respond differently to tones that are similar to their tinnitus than to tones that are not similar (Brozoski & Bauer, 2005, 2008). Specifically, an animal is trained to press a lever to receive food in the presence of 60-dB SPL broadband noise. Next, trials are presented in which the broadband noise is turned off for 60 s, at the end of which the animal receives foot shock. However, the shock is not delivered if the animal reduces the number of lever presses during a silent trial to a specified criterion, such as less than 25% of the number emitted during the preceding 60-s noise interval. Once the animal has learned to discriminate sound from silence, additional trials are presented in which the noise is turned off and replaced by a tone. Tones of different frequency and intensity are presented to determine the frequency at which the average performance of animals exposed to a tinnitus-inducing agent differs statistically from the average performance of unexposed control animals; the frequency at which the two groups differ is considered to match the pitch of the animals' tinnitus. Because the animals are still shocked during testing when their responding during silent trials exceeds the criterion, their response to silence does not extinguish and testing is continued indefinitely. The procedure requires carefully trained animals and can take several months for training and testing (e.g., Brozoski et al., 2007b).

As with Jastreboff's procedure, the response of an animal depends on whether it is exposed to a tinnitus-inducing agent before or after training. In the most commonly used variation, animals are exposed to the tinnitus-inducing agent before training so that any tinnitus they may develop is perceived during the silent intervals and becomes associated with shock (it is assumed that the background noise renders their tinnitus inaudible or at least less audible). Accordingly, tones that resemble an animal's tinnitus are expected to decrease lever presses, as compared to control animals with no tinnitus, although none of the tone trials is ever followed by shock. In the second variation, the animals are exposed to a tinnitus-inducing agent after training; in this case, it is believed that any tinnitus the animals develop will interact with tones similar in pitch to produce a "noisier" sensation, making it sound more like the background noise and cause the animals to be more likely to continue lever pressing than control animals.

The most common tinnitus-inducing agent used in these studies is octave noise centered at 16 kHz and applied to one ear at an intensity of 110–120 dB for an hour (e.g., Brozoski et al., 2007a). Interestingly, the animals do not test positive for tinnitus

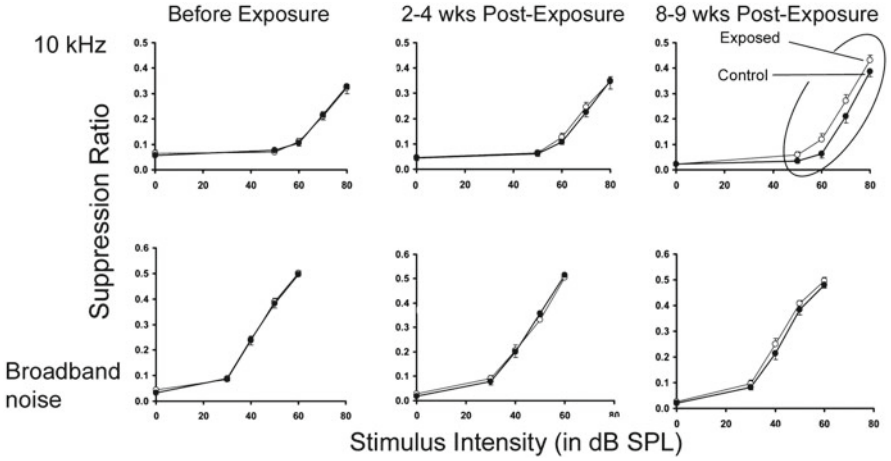

Fig. 2.4 Example of the results obtained with the Bauer and Brozoski avoidance procedure (from Turner et al., 2006). Rats were trained to stop pressing a lever for food when a background sound was turned off (i.e., silence) to avoid shock. The animals were then exposed to a loud sound (16-kHz octave noise, 116 dB, 1 hour) in one ear and tested by replacing the background sound with another sound, such as a 10-kHz tone or broadband noise. Four different intensity levels were used for each sound. Scores were calculated using the same formula as used in Figures 2.2 and 2.3. Thus, a score of 0.5 indicates no suppression of lever pressing whereas a score of 0.0 indicates complete suppression. The exposed rats showed less suppression than the control animals 8–9 weeks later when a 10-kHz tone was presented (top right panel) than when broadband noise was presented (bottom row), indicating that they developed tinnitus that was similar to the 10-kHz tone, but not to the broadband noise. Note that 0 dB actually indicates no sound (silent interval) and the rats were not shocked if their lever presses during a silent interval was less than 25% of their lever presses during the preceding background noise interval. (Modified from Turner et al., 2006.)

until weeks or months after exposure, which is interpreted as indicating that the exposure causes delayed chronic but not acute tinnitus (Fig. 2.4). Animals exposed to the 16-kHz noise have differed from control animals at 10, 16, 18, 20, 22, and 24 kHz (Bauer & Brozoski, 2001; Turner et al., 2006). Overall, 20 kHz is the most common frequency at which the exposed animals differ from the controls, leading to the conclusion that exposure to the 16-kHz octave noise band typically results in tonal tinnitus that most closely matches 20 kHz. The basis of the explanation of why exposed animals sometimes differ from controls on more than one frequency is that tinnitus of those animals might be noise-like and lack a clear tonal quality.

Hearing loss does not seem to be an explanation for the results. Although an initial study indicated that the 16-kHz octave-noise exposure caused a permanent threshold shift in the auditory brain stem response of about 60 dB for tones from 4 to 31.5 kHz, as well as for clicks (Bauer & Brozoski, 2001), later studies indicated a temporary threshold shift in the ABR with recovery to near preexposure levels over time (e.g., Brozoski et al., 2007a). In any case, exposing only one ear leaves hearing intact in the other ear and a control study in which earplugs were inserted in one ear demonstrated that a monaural hearing loss did not affect the response of animals to tones (Bauer & Brozoski, 2001).

The explanation for why the exposed animals differ from the controls on some tones has changed over the years. Initially, it was proposed that the tinnitus caused the animals to perceive the tones as louder or noisier, which would explain why animals exposed to a tinnitus-inducing agent after training would be more likely to maintain lever pressing when the background noise had been turned off and replaced by a tone (Bauer et al., 1999). However, as previously noted, there is no evidence that tinnitus in humans affects the perception of external sounds in this or any other way, although hyperacusis does. More recently, it has been proposed that the animals are likely to respond to external tones that resemble their tinnitus; that would explain why animals exposed to a tinnitus-inducing agent before training, and that then come to associate their tinnitus with shock, would be more likely to suppress to tones that are perceived to be similar to their tinnitus (Brozoski & Bauer, 2005). One way to support this interpretation would be to simulate tinnitus with an external tone to see how readily animals generalize to tones of similar frequency—this has not yet been done.

The most remarkable aspect of this research is the idea that an animal can be exposed to a sound that is too low to cause instantaneous tinnitus, but is sufficient to cause permanent tinnitus that emerges months later. Although there is no documented evidence that this occurs in humans, two lines of evidence may be offered in its support. First, it has been claimed that there are patients who, after years of exposure to loud sound, have developed tinnitus for the first time (e.g., Kaltenbach & Godfrey, 2008). However, such reports must be viewed with caution; do the patients mean that this is the first time they have ever experienced tinnitus or is it the first time their tinnitus has become persistent or distressing? The second line of evidence relies on the observation that exposure to loud sound causes an increase in spontaneous activity in the dorsal cochlear nucleus (DCN), activity that might be the source of tinnitus and that reaches a maximum a week or so after exposure (Kaltenbach & McCaslin, 1996). However, the limited behavioral evidence on this point indicates that the increased spontaneous activity in the DCN is related, not to tinnitus, but to the accompanying hearing loss (Zhang et al., 2004), possibly the result of release from inhibition in the cochlear nucleus due to hair cell damage in the cochlea; there is also evidence that the increased activity could be due to a greater sensitivity to somatic inputs to the DCN after hearing loss (Shore et al., 2008).

Another issue is whether the exposed and control groups are differing by chance. That is, what is the likelihood that two groups of animals, tested over time on half dozen different sounds, might begin to differ statistically on at least one of the sounds. This question could be answered by a control test in which one group of animals is given sham exposures to see if they eventually differ from a control group on some frequency.

Finally, the claim that exposure to the 16-kHz octave-noise results in tinnitus that does not appear until weeks or months later raises a question that has not yet been addressed. According to the Bauer/Brozoski procedure, exposing animals to a loud sound *before* initial training causes them to associate their tinnitus with shock and press a lever less than a control group when presented with a tone similar in pitch to their tinnitus. On the other hand, exposing animals to a loud sound *after* initial training implicitly trains them to use their tinnitus as a cue that it is safe to press the lever and

causes them to lever press more than the control group when presented with a tone that resembles their tinnitus (Brozoski & Bauer, 2008). However, if exposing rats to 16-kHz octave-noise (110–120 dB for an hour) results in tinnitus that does not appear until weeks later, when the animals are in the testing phase, then it would seem that that there was no tinnitus for the group that was exposed before training to associate with shock and their behavior should not differ from the group that was exposed after initial training. Furthermore, because all animals are shocked during testing when their response rate on silent trials exceeds the criterion, both groups are now receiving identical training, which might be expected to override their initial training.

Evaluating Bauer and Brozoski's conditioned avoidance procedure on the nine points:

1. The form of tinnitus being studied has not been observed in humans, as there is little evidence of exposure to loud sound causing tinnitus that does not appear until weeks after the exposure.
2. It is not known if the procedure would reveal tinnitus in humans, as there is no evidence in the human literature for tinnitus modifying the perception of physical sounds. Although it is conceivable that an external sound could be confused with tinnitus, this has not been studied.
3. The procedure has not been tested by simulating tinnitus with external sounds to determine how well animals generalize to different tones.
4. Hearing loss is eliminated as a factor by exposing only one ear to loud sound, leaving the other ear with normal hearing.
5. If exposing an ear to a loud sound makes some sounds appear "noisier," this could be explained by hyperacusis, as opposed to tinnitus interacting with the sounds.
6. The procedure has been used to determine the pitch of tinnitus.
7. The tones to which the tinnitus is pitch matched vary from study to study. Although this may be because of the variable nature of tinnitus, the possibility that the results are random variation needs to be addressed.
8. Animals are tested in groups, with an untreated control group for comparison; this reduces the statistical power of such studies and requires large numbers of animals.
9. The procedure is used to follow tinnitus over time. However, the fact that all animals are shocked during testing when their response rate to silent trials exceeds a criterion would be expected to reduce any differences in the responses to tinnitus between animals that were exposed before versus after initial training.

4.3 Conditioned Avoidance Procedure of Rüttiger

As with the previous procedures, the one devised by Rüttiger and colleagues is based on training animals to discriminate the presence of a background sound from its absence (Rüttiger et al., 2003). Their goal was to devise a procedure that required only mild deprivation (15–18 hours of water deprivation) and used avoidable, as opposed to unavoidable, foot shock (although Jastreboff's procedure can also be used with avoidable shock, e.g., Heffner & Harrington, 2002).

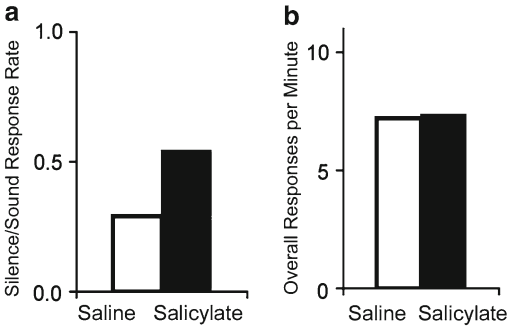

Fig. 2.5 Illustration of the results obtained by Rüttiger and colleagues using the alternation procedure in which rats stop responding when the background sound is turned off. (**a**) The ratio of activity during silent periods versus sound periods is greater in animals given salicylate (filled bar) than when they are given saline (open bar). (**b**) The overall responding per minute is not affected by salicylate (filled bar) as compared to saline (open bar), indicating that the greater response rate of the salicylate animals during silence is not due to a general increase in their response rate. (Modified from Rüttiger et al., 2003.)

Rüttiger's procedure is an alternation task in which an animal is trained to alternate between two drink tubes that dispense a 3% sucrose solution, which rats prefer to plain water. After obtaining a reward from one drink tube, the rat has to go to the other one to obtain the next reward. The animal is then trained to go to the drink tubes only when a 70-dB SPL broadband noise is on by rewarding it when the sound is on and shocking it if it licks a tube when the sound is off. The animal's performance is calculated as the ratio of its response rate during 60-s silent intervals divided by its response rate when the broadband noise is on. An animal is trained until its response rate during the silent intervals is 20% or less of its response rate during the broadband noise intervals.

Once the animal has learned to reliably perform the discrimination, it is put on a partial reward schedule in which only every second or third alternation is rewarded. This is to prevent the animal from extinguishing too quickly during tinnitus testing, which is conducted with both reward and shock turned off; that is, the animals are run in extinction. However, if the tinnitus is transient, as it is expected to be when induced by salicylate, the animals can be retrained and tested again later.

Testing for tinnitus involves comparing the response of the animals after they receive salicylate with the response of the same animals after they receive saline. Specifically, an animal is injected with either saline or salicylate and placed, 3 hours later, into the alternation box for 12–15 minutes. Sound and silent periods are presented as before, but the animal is not shocked and it receives the sucrose solution only for the first 4 minutes of the session to get it to start responding (the data from the first 4 minutes are not used). Responding more often during the silent intervals after receiving salicylate is taken as a sign that the salicylate has caused tinnitus which the rat interprets as a signal that it will be rewarded, and not shocked, for licking the drink tubes (Fig. 2.5). This procedure has been used to detect tinnitus after exposure to loud sound as well as to salicylate (Tan et al., 2007).

Potential alternative explanations of these results have been addressed in control tests (Rüttiger et al., 2003). To begin, the possibility that the results could be explained by a general effect of salicylate on activity was ruled out two ways; the first was by showing that animals given salicylate continue to respond at the same rate as untreated animals; the second was by showing that salicylate had no effect when a light, instead of a sound, was used to signal when it was appropriate to respond.

Another possible explanation is that the hearing loss caused by salicyalte could have affected these results, either by increasing or decreasing activity during silent intervals. That is, if animals are particularly fearful of the shock, a decreased ability to discriminate silent from sound intervals would cause their response rate to decrease. If, on the other hand, the animals are highly motivated to obtain the sucrose solution, their response rate after the reward is turned off might increase in what is known as an "extinction burst" (e.g., Miller, 2006). When the effect of a hearing loss was simulated in untreated rats by reducing the intensity of the broadband noise in stepwise fashion, it was found that the broadband noise could be reduced by 20 dB without significantly affecting their performance; reducing the intensity further caused their response rate during the silent intervals to decrease whereas the overall response rate of rats given salicylate is the same as when they are given saline. Thus, it appears that any reduced ability to hear the broadband noise would not be a factor in this test.

The main reason for determining the effect of reducing the intensity of the broadband noise was to estimate the perceived intensity of the animals' tinnitus. That is, by reducing the level of the broadband noise it was possible to find the intensity at which untreated rats matched the scores of the salicylate-treated animals; the estimate of the tinnitus intensity for rats given 350 mg/kg of salicylate was 28 dB SPL.

Evaluating Rüttiger's conditioned avoidance procedure on the nine points:

1. Humans given the tinnitus-inducing agents used here (salicylate and loud sound) would be expected to develop tinnitus.
2. The procedure of having subjects report the presence or absence of sound as a way of determining if they have tinnitus would also reveal tinnitus in humans.
3. The procedure has not been tested by simulating tinnitus with external sounds.
4. Hearing loss as a factor has been addressed by determining the effect of reducing the level of the broadband noise for untreated animals.
5. Because the animals are trained to discriminate sound from silence, as opposed to responding to the quality of the sound, hyperacusis would not be expected to affect the results.
6. The procedure does not indicate the pitch of the animals' tinnitus; it has, however, been used to indicate the perceived intensity of the tinnitus.
7. The results are generally consistent with previous experiments that have found evidence of tinnitus after similar doses of salicylate and exposure to loud sound.
8. The animals are used as their own controls, making it possible to assess tinnitus in individual animals, although group data are usually presented.

9. The procedure cannot be used to follow the animals' tinnitus over time because both the reward and shock are turned off (they are tested in extinction), which causes them to eventually stop responding to the sound.

4.4 Conditioned Avoidance Procedure of Guitton

Guitton and his colleagues have devised an avoidance procedure to assess rats for tinnitus in which an animal climbs a pole to avoid shock when it perceives a sound (Guitton et al., 2003). The procedure consists of placing a rat in a test box that has a grid floor and a pole; the animal is trained to climb the pole to avoid electric shock delivered through the floor whenever a 10-kHz 50-dB SPL tone is presented. Unlike the previous procedures, the shock is associated with the *presence* of sound rather than its absence. A rat is trained in 10-minute sessions in which the tone is presented 10 times and the animal required to climb the pole to avoid or escape the shock. Training is considered complete when the rat successfully avoid the shock 80% of the time or better in three consecutive sessions; more than one session can be conducted in a day, so training takes only 2–3 days. Having the animal climb a pole to avoid the shock is a novel procedure which may have been chosen to increase the response costs to the animal, thus decreasing its false-positive rate; other avoidance tasks, such as one in which an animal need only cross from one side of a cage to another to avoid shock, have the drawback in that an animal that becomes too fearful of the shock may avoid it by constantly crossing back and forth regardless of whether the sound is on.

The 10-kHz tone was chosen as the training signal because the work of Jastreboff and his colleagues has indicated that the pitch of the tinnitus caused by salicylate may be close to that frequency (although as previously noted, the pitch may be higher). Testing is conducted with the shock delivered when an animal fails to response to the tone and tinnitus is expected to increase an animal's responding during silent intervals. Injecting rats with salicylate caused the animals' average tone detection rate to decline slightly and their false positive rate to increase markedly, results that could be explained by either tinnitus, which resembles the tone that signals shock, or a hearing loss, which makes it difficult for the animal to discriminate the tone trials from the silent intervals (Fig. 2.6). However, increasing the intensity of the tone to compensate for the animals' hearing loss, as estimated by the compound action potential, prevented their detection rate from decreasing, but did not keep their false-positive rate from increasing, a result consistent with the animals having developed tinnitus to which they responded as if it were the warning tone. A control test in which the animals were trained to climb the pole when a 4-kHz tone was presented found that although salicylate reduced the animals' detection rate slightly, it did not increase their responding during silent intervals, presumably because the animals did not generalize from 4 kHz to the higher pitch of their tinnitus (although it may be noted that salicylate causes a noticeable hearing loss at 10 kHz, but little or no hearing loss at 4 kHz, Brennan et al., 1996).

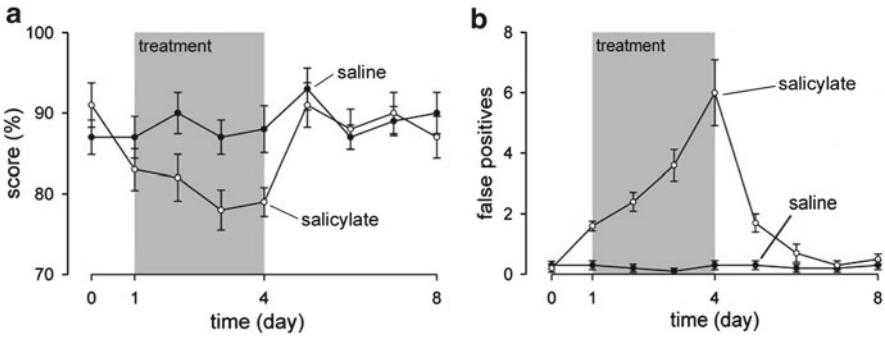

Fig. 2.6 Example of the results obtain by Guitton et al. in which rats climb a pole to avoid shock when a sound is turned on. The results show that salicylate lowers the score (**a**, hit rate), but increases the false-positive rate (**b**, responding during silence), which is interpreted to indicate that the animals perceive sound (tinnitus) during silent periods. (Modified from Guitton et al., 2003.)

Evaluating Guitton's avoidance procedure on the nine points:

1. Humans given salicylate would be expected to develop tinnitus.
2. The procedure of having subjects report the presence or absence of sound as a way of determining if they have tinnitus would reveal tinnitus in humans.
3. The procedure has not yet been tested by simulating tinnitus with different external sounds to determine how well animals generalize to different sounds. Knowing how well the animals generalize to other sounds could lend support for the interpretation that rats trained to respond to a 4-kHz tone do not test positive for tinnitus when given salicylate because it is too different in pitch from the training tone.
4. Hearing loss as a factor was addressed by showing that the results did not change when the level of the 10-kHz tone was increased to compensate for the salicylate-induced hearing loss. (It should be noted that the hearing loss was estimated with the compound action potential [CAP], an imperfect measure of behavioral hearing loss, and distortion produced otoacoustic emissions [DPOAEs], which have not been evaluated as a measure of behavioral threshold shift.)
5. Because the animals are trained to discriminate sound from silence, as opposed to responding to the quality of the sound, hyperacusis would not be expected to affect the results.
6. The procedure has not been used to indicate the pitch of an animal's tinnitus.
7. The results are generally consistent with previous experiments that have found evidence of tinnitus following similar doses of salicylate.
8. Although the procedure can reveal tinnitus in individual animals by demonstrating an increase in false-positive rate after treatment, comparisons are typically made between groups of treated and untreated control animals.
9. Because the animals receive shock on tone trials if they do not respond, the response does not extinguish and the animals' tinnitus could be followed over time.

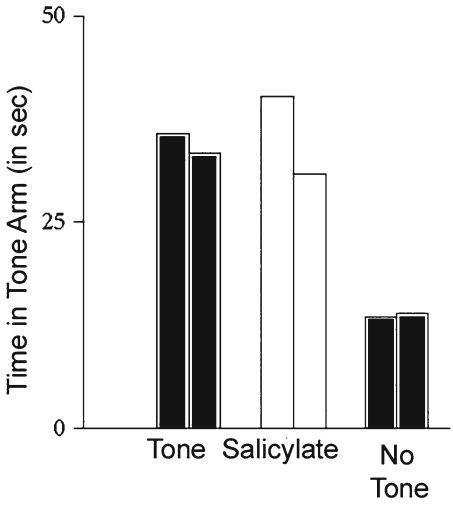

Fig. 2.7 Example of the results of the water T-maze procedure developed by Guitton and Dudai (2007). The paired bars represent the amount of time the rats spent in the "tone" arm during the first and second 50 s of testing. Salicylate caused the rats to spend more time than the control animals in the tone arm when no tone was present, indicating that they were hearing a sound (i.e., their tinnitus). (Modified from Guitton & Dudai, 2007.)

4.5 Water T-Maze Procedure of Guitton

Guitton and colleagues have also devised a two-choice procedure to test for tinnitus that consists of a water T-maze in which rats swim to the left or right side depending on whether or not they perceive a sound (Guitton & Dudai, 2007). This procedure has the advantage of not using either deprivation or electric shock; instead, rats are motivated to find a resting place in the water maze by swimming to a submerged platform. Specifically, rats are placed in the start arm of the T-maze and trained to swim to the right arm when a tone is on and to swim to the left arm when there is no tone. The training stimulus consists of a 10-kHz tone as the researchers expect that tinnitus induced by salicylate or by exposure to a 130-dB, 6-kHz tone will be similar in pitch to that frequency. The rats are trained in 3 daily sessions in which they receive 12 trials per session with the tone and no-tone trials alternated in blocks of 3; this may not be the best choice of trial presentation because an animal could ignore the sound altogether and still perform well by doing a triple alternation (the use of a Gellermann schedule would eliminate this possibility; Gellermann, 1933). In addition, water maze tests are generally conducted with a substance added to the water to make it milky (e.g., powered milk) so that the rats cannot see the submerged platform, a point not mentioned by the authors. Testing is conducted in a single trial session in which an animal is placed in the T-maze with no platform. The primary measure of an animal's performance is the amount of time it spends in each of the two arms over a period of 100 s (which is broken into the first and second 50-s intervals); the first arm chosen by the rat is also recorded, although not always considered in analyzing its performance.

The authors validate the T-maze test by demonstrating that rats given 4 days of injections of salicylate spend more time in the right (tone) arm than in the left (no-tone) arm even though no sound is presented (Fig. 2.7). Similarly, rats whose

cochleas are treated with ifenprodil, which the authors expect will block tinnitus, causes the animals to spend more time in the no-tone than in the tone arm of the maze.

Exposing rats to a 130-dB, 6-kHz tone for 15 minutes (both ears are apparently exposed to the sound) and testing them 2 weeks later, however, resulted in a more complicated situation. As expected, the authors found that rats trained in the T-maze with a 6-kHz tone did not test positive for tinnitus, presumably because any tinnitus they might have had did not match the pitch of the 6-kHz training tone. However, of the 26 animals trained with the 10-kHz tone, only 12 of them tested positive for tinnitus. The authors interpret this as indicating that not all animals develop tinnitus after exposure to loud sound. There is, however, an alternative interpretation.

Exposure to loud sound causes immediate tinnitus that declines over time. Based on what can be gleaned from Davis et al. (1950), it appears that exposures in the range used on the rats in this study may not cause either permanent hearing loss or permanent tinnitus. Similarly, a recent study that used sound exposures somewhat less than used here (110-dB, 10-minute tone exposures) found that rats stopped testing positive for tinnitus within a few days after the exposure (Heffner, 2011). Thus, it is possible that few, if any, of the rats had tinnitus by the time they were tested in the water maze two weeks after exposure. In this case, the observation that roughly half the animals went to one arm of the T and the others went to the other arm might indicate that, as a group, they were responding randomly.

Evaluating Guitton's water T-maze procedure on the nine points:

1. Humans given salicylate would be expected to develop tinnitus. However, the exposures to loud sound may not have been sufficient to produce chronic tinnitus.
2. Requiring subjects to respond left or right depending on whether they perceive a sound would reveal tinnitus in humans.
3. The procedure has not been tested by simulating tinnitus with different external sounds to determine how close in pitch a sound must be to the training sound for an animal to test positive.
4. Hearing loss would not be expected to affect results as no sound is presented during testing.
5. Because the animals are trained to discriminate sound from silence, as opposed to responding to the quality of the sound, hyperacusis would not be expected to affect the results.
6. The procedure could be used to study the pitch of tinnitus by training animals with different tones to determine which result in the highest tinnitus scores.
7. The results are generally consistent with previous experiments that have found evidence of tinnitus after similar doses of salicylate. The results of the exposure to loud sound are inconclusive.
8. Although individual animals may be tested, group data compared to an untreated control group is presented.
9. The procedure cannot be used to follow tinnitus because the animals are tested in extinction, that is, with no platform available to swim to.

4.6 Schedule-Induced-Polydipsia Avoidance Conditioning of Lobarinas

Schedule-induced-polydipsia avoidance conditioning involves training an animal to stop licking a water spout whenever it perceives a sound by shocking it if it licks when an external sound is present; thus, tinnitus is indicated when an animal treated with a tinnitus-inducing agent reduces its responding during silent intervals (Lobarinas et al., 2004). A novel aspect of this procedure is that the animals are not water deprived, but are food deprived and lick a water spout while waiting for food pellets. Because rats in this situation will consume excessive water, their behavior is referred to as polydipsia. Using a schedule of food reward to get the animals to drink (instead of depriving them of water) maintains their licking at a constant rate that does not vary with their level of thirst (although it may vary with the level of food satiation).

Specifically, a food-deprived rat is placed in a test cage and allowed to lick a water spout while food pellets are delivered at the rate of one per minute; if a rat does not spontaneously lick the spout, it is water deprived for a day or two to get it to begin drinking. For testing, a food pellet is delivered and followed by a 30-s period during which an external sound may or may not be presented; the animal is shocked if it licks in the presence of a sound, but not if there is no sound. This 30-s test period is followed by another 30-s period during which a sound is always presented and the animal shocked if it licks during that period; a food pellet is delivered at the end of this period and the next trial begins. The sounds consist of narrowband noise centered on frequencies ranging from 4 to 20 kHz to cover the presumed pitch range of tinnitus. Thus, the rats learn to lick during intervals of silence, but not during sound.

This procedure has been used to test rats for tinnitus after administration of salicylate, quinine, or loud sound (Lobarinas et al., 2006). The low incidence of licking during silence after exposure to a tinnitus-inducing agent is taken as a sign that the animals now hear a sound—their tinnitus (Fig. 2.8). Tests of unilateral exposure to 115-dB SPL narrowband noise for 2 hours were conducted on “a few rats,” the results of one were shown.

No control tests have been conducted to determine whether the procedure might be affected by an accompanying hearing loss. Because the animals are always shocked when the external sound is on, their response rate during sound trials will always be low either because they hear the sound or, if they cannot hear the sound, because they receive a shock every time they lick. Furthermore, it is conceivable that an animal that was shocked during the sound trials because of the salicylate-induced hearing loss prevented it from hearing the sound would cease licking during silent intervals. Indeed, because the animals are not licking to satisfy thirst, it would probably take very few unwarned shocks to suppress their licking. Thus, a hearing loss could cause an animal to test positive for tinnitus.

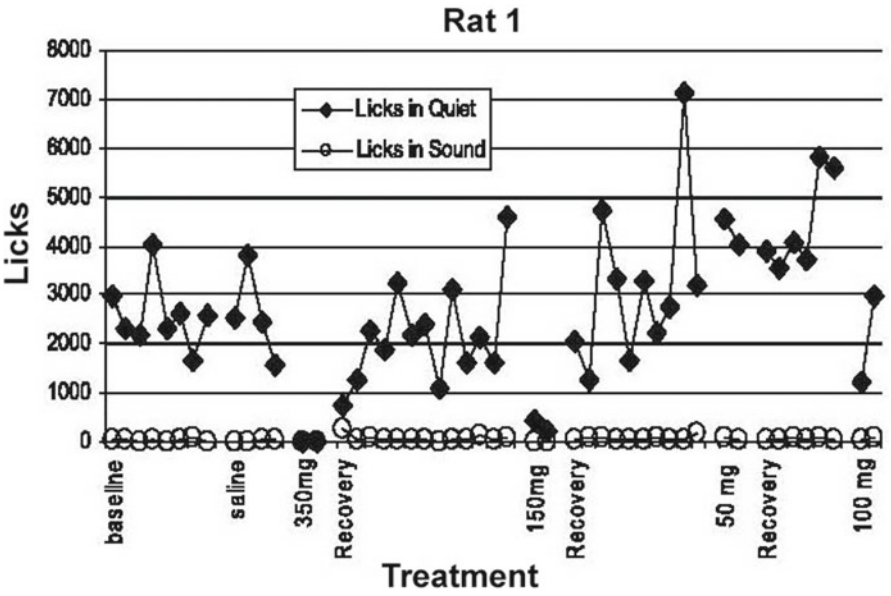

Fig. 2.8 Example of the response of one rat in the schedule-induced-polydipsia avoidance conditioning procedure of Lobarinas and colleagues. The animals were shocked if they licked a waterspout when the background sound was on (open circles). Note that the rat stopped licking during the silent intervals after receiving 350 and 150 mg of salicylate (filled diamonds), suggesting that it perceived its tinnitus as a signal for shock. A lower dose of salicylate (50 mg), like saline, had no effect on performance. (From Lobarinas et al., 2004.)

Evaluating the polydipsia procedure on the nine points:

1. Humans given the tinnitus-inducing agents used here (salicylate and loud sound) would be expected to develop tinnitus.
2. The procedure of having subjects report the presence or absence of sound as a way of determining if they have tinnitus would also reveal tinnitus in humans.
3. The procedure has not been tested by simulating tinnitus with different external sounds.
4. Hearing loss has not been ruled out as a possible confound and, indeed, it is expected that a hearing loss would cause animals to test positive for tinnitus.
5. Because the animals are trained to discriminate sound from silence, as opposed to responding to the quality of the sound, hyperacusis would not be expected to affect the results.
6. The procedure has not been used to determine the pitch of tinnitus.
7. The results are generally consistent with previous experiments that have found evidence of tinnitus after similar doses of salicylate and exposure to the level of loud sound that was used.
8. The test can be conducted on individual animals as well as on groups.
9. The procedure has been used to follow tinnitus over time.

4.7 Startle Reflex Inhibition Procedure of Turner

The startle reflex inhibition procedure involves reducing an animal's startle response to a sudden, loud sound by presenting another stimulus just before the startle sound is presented. A reduction in the amplitude of the startle response when it is preceded by the stimulus indicates that the animal perceived that stimulus. A common use of this procedure has been to determine the audibility of sounds by observing if they reduce the startle reflex. However, to test for tinnitus, the startle stimulus is preceded by a brief gap in a background sound with the idea that an animal's tinnitus will make the gap less salient and therefore less effective in reducing the startle response. Moreover, the degree to which an animal's tinnitus affects gap detection is expected to depend on its similarity to the sound in which the gap is imbedded. In addition to testing for tinnitus, the startle reflex by itself has been used to determine hyperacusis because it is believed that hyperacusis will increase the size of the startle reflex.

4.7.1 Gap Detection Test for Tinnitus

Thresholds for detecting gaps in sound are a common measure of the temporal resolution of the auditory system and have been used in studies of the effects of auditory trauma on hearing. When it was found that exposing rats to loud sound increases their gap detection thresholds, it was suggested that this might be because the exposure caused tinnitus that masked the gaps, making them more difficult to detect (Rybalko & Syka, 2005). The next step was to use gap detection to determine if an animal has tinnitus and, if so, the pitch of the tinnitus (Turner et al., 2006). The hypothesis is that when an animal's tinnitus is similar in quality to the sound in which the gap occurs, it will fill in or otherwise interfere with the animal's ability to detect the gap (Turner & Parrish, 2008). Thus, tinnitus is detected by determining an animal's ability to detect gaps in tones and narrowband noise.

In the startle reflex inhibition tinnitus test, an animal is placed in a test cage in which a low-level background sound is playing, such as 60-dB SPL narrowband noise. A startle sound (e.g., 115-dB SPL, 20-ms broadband noise burst) is presented at random intervals and the animal's startle response is measured by a strain gauge attached to the test cage. The startle sound is either presented alone or is preceded by a gap in the background sound, typically a 50-ms gap beginning 100 ms before the startle stimulus. A reduction in the average startle response that is caused by preceding the startle sound with a gap is used to indicate that the animal perceived the gap (Fig. 2.9).

The pitch of an animal's tinnitus is estimated by presenting gaps in background sounds that differ in frequency. Although pure tones are occasionally used, most studies have used narrowband noise (e.g., narrowband noise with a bandwidth of 1 kHz centered at 4, 8, 10, 16, 24, and 32 kHz), as well as broadband noise, because tinnitus is often described as an impure tone or a tone embedded in narrowband noise (McFadden, 1982). The degree to which gaps in the background sounds reduce

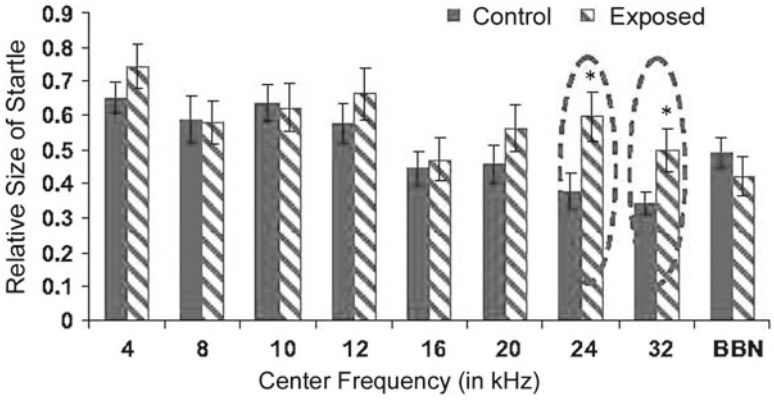

Fig. 2.9 Example of the gap startle reflex inhibition procedure for detecting tinnitus in rats. The bars show the size of the startle reflex relative to the unmodified startle when the startle sound is preceded by a 50-ms gap in the background sound. Background sounds were 1-kHz band noise centered at frequencies from 4-32 kHz, as well as broadband noise (BBN). Solid bars are the results of the control animals; diagonal stripped bars are the results of animals that were exposed in one ear to octave band noise (116 dB, with a peak at 17 kHz). Note that the gaps in the 24- and 32-kHz noise bands were less effective in reducing the size of the startle reflex in the rats given salicylate, suggesting that the animals had tinnitus in the pitch range that made the gaps less salient; the differences between the two groups did not emerge until 16 weeks after exposure. (Modified from Wang et al., 2009.)

the startle reflex can be determined both before and after exposing an animal to a tinnitus-inducing agent; a decrease in the effectiveness of the gap in a particular background sound is believed to indicate that the pitch of an animal's tinnitus is similar to that sound. Thus, for example, a decrease in the effectiveness of a gap in a 10-kHz background sound would indicate tinnitus with a pitch of 10-kHz whereas a decrease in the effectiveness of a gap in broadband noise would indicate that the perceived tinnitus was noise-like (Fig. 2.9).

The startle reflex gap detection task has several advantages (Turner & Parrish, 2008). First, it does not require food or water deprivation or the use of shock. Second, because the animals do not have to learn anything, there is no memory or complex motor component. Third, startle trials may be given at a rate of several per minute with the result that the entire test can be conducted on an animal in less than an hour. Finally, by testing an animal before and after exposure to a tinnitus-inducing agent, it is possible to use each animal as its own control, although, in practice, the performances of animals are usually considered in groups rather than individually.

There are five issues regarding the validity of the startle reflex gap detection task as a measure of tinnitus. The first is whether the procedure would detect tinnitus in humans. As mentioned earlier in this chapter, there are examples in which the perception of one's tinnitus is affected by external sounds, such as the suppression of tinnitus, but there are no known examples in which tinnitus affects the perception of

physical sounds. Although the use of the gap procedure is being investigated in humans, no definitive results have yet been reported (e.g., Hébert et al., 2010).

The second issue is whether the gap detection procedure would be affected by the hearing loss that typically accompanies induced tinnitus. In humans, salicylate is known to increase gap detection thresholds at low SPLs and increasing the sound level to compensate for the hearing loss is necessary to bring the thresholds back to pretreatment levels (McFadden et al., 1984). Similarly, a study using startle reflex inhibition to study the effect of salicylate on gap detection thresholds in rats found that the SPL of the noise in which the gap was embedded had to be increased by 20 dB to bring the rats' performances up to pretreatment levels (Deng et al., 2010). However, the issue of hearing loss in tinnitus studies has been addressed by demonstrating that the audibility of the background sounds in which the gaps are embedded is not affected by salicylate; this is done by using the sounds themselves as prepulse stimuli, that is, presenting a 100-ms burst of the noise, instead of a gap in the noise, before the startle stimulus (Ralli et al., 2010). A more direct approach to the potential effect of hearing loss on the gap procedure would be to determine behaviorally the absolute thresholds of the animals under test and then increase the SPL of the background sound to compensate for the hearing loss caused by the treatment; this, however, has not yet been done.

The third issue is how closely an animal's tinnitus must match the sound in which the gap is imbedded to interfere with its detectability. This question can be approached by determining the ability of physical sounds of various frequencies to degrade gap detection. However, no reports of simulated tinnitus have yet been published for this procedure.

Fourth, the main source of validation of the gap detection procedure comes from two studies that compared its results with those of other tinnitus procedures. The first study compared the gap detection procedure with the avoidance procedure developed by Bauer and Brozoski by testing rats that had been exposed to 16-kHz octave noise at 116 dB for 1 hour (Turner et al., 2006). Testing exposed and control rats on broadband noise and a variety of tones, the avoidance procedure showed a difference between the two groups that emerged after 8–9 weeks on the 10-kHz tone, but not on broadband noise; these results were taken as a sign of tinnitus with a pitch of about 10 kHz. (Although the animals were said to have been tested on other tones, neither the number of tones used nor the results were given). Subsequent testing on the same animals was conducted with the startle reflex gap detection test using three background sounds: the same broadband noise as in the avoidance procedure and two 1-kHz narrow noise bands, one centered at 10 kHz, the other at 16 kHz. The results of the gap detection task showed that the exposed and control groups differed only on the 10-kHz narrowband noise, which, in conjunction with the results of the avoidance conditioning procedure at 10 kHz, was taken as evidence that both procedures were detecting tinnitus that had a pitch of around 10 kHz.

Although the correspondence between the gap detection and the avoidance procedures is noteworthy, questions remain. First, as previously noted, there is no documented evidence in the literature on human studies that exposing a person to a

sound that does not immediately produce tinnitus will result in chronic tinnitus that appears months later. Second, although the authors state that the 16-kHz stimulus they used to induce tinnitus routinely produces signs of tinnitus at 10 kHz, a survey of the literature indicates otherwise; indeed, studies conducted both before and after this one have found signs of tinnitus not at 10 kHz, but at 20 kHz (e.g., Brozoski & Bauer, 2005; Brozoski et al., 2007a,b; Brozoski & Bauer, 2008). Finally, the reported probabilities for the differences between the exposed and control groups for the gap detection and the avoidance procedures were close to the standard $p = .05$ used to reject the null hypothesis ($p = .036$ and .03, respectively) and, although the animals were tested on multiple sounds, it is not stated whether the appropriate statistical corrections necessary for making multiple comparisons were made (e.g., Abdi, 2007). Thus, the results of this study are supportive but not conclusive.

The second comparison of methods was between the gap detection and polydipsia avoidance procedures in which rats were tested before and after being given salicylate (Yang et al., 2007). In the first part of the study, one group of rats was tested using the polydipsia procedure while a different group of animals was tested with the gap procedure. The polydipsia avoidance procedure found that salicylate significantly decreased the animals' licking during periods of no external sound, a result interpreted as indicating tinnitus. The gap detection procedure found that the salicylate reduce the effectiveness of a gap in 16-kHz narrowband noise to reduce the startle reflex, but not gaps in 6- or 12-kHz narrowband noise, which was interpreted as indicating tinnitus with a pitch of around 16 kHz. Thus, both procedures found evidence of tinnitus in rats given the same dose of salicylate. In the second part of the study, four rats were tested using both procedures. The results of this part of the study, shown for one rat, also indicated that salicylate caused tinnitus, with the gap procedure again indicating tinnitus at 16 kHz; although the results of the other three rats were said to be similar, it would have instilled more confidence if those results had also been shown.

Finally, because the gap detection procedure is used to determine the pitch of an animal's tinnitus, it is of interest to compare the results of the various gap detection studies of salicylate with each other as well as with those of other procedures.As previously noted, Jastreboff and his colleagues placed the pitch of tinnitus caused by salicylate at 10 kHz, although it might be higher (Jastreboff & Sasaki, 1994). In comparison, two of the gap detection studies have placed the pitch of salicylate-induced tinnitus at 16 kHz (Yang et al., 2007; Ralli et al., 2010). However, the results of a third gap detection study suggested that salicylate-induced tinnitus was noise like (Turner & Parrish, 2008); specifically, they found that salicylate reduced the effectiveness of gaps in broadband noise, but not in 1-kHz narrowband noise ranging in center frequency from 4 to 32 kHz. As the authors noted, the effect of salicylate is variable and salicylate is known to produce noise-like tinnitus in humans (McFadden, 1982); while true, this means that virtually any outcome of this test can be taken to indicate that it is a test of tinnitus, and any support it provides for a hypothesis is accordingly weakened. Equally interesting was Turner and Parrish's finding that salicylate enhanced the effect of the gaps in the narrowband noises; that is, contrary to previous findings, salicylate caused these gaps to be *more*

effective in reducing the startle response, a result the authors suggest may be a sign of hyperacusis (see later).

Because of its relative ease of use, and the ability to obtain results in as little as a day, the gap detection procedure is becoming widely used, thus making its validation especially urgent (e.g., Engineer et al., 2011; Holt et al., 2010).

Evaluating the gap startle reflex inhibition procedure on the nine points:

1. Humans given salicylate would be expected to develop tinnitus. On the other hand, there is no documented evidence that exposure to loud sound causes tinnitus that does not appear until weeks after the exposure.
2. There is little evidence that tinnitus affects the perception of physical sounds and the possibility that it affects the detection of gaps has not yet been established.
3. This procedure has not been tested with simulated tinnitus to indicate how close in pitch a sound must be before it affects gap detection.
4. Hearing loss may be a factor as salicylate affects gap detection thresholds at low intensities.
5. The startle reflex may be affected by hyperacusis (see later).
6. The procedure has been used to determine the pitch of tinnitus.
7. The pitch of tinnitus after the noise exposure and treatment with salicylate has varied between studies.
8. Animals can be used as their own controls, making it possible to test individual animals.
9. The procedure is designed to follow the animals' tinnitus over time.

4.7.2 Hyperacusis and the Startle Reflex

As noted earlier in this chapter, both salicylate and exposure to loud sound can cause hyperacusis, an oversensitivity to certain sounds making them irritating and unpleasant. Indeed, sounds, especially abrupt sounds (transients) that previously caused no problems are described as clanking, penetrating, aversive, and painfully loud (R. S. Heffner, personal observations). Recently, it has been found that salicylate has at least two effects that may contribute to hyperacusis. First, salicylate increases the amplitude of sound-evoked potentials in auditory cortex (Sun et al., 2009), suggesting that it may make sounds more salient. Second, salicylate increases the amplitude of the startle response to sound (Ison et al., 2007), suggesting, again, that it makes sound more salient. Indeed, hyperacusis was used to explain why one study found that gaps in narrowband noise became more (rather than less) effective in reducing the startle reflex in rats after they were given salicylate (Turner & Parrish, 2008).

Although the evidence that salicylate increases the startle response to sounds by causing hyperacusis is persuasive, there is at least one question that remains to be addressed. Specifically, it is necessary to rule out the possibility that salicylate causes a *general* increase in startle to all stimuli, auditory and nonauditory. This can be done by determining whether salicylate increases the startle response to a nonauditory stimulus such as foot shock, and by determining the inhibitory effect of

nonauditory pre-pulse stimuli such as a flash of light. Thus, we do not yet know if the effect of salicylate on the startle reflex is a general increase in reactivity or is specific to auditory stimuli.

4.8 Sound Localization Procedure of Heffner

The sound localization procedure devised by Heffner and colleagues is based on the idea that exposing one ear to a loud sound will cause tinnitus in that ear and that an animal trained to report whether a sound came from its left or right side will respond, in the absence of a physical sound, as though it perceives a sound (tinnitus) on the side of the exposed ear (Heffner & Koay, 2005; Heffner, 2011). In this test, an animal is trained on a sound localization task to make a left or right response to sounds coming from its left or right side, respectively; correct responses are rewarded with water whereas incorrect responses are shocked. Silent trials, in which no sound is presented, are interspersed among the sound trials; the animal receives neither reward nor punishment for its responses on these trials and its side preference on the silent trials is determined. At this point, feedback on the sound trials is changed so that, randomly, only half of the sound trials are followed by reward or punishment to reduce the possibility that an animal will notice that responses to silent trials are never rewarded or punished.

The animal is then exposed to a loud sound in the ear opposite its side preference on the silent trials and tested to see if it shifts its responding on those trials to the side of the exposed ear; doing so would indicate that the animal perceives a sound (tinnitus) that is lateralized to that side (Fig. 2.10). This is conceptually equivalent to human patients reporting the ear in which they hear their tinnitus. Besides being able to indicate whether an individual animal has lateralized tinnitus, the two-choice procedure would not be expected to be confounded by the hearing loss that accompanies exposure to loud sound, an expectation that has been verified by demonstrating that a conductive hearing loss caused by plugging one ear does not cause a shift in responding on silent trials (Heffner & Koay, 2005). Moreover, because the animals are never given feedback on the silent trials, and their responses on sound trials are given feedback only half of the time, their responding to their tinnitus may not habituate, making it possible to follow the time course of the tinnitus. A key assumption is that exposing an ear to a loud sound will induce tinnitus that is lateralized to that ear—that the tinnitus will neither be lateralized to the *un*exposed ear nor be bilateral (for a discussion of the human evidence on this point, see Section 2.1 of this chapter).

Rats were tested after exposure to tones ranging in frequency from 1 kHz to 45 kHz at 110 dB for 10 minutes with the finding that many of them tested positive for tinnitus for one or more days (Heffner, 2011). In addition, a simulated tinnitus test was given in which low-level (25 dB SPL) 16-kHz 1/3-octave band noise was presented continuously from one side. The results of the simulated tinnitus test indicated that although all six rats responded to the simulated tinnitus on the first day, two failed to significantly shift their responding on one or more of the following

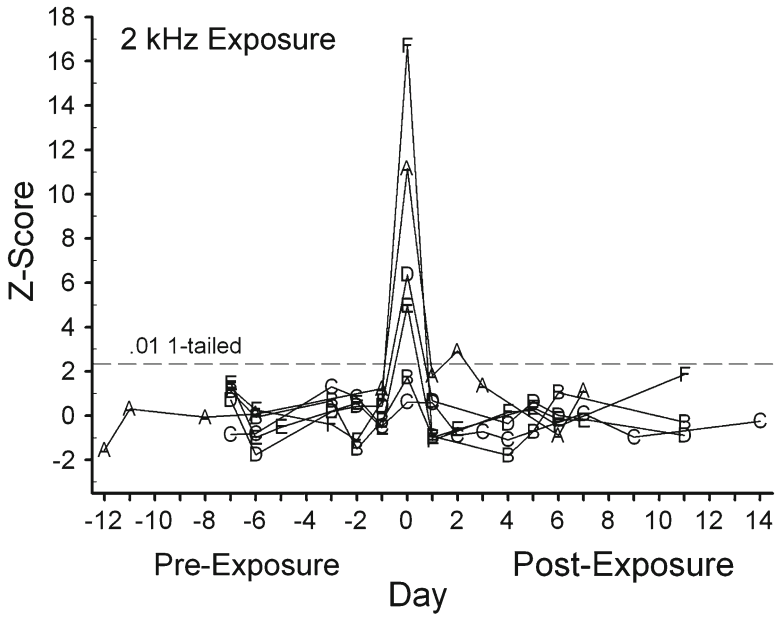

Fig. 2.10 Example of the results of the sound localization procedure for detecting tinnitus in animals. Six rats were exposed in one ear to 2-kHz at 110 dB SPL for 10 minutes. Immediately after exposure (Day 0), four of the six animals shifted their responding on silent trials to the side of the exposed ear with a chance probability of $p < 0.01$ (one-tailed distribution). The shift of their responding on the following days back to their preexposure side preference suggests that their tinnitus had subsided, although simulated tinnitus tests indicate that some animals may cease responding to low-level sounds when their responses are not rewarded or punished. (From Heffner, 2011.)

days; this suggests that animals vary in their reliability of responding, which might be corrected by training the animals to respond to a wider variety and intensity of sounds.

The procedure has revealed an unexpected effect of anesthesia (halothane/nitrous oxide) on tinnitus. That is, whereas anesthetizing unexposed rats did not cause them to test positive for tinnitus, anesthesia alone would sometimes *reinstate* tinnitus in animals that had previously been exposed; that is, a rat that was no longer testing positive for tinnitus would occasionally shift its responding on the silent trials to the side of its previous exposure after being anesthetized even though it was not exposed to any sound at that time (Heffner, 2011). This finding suggests that something that does not cause tinnitus itself may cause tinnitus to reappear in previously traumatized ears, an observation that supports the view that exposing one ear to loud sound could reinstate tinnitus in the other ear if that ear has previously had tinnitus.

Finally, with regard to whether exposing one ear to a loud sound results in tinnitus lateralized to that ear, studies using this procedure to detect tinnitus in rats and hamsters after exposure to one ear (the other ear was never exposed) found evidence of ipsilateral, but not contralateral tinnitus (Heffner & Koay, 2005; Heffner, 2011).

Although this supports the view that exposing one ear to a loud sound does not in itself induce tinnitus in the opposite ear, it does not rule out the possibility that some of the animals that did not test positive for unilateral tinnitus may have experienced bilateral tinnitus.

Evaluating the sound localization procedure on the nine points:

1. The level of sound exposures used in these studies would be expected to cause tinnitus in humans.
2. The procedure is based on exposure to a loud sound in one ear causing tinnitus lateralized to that ear. Although the human evidence on this point is conflicting, there is reason to believe that the tinnitus would be lateralized to the side of the exposed ear. The procedure is not suitable for testing for bilateral tinnitus which may result from exposure to ototoxic drugs.
3. The procedure has been tested with simulated tinnitus, which shows that although all animals respond to it on the first day, some animals are less reliable in reporting the simulated tinnitus on following days. This suggests that animals might be selected for exposure based on the consistency of their responding to simulated tinnitus.
4. Hearing loss is not a factor and, if anything, would work against the procedure as a hearing loss after exposure causes sounds to be perceived primarily on the side of the unexposed ear.
5. Because the animals are trained to indicate the side from which a sound comes, as opposed to responding to the quality of the sound, hyperacusis would not be expected to affect the results.
6. The procedure does not indicate the pitch of the tinnitus.
7. The results appear consistent in that the higher the intensity of an exposing sound, the more likely it is to cause tinnitus (Heffner & Koay, 2005).
8. The sound localization procedure uses each animal as its own control and is ideal for testing individual animals. However, this increase in power comes at the cost of time because it can take over a month to train the animals.
9. The sound localization procedure can be used to follow an animal's unilateral tinnitus.

5 Conclusion

A number of procedures have been devised for detecting tinnitus in animals and a summary is presented in Table 2.2. In selecting a procedure, it is important to consider not only ease of use, but also the degree to which confounding factors such as hearing loss have been ruled out. The procedures for which the most control tests have been conducted are the conditioned suppression procedure of Jastreboff and the sound localization procedure of Heffner. In terms of power, those procedures that use each subject as its own control provide the most power, and the sound localization and startle reflex gap procedures can obtain useful information from single animals. Of the various procedures, the startle reflex gap procedure shows the

Table 2.2 Nine-point comparision of the procedures for detecting tinnitus in animals[a]

Points of comparison	Jastreboff conditioned avoidance	Bauer & Brozoski conditioned avoidance	Rüttiger conditioned avoidance	Guitton conditioned avoidance	Guitton water T-maze	Lobarinas polydipsia avoidance	Turner gap detection	Heffner two-choice sound localization
1. Agent causes tinnitus in humans	Yes	Unknown	Yes	Yes	Yes	Yes	Yes/unknown	Yes
2. Would work on humans	Yes	Unknown	Yes	Yes	Yes	Yes	Unknown	Yes[b]
3. Tested with simulated tinnitus	Yes	No	No	No	No	No	No	Yes
4. Hearing loss not a concern	Yes	Yes	Yes	Yes	Yes	No	No	Yes
5. Hyperacusis not a concern	Yes	No	Yes	Yes	Yes	Yes	No	Yes
6. Used to determine pitch of tinnitus	Yes	Yes	No[c]	No	Yes	No	Yes	No
7. Results generally consistent	Yes	No	Yes	Yes	Yes	Yes	No	Yes
8. Does not require control group	No	No	Yes[d]	Yes[d]	Yes[d]	Yes	Yes	Yes
9. Follow tinnitus over time	No	Yes	No	Yes	No	Yes	Yes	Yes

[a] Note that some of these evaluations may change as further results become become available.
[b] Does not detect bilateral tinnitus.
[c] Used to determine intensity of tinnitus.
[d] Control groups used in some studies.

greatest promise, not only because of its ease of use but also because it may indicate the pitch of an animal's tinnitus. However, there are many questions that must be addressed before it is adopted for use, including whether it is reasonable to expect tinnitus to interfere with gap detection.

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Chapter 3
Molecular Mechanism of Tinnitus

Marlies Knipper, Marcus Müller, and Ulrike Zimmermann

1 Introduction

Tinnitus (phantom noise) is predicted to occur due to a broad variety of etiologies and pathogeneses (Eggermont, 2007; Jastreboff, 2007). In a current common view, tinnitus is primarily linked to damage in the periphery of the auditory system, probably even in cases in which an impairment cannot be assessed by clinical routine audiometry (Shiomi et al., 1997; Lockwood et al., 2002; Saunders, 2007). From animal studies, it is hypothesized that an increased spontaneous discharge rate in subcortical auditory neurons and increased neural synchrony and hyperactivity in the auditory cortex (AC) are correlates of tinnitus (Bauer, 2004; Kaltenbach, 2010; Roberts et al., 2010). The subcortical hyperactivity is currently interpreted as a consequence of the loss of the stimulus-driven activity that triggers centrally compensating synaptic adjustments (Schaette & Kempter, 2009).

Paradoxically, sensory deprivation typically causes hyperactivity as part of the homeostatic response of a "healthy" system (Turrigiano & Nelson, 2004; Nelson & Turrigiano, 2008). If hyperactivity is the general consequence of the cochlear damage that leads to tinnitus, why is it that not any cochlear damage and any type of hearing loss lead to tinnitus? Only a fraction of subjects suffering from hearing loss are affected by tinnitus (Lockwood et al., 2002). Moreover, hyperactivity, as part of a homeostatic adaptation response to sensory deprivation, is presumed to be associated with lateral inhibition. Reduced lateral inhibition, however, would put the activity peaks present in the AC during tone perception at the transition border of the cochlear-deprived frequencies (Gerken, 1996). By contrast, tinnitus patients report that the pitch of their perceived tinnitus tone is in the frequency regions in which their hearing is impaired and not at the transition border (Noreña et al., 2003; König et al., 2006).

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To tackle these issues, this chapter discusses etiologies of tinnitus in the context of molecular changes in the *peripheral auditory system* (Section 3.2), in *subcortical* areas (Section 3.3), and in the *auditory cortex* (Section 3.4). The chapter also discusses possible bidirectional (feedback) interactions between the central and the peripheral auditory system that may influence tinnitus generation (Section 3.5).

2 The Inner Ear

In the majority of cases, tinnitus is associated with hearing loss induced by noise exposure or aging (Lockwood et al., 2002; Saunders, 2007). Recent findings indicate that even the mildest hearing loss at a young age has the potential to progress into severe hearing loss over time (Kujawa & Liberman, 2009). Therefore, for example, the growing use of personal headsets together with demographic changes may lead to tinnitus becoming an increasingly serious health issue (Langguth et al., 2009). Acoustic trauma and high dosages of salicylate, the active component of aspirin, are the most commonly used conditions to investigate the basis of tinnitus in animal models (for review see Eggermont & Roberts, 2004; Eggermont, 2007; Jastreboff, 2007). This chapter summarizes open questions and controversial aspects of the molecular basis of both salicylate- and acoustic trauma–induced tinnitus that may lead to a critical reconsideration of our current understanding of tinnitus pathology.

2.1 Molecular Correlates of Tinnitus at the Level of Outer Hair Cells

Studies investigating the molecular mechanism of tinnitus using salicylate treatment or acoustic trauma analyzed effects at the outer hair cell (OHC) level in the context of tinnitus. Salicylate was found to interact with prestin, the protein causally related to the mechanical properties of OHCs that drive amplification of vibration in the cochlea (Zheng et al., 2000). Salicylate application results in an acute reduction in nonlinear capacity. This is an indication of the obstruction of active cochlear mechanics by blocking OHC motility responses (Oliver et al., 2001; Zheng et al., 2002).

Acute administration of salicylate was also shown to reversibly eliminate spontaneous otoacoustic emissions and reduce the amplitude of distortion product otoacoustic emissions (DPOAEs), reflecting a reduction in the OHCs' electromotility (Fitzgerald et al., 1993; Janssen et al., 2000; Huang et al., 2005). Paradoxically, however, chronic salicylate administration raised the amplitude of DPOAEs in guinea pigs (Huang et al., 2005) and increased prestin mRNA levels, both leading to enhanced active cochlear mechanics (Yu et al., 2008; Yang et al., 2009; Chen et al., 2010). Divergences of acute and long-term salicylate effects on OHC motility were difficult

to bring in line with salicylate being a trigger for tinnitus. In addition to the evidence from experiments using salicylate, acoustic trauma–induced tinnitus can obviously appear independently of the integrity of OHCs. Acoustic trauma is presumed to cause OHC death through phosphorylation of so-called c-Jun N-terminal kinases (JNK) after the upregulation of intracellular Ca^{2+} levels (Murai et al., 2008; Meltser et al., 2009). Phosphorylation of JNK can be reduced by a highly specific JNK inhibitor (AM-111) that, when given before or shortly after trauma, can prevent OHC death and hearing loss (Pirvola et al., 2000; Zine & van de Water, 2004; Barkdull et al., 2007). Considering that JNK inhibition has been shown to protect from hearing loss induced by noise trauma (Wang et al., 2003) as well as from oxidative stress of cochlear neurons (Scarpidis et al., 2003) and cortical neurons (Borsello et al., 2003), one may expect that D-JNK-1, a potent peptide inhibitor of JNK, would have a therapeutic effect on tinnitus. Interestingly, AM-111 did not show any reduction in tinnitus in rats tested in a behavioral model (Suckfuell et al., 2007). The rescue from OHC death without effect on tinnitus may therefore also suggest that OHC death is not primarily linked to tinnitus. Also, various investigations that show tinnitus occurs even when hearing impairment cannot be detected by hearing threshold tests (Eggermont, 2003; Weisz et al., 2006; Roberts et al., 2008) support the notion of OHCs not being the first trigger for tinnitus. As OHCs determine the thresholds for sound-evoked neural potentials (El-Badry & McFadden, 2007), tinnitus would otherwise exclusively appear in correlation with detectable hearing loss. This finding was supported by testing DPOAEs in tinnitus subjects with normal audiograms. Decreases in DPOAEs (Shiomi et al., 1997) as well as an increase in OHC activity in the tinnitus frequency region (Gouveris et al., 2005) were found, strengthening the notion of a rather secondary role of OHCs in tinnitus (Weisz et al., 2005).

In conclusion, physiological (Kaltenbach et al., 2002), otoacoustic (Job et al., 2007), and computational (Schaette & Kempter, 2006) evidence that implies that damage to OHCs may be predisposing, for tinnitus should be questioned, as previously already suggested (Bauer et al., 2007; Roberts et al., 2010).

Hypothesis I: OHC dysfunction is unlikely a primary cause of tinnitus.

2.2 *Molecular Correlates of Tinnitus at the Level of the Auditory Nerve*

If OHCs are not a primary source of tinnitus induction, how does cochlear damage contribute to tinnitus pathology? The next elements downstream from the OHCs are the inner hair cells (IHCs), the synaptic apparatus, and the auditory nerve. Central hyperactivity is discussed to occur as a consequence of sensory deprivation after cochlear damage and reduced auditory nerve activity (Roberts et al., 2010).

As illustrated in Figure 3.1, IHCs release the transmitter glutamate during sound-induced excitation (Klinke, 1986) acting on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors (GluR) GluR2/3 and GluR4 (Matsubara et al., 1996; Ruel et al., 2007; Meyer et al., 2009), but also

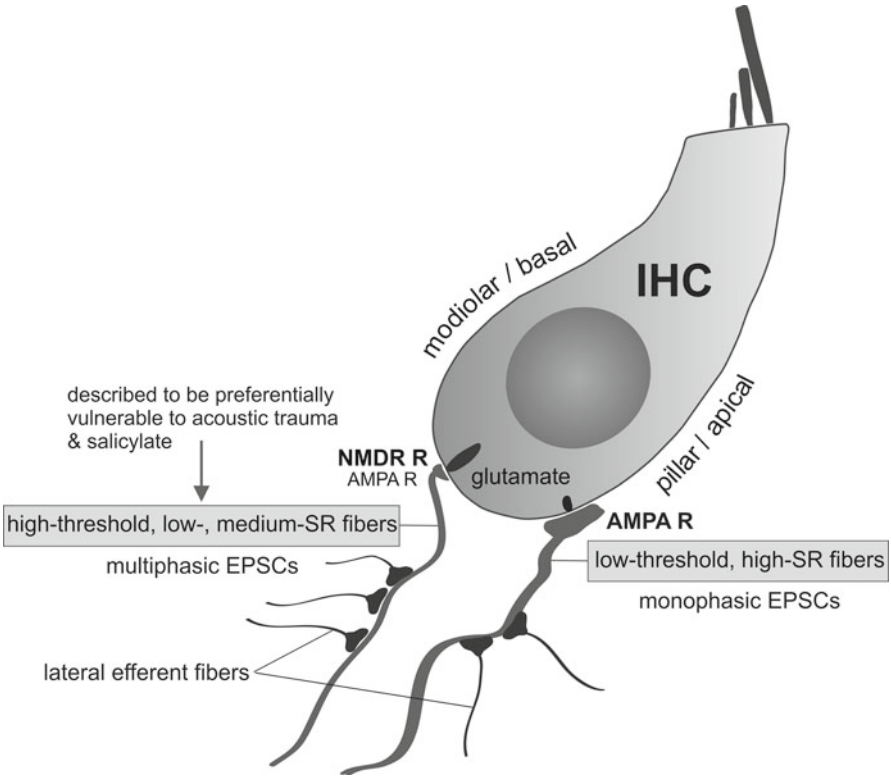

Fig. 3.1 Predicted subcellular orientation of high- and low-SR fibers related to AMPA receptors (AMPA R), NMDA receptors (NMDA R), and ribbons at the inner hair cell (IHC). (Modified after Liberman et al., 2011). Note that current data point to smaller ribbons opposing larger AMPA R patches of high-SR fibers, and larger ribbons associated with smaller patches of NMDA R and AMPA R expressing low-SR fibers that presumably exhibit preponderance of lateral efferent fibers

N-methyl-D-aspartate (NMDA) receptors (Felix & Ehrenberger, 1990; Pujol et al., 1992; Eybalin, 1993) at the postsynapse of the afferent fiber. Each IHC is innervated by unbranched radial afferent fibers from 8 (humans) up to 20 (rodents) separate spiral ganglion neurons, which represent about 90–95% of all afferent fibers in the auditory nerve (AN). AN fibers were classified according to their spontaneous action potential (AP) discharge rate (SR): high-SR, >18 AP/s (60%); medium-SR, 0.5–18 AP/s (30%); and low-SR, <0.5 AP/s (10%) (Liberman, 1978; Heinz & Young, 2004). High-SR fibers are sensitive to low sound pressure levels (SPLs), whereas low-SR fibers have thresholds elevated by about 20–40 dB (Sachs & Abbas, 1974; Müller & Robertson, 1991; Yates, 1991). In humans, for example, AN fibers comprise approximately 17,000 high-SR (61%) and 4500 low-SR fibers (16%) (Spoendlin & Schrott, 1989). Afferent fiber characteristics and the IHC synaptic apparatus change with the SR (Merchan-Perez & Liberman, 1996). Fibers with different SRs make synaptic contact at different positions at the IHC basal pole (Liberman, 1982a,b) (Fig. 3.1), and are linked to gradients of heterogeneity

of excitatory postsynaptic current (EPSC) waveforms (Grant et al., 2010) and opposing gradients of ribbon size and AMPA receptor size (Liberman et al., 2011).

Accordingly, orientated in a spatial gradient in IHCs, high-threshold, low-SR fibers are found on the modiolar side in the basal part of IHCs (Liberman, 1982b), where synapses with smaller receptor patches and larger ribbons are located (Liberman et al., 2011) (Fig. 3.1). In contrast, synapses with large receptor patches and small ribbons corresponding to high-SR fibers are oriented mainly toward more apical positions at the pillar side (Liberman et al., 2011) (Fig. 3.1). The difference in the synaptic ribbon size was suggested to contribute to the described heterogeneity in EPSC shape seen in cochlear nerve terminals in dissected organ of Corti preparations of hearing rats (P19–P21) (Grant et al., 2010). Recorded from mainly apical regions of the cochlea, in which sound frequencies of 2–5 kHz are represented (Müller, 1991), a majority of terminals show large, fast monophasic EPSCs (Grant et al., 2010) that are predicted to result from coordinated vesicle release of compact, spherical ribbons opposite of high-SR fibers (Liberman et al., 2011) (Fig. 3.1). In contrast, uncoordinated vesicular release along the extremely elongated ribbons that sometimes span multiple AMPA receptor patches are suggested to generate low multiphasic EPSCs in presumed low- or medium-SR fibers (Grant et al., 2010; Liberman et al., 2011).

This information is most important considering that various studies indicate a selected and differential vulnerability of distinct fiber types for auditory trauma. Accordingly, high-threshold, low- and medium-SR fibers have been suggested to exhibit preferential vulnerability to acoustic overstimulation (Heinz & Young, 2004) as well as to tinnitus-inducing salicylate intoxication (Ruel et al., 2008). In the latter study, perilymphatic perfusion of salicylate was found to increase the spontaneous discharge rate of auditory nerve fibers in guinea pigs from an average of 17 AP/s to 40 AP/s. The SR changes after salicylate treatment were suggested to be initiated through an NMDA receptor-mediated event on high-threshold, low- and medium-SR fibers (Puel, 2007; Ruel et al., 2008). Presumably, NMDA receptors are predominantly located on the modiolar side of IHCs (Pujol et al., 1992; for review see Knipper et al., 2010) (Fig. 3.1), where high-threshold, low-SR fibers were shown to contact (Liberman, 1982b; Liberman et al., 2011) and where fibers from the lateral efferent system preferentially terminate (Liberman, 1980). Cyclooxygenase-induced alteration of membrane fluidity through salicylate metabolism is suggested to alter the NMDA receptor kinetic, and thus the spike rate in postsynaptic afferent synapses (Ruel et al., 2008; Hwang et al., 2011). This would give a molecular possibility of how the discharge rate of fibers may be altered after salicylate treatment. In contrast, other studies done on rats suggested a deafferentation of large-diameter auditory fibers, that is, low-threshold, high-SR fibers, after tinnitus-inducing acoustic trauma (Bauer et al., 2007). A crucial future issue, therefore, is to elucidate if and how the larger size of ribbons (Liberman et al., 2011), multiphasic EPSCs (Grant et al., 2010), and NMDA receptors are linked with the predicted higher vulnerability of AN fibers. Also, the exclusiveness or preference of vulnerability of high-threshold, low-SR fibers (Ruel et al., 2008; Kujawa & Liberman, 2009; Schaette & Kempter, 2009) needs to be questioned. In this context, it is noteworthy to mention what computational models predicted as a prerequisite for achieving subcortical hyperactivity (Schaette & Kempter, 2009). Hyperactivity at the level of the projection neurons (PN)

in the dorsal cochlear nucleus (DCN), the earliest point where changes of AN fibers are compensated (see Nouvian et al., Chapter 4), can occur only when a critical number of auditory fibers continue to increase their discharge rate sufficiently after cochlear injury (Schaette & Kempter, 2009). This increase is expected to occur only when deafferentation (e.g., after tinnitus-inducing trauma) does not affect high-SR fibers (Schaette & Kempter, 2009). As up to this time, subcortical hyperactivity has been assumed to be a correlate of tinnitus (Bauer et al., 2000; Kaltenbach et al., 2000; Milbrandt et al., 2000), a loss of low-SR fibers rather than high-SR fibers is favored to be a correlate of tinnitus (Schaette & Kempter, 2009), but needs to be verified in further investigations.

One would not expect a clarification of this question at least from studies that investigated salicylate or acoustic trauma effects on discharge rates of afferent fibers. Until now, investigations regarding the spontaneous discharge rate of afferent fibers after acoustic trauma or salicylate are highly controversial. In chinchilla, SRs of auditory nerve fibers were found to be *elevated* after noise-induced hearing loss (Salvi & Ahroon, 1983) An increase in SRs was described in rats after high dosages of salicylate (Ruel et al., 2008). In cats, an increase in spike activity of auditory nerve fibers after salicylate treatment was reported (Kiang et al., 1976; Evans et al., 1981), but others could not confirm this in other species. In guinea pigs or gerbils, no changes or even a reduction in the SR after salicylate treatment were described (Stypulkowski, 1990; Müller et al., 2003). In these studies, a presumptive elevation of the SR after salicylate treatment was suggested to occur in cat as a result of a toxic effect due to lack of glucuronyl transferase, a metabolizing enzyme (Müller et al., 2003). In line with a reduction of the SR by salicylate, the local application of salicylate through round-window application reduced the response amplitude of the cochlea (Sun et al., 2009), which is expected to occur when the mean sound-evoked discharge rate of every responding auditory fiber declines (Johnson & Kiang, 1976). It can be concluded that afferent fibers are likely to be affected after cochlear trauma and salicylate treatment. It remains elusive, however, if altered discharge rates observed in various studies are linked to hearing loss without or hearing loss with tinnitus. Investigations of discharge rates of persisting fibers in equally hearing impaired animals with or without tinnitus are essential to elucidate the basis of presumably controversial findings.

Hypothesis II: Deafferentation of auditory fibers rather than OHC loss is a molecular correlate of tinnitus.

3 Subcortical and Limbic or Paralimic Structures

3.1 Molecular Basis of Subcortical Hyperactivity in the Context of Tinnitus

Hypothesizing that cochlear damage is a likely molecular correlate for tinnitus, even if a functional cochlear impairment cannot be detected, and assuming deafferentation rather than OHC loss is a characteristic feature of tinnitus above,

the mean auditory nerve activity in targeted synapses of the cochlear nucleus is expected to be reduced.

For decades, it has been assumed that if the inner environment of the body is challenged (injury, sensory deprivation, activity changes, disease, altered environmental conditions, etc.) a homeostatic process operates to resist the changes and, therefore, recover to the set point so that the system can function appropriately (Cannon, 1932). Network stability of the brain is retained through altered strength of all connected synapses that are adjusted or 'scaled' up or down, shown by many in vitro and in vivo studies during development and after sensory deprivation (Turrigiano & Nelson, 2004; Rich & Wenner, 2007; Pozo & Goda, 2010). This increase in synaptic strength serves to maintain network stability, stable output activity, and function (Goaillard & Marder, 2006). On the molecular level, this process has been studied in detail in the visual system (Maffei & Turrigiano, 2008), and in cultured rat hippocampal neurons (Jakawich et al., 2010), where, for example, through lid closure, through chronic AMPA receptor blockade with 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX, an AMPA receptor antagonist), or through chronic action potential blockade using tetrodotoxin (TTX), a functional restoration of synaptic strength was observed (Turrigiano & Nelson, 2004; Davis, 2006; Maffei & Turrigiano, 2008). The processes involved always seem to follow similar mechanisms that include compensatory changes in the expression of excitatory and inhibitory neurotransmitter receptors (Kilman et al., 2002; Gainey et al., 2009; Tyagarajan & Fritschy, 2010). An increase in brain-derived neurotrophic factor (BDNF), a key regulator of synaptic homeostasis and plasticity (Minichiello, 2009; Bramham et al., 2010; Jakawich et al., 2010), and its receptor trkB, seems to result in an increase in transmitter release due to an increase in AMPA receptors (Jakawich et al., 2010; Lindskog et al., 2010) and a reduction in surface γ-aminobutyric acid-A ($GABA_A$) and glycine receptors (Tyagarajan & Fritschy, 2010) (Fig. 3.2).

Assuming that this general principle also holds for the auditory system, an increase in neuronal activity (hyperactivity) in targeted brain stem synapses after auditory deprivation would occur as a compensatory homeostatic plasticity response of a *healthy* system, aiming to restore deprived synaptic strength toward original levels (Turrigiano, 1999). The first level where a compensation of reduced mean neuronal activity of the auditory nerve after trauma can occur, is at the so-called projection neurons (fusiform and giant cells) in the DCN (Kaltenbach & McCaslin, 1996). These cells receive excitatory input from the ipsilateral AN and input from auditory interneurons (e.g., vertical cells), as well as from other sensory modalities like the somatosensory system (Fig. 3.3) (for a review see Dehmel et al., 2008; Roberts et al., 2010; see also Dehmel et al., Chapter 5). The DCN projection neurons become hyperactive even after mild acoustic trauma, making them most suitable for feedforward responses required for homeostatic plasticity responses (Kaltenbach, 2007; Kaltenbach & Godfrey, 2008).

The response behavior described for projection neurons in the DCN after trauma also exhibits on the molecular level significant similarity to homeostatic synaptic adaptation responses shown in the hippocampus or the visual system after deprivation. Accordingly, hyperactivity of PN after auditory trauma is described to be associated

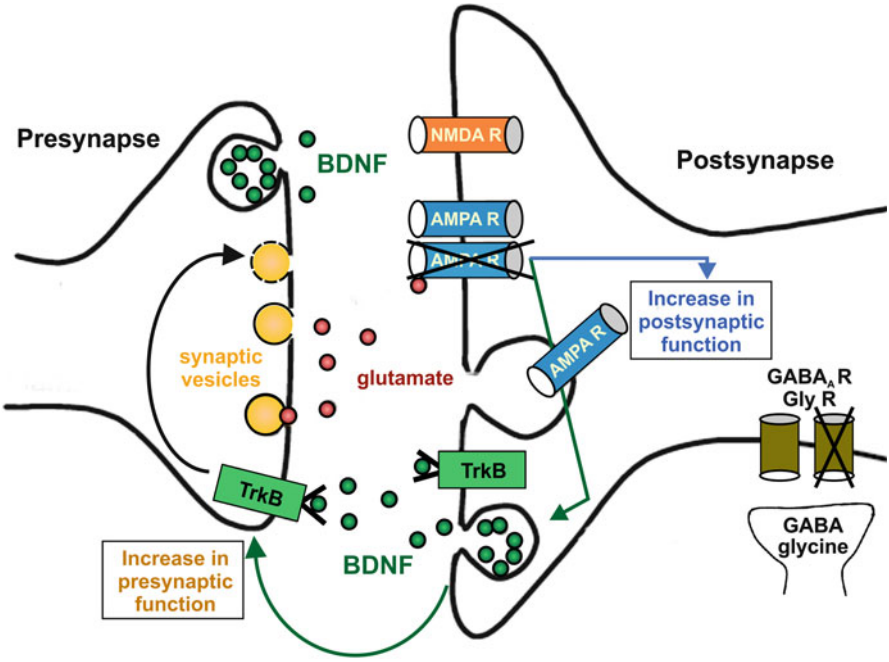

Fig. 3.2 Schematic illustrating the hypothesis of molecular processes participating in an increase of synaptic strength following deprivation through AMPA receptor (AMPA R) blockade in hippocampal neurons (Modified from Jakawich et al., 2010)

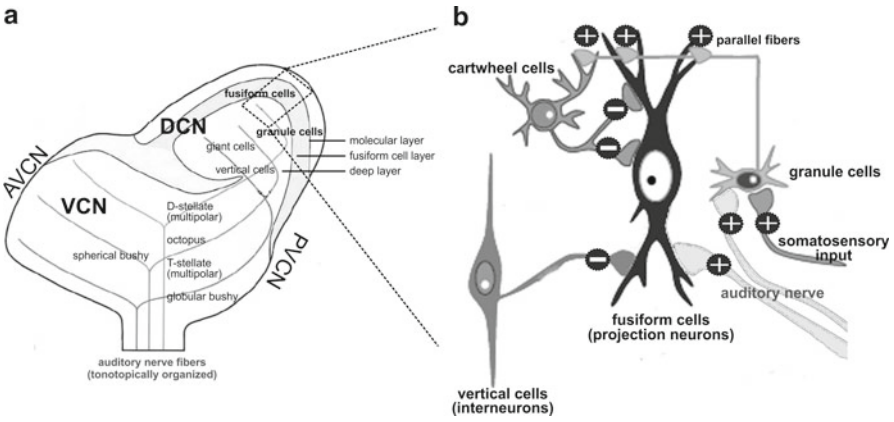

Fig. 3.3 (**A**) Schematic illustration of the cochlear nucleus indicating its major subdivisions, ventral (VCN) and dorsal cochlear nucleus (DCN). AVCN, anterior ventral cochlear nucleus; PVCN, posterior ventral cochlear nucleus. (Modified from Oertel et al., 2000.) (**B**) Schematic of excitatory and inhibitory circuitry on fusiform cells. Direct auditory input to fusiform cells through excitatory terminals on their basal dendrites. Somatosensory input is indirect through granule cells. Granule cell axons, the parallel fibers, directly excite fusiform cells through terminals on apical dendrites of fusiform cells, and inhibit fusiform cells through inhibitory interneurons, the cartwheel cells. Deep-layer vertical cells, also known as tuberculoventral cells, project inhibitory terminals on fusiform basal dendrites (Modified from Rubio, 2006)

with selective downregulation of glycinergic inhibitory neurotransmission onto projection neurons (Wang et al., 2009). After sound deprivation by ear plugs, an upregulation of specific AMPA receptors in fusiform cell synapses occurs parallel to the downregulation of inhibitory receptors (Whiting et al., 2009). Finally, BDNF protein levels were found to be significantly upregulated in fusiform cells in young and aged animals after sound exposure (Wang et al., 2011). From these findings it can be concluded that hyperactivity in the DCN, when occurring in the ascending *sound-driven pathway* after cochlear damage, can be a "healthy" (homeostatic plasticity-restoring) response that may serve to counteract hearing loss. It remains an open question if previous studies hypothesizing an increased spontaneous discharge rate in DCN principal cells as a correlate of tinnitus (Kaltenbach, 2007; Knipper et al., 2010; Roberts et al., 2010) observe "healthy" hyperactivity, or the hyperactivity that has been described to survive even after ablation of the auditory nerve or the cochlea (Kaltenbach, 2007). Indeed, different kinds of hyperactivity would explain that even within the same animal model contrasting activity responses in the DCN after trauma have been described: for example, increased PN activity after acoustic overstimulation was shown in mice with evidence of tinnitus using the gap detection method (Li et al., 2011). Another study using similar animal models and similar technical conditions but a slightly altered trauma condition described a decrease in excitability of PN (Pilati et al., 2011). Decreased PN activity was also shown as a result of the pairing of acoustic and somatosensory stimulation lasting for minutes (Zhang & Guan, 2008) or even hours (Dehmel et al., 2011). Depending on the role that hyperactivity in the DCN might play in tinnitus, the interpretation of this finding would differ, emphasizing the urgent need to clarify this aspect. Accordingly, considering *hyperactivity* in the DCN as being a direct neural correlate of tinnitus, this finding justifies to consider suppression of DCN hyperactivity as a *tinnitus-suppressing* therapeutic target (Zhang & Guan, 2008). Alternatively, assuming that tinnitus would correlate with a decrease in PN activity (Li et al., 2011) and hyperactivity at the level of the DCN would be of noncochlear origin (Kaltenbach, 2011), somatosensory stimulation would be a *tinnitus-inducing* activity that would perfectly explain why patients often attribute the onset of their tinnitus to a somatic insult in the head and neck regions (Levine, 1999). Data strongly argue for a reevaluation of subcortical hyperactivity in auditory pathways after auditory trauma from the perspective of a "healthy" homeostatic plasticity-restoring response that prevents tinnitus, or from the perspective of an alternative source of hyperactivity that, for example, through refilling of sensory-deprived DCN neurons by somatosensory inputs (Dehmel et al., 2008; Kaltenbach, 2010), produces neuronal activity responses independent of sound-driven signal responses. The presumably divergent sources of hyperactivity in the DCN may in the future also be regarded in the context of divergent ways of how hyperactivity in the DCN progresses along the auditory pathway.

Accordingly, disturbed though divergent GABAergic network responses were described in the inferior colliculus (IC) after tinnitus-inducing auditory trauma (Chen & Jastreboff, 1995; Bauer et al., 2000; Milbrandt et al., 2000). Monaural acoustic trauma (a continuous 10-kHz pure tone at 124 dB SPL for 1 hour) resulted

in hyperactivity in the IC that was associated with a downregulation of $GABA_A$ receptors in the IC contralateral to the traumatized cochlea (Dong et al., 2010). In contrast, another study using 10-kHz center frequency at 115 dB SPL for 3 hours found significantly lower neuronal spontaneous activity in all investigated isofrequency laminae 21 days after acoustic trauma that could be eliminated by $GABA_A$ receptor antagonist bicuculline (Basta & Ernest, 2004). This latter finding would support elevated GABA levels in the IC after intense acoustic trauma (Tan et al., 2007). Divergent inhibitory responsiveness has also been shown in the IC after high dosages of salicylate. An increase of spontaneous activity in IC neurons after salicylate treatment was linked with increased gain control (Parra & Pearlmutter, 2007) through a decrease in GABA (Sun et al., 2009) and decrease in $GABA_A$ binding sites (Bauer et al., 2000). L-type calcium channels were suggested to contribute to salicylate-induced decrease in GABA release in the IC (Liu et al., 2005). In contrast to decreased inhibitory responses in the IC, other studies report significantly enhanced glutamate decarboxylase (GAD) levels in the dorsal and central parts of the IC after chronic exposure to salicylate (Bauer et al., 2000). Future work may be required to investigate if partly contrasting inhibitory responses at the level of the IC may reflect differences in brain responses toward either hearing loss without tinnitus or hearing loss with tinnitus.

Hypothesis III: Two divergent kinds of hyperactivity at the level of the DCN may differently influence higher brain areas after auditory trauma. Hyperactivity in sound-driven pathways may be regarded in the context of a rather typical compensatory response of a healthy system that, after sensory deprivation, adapts the synaptic strength toward original levels through homeostatic scaling.

3.2 Molecular Aspects at the Level of Limbic and Paralimbic Structures in the Context of Tinnitus

There is an increasing number of studies that predict a crucial role of stress, and consequently of the limbic/paralimbic system, for tinnitus (Møller, 2003; Zenner et al., 2006; Rauschecker et al., 2010). In a complex interrelationship, the neurotransmitter/neuromodulator serotonin (5-hydroxytryptamine [5-HT]) is connected to altered hypothalamic–pituitary–adrenal (HPA) axis activation, cortisol release, and stress (Dinan, 1996). Several studies point to a role of 5-HT in tinnitus. In our context, this may serve as an example to elucidate current open questions of the relationship between tinnitus and stress. The $5\text{-}HT_3$ receptor is a ligand-gated ion channel activated by serotonin. Although originally identified in the peripheral nervous system, the $5\text{-}HT_3$ receptor is also expressed in the central nervous system. Sites of expression include several brain stem nuclei and higher central areas such as the amygdala, hippocampus, and cortex. Serotonin (5-HT) obviously influences tinnitus through imbalances in inhibitory/excitatory inputs (Simpson & Davies, 2000; Rothlin et al., 2003; Wang et al., 2008). Salicylate has been described to trigger

a decrease in GABAergic inhibition by a suppression of serotonin-containing fibers that preferentially innervate inhibitory GABA neurons, for example, in the central nucleus of the IC (Peruzzi & Dut, 2004; Wang et al., 2008). Through such a mechanism 5-HT is predicted to be responsible for the salicylate-induced hyperactivity in the IC (Wang et al., 2008). Tinnitus-inducing salicylate dosages were also found to activate serotonergic neurons in the rostral serotonergic neurons (J. Liu et al., 2003; Caperton & Thompson, 2011). Anatomical data indicate that serotonergic axons from the dorsal raphe nucleus and the nucleus accumbens (NAc) innervate the so-called thalamic reticular nucleus (TRN) and the dorsal thalamus (O'Donnell et al., 1997; Brown & Molliver, 2000; Rauschecker et al., 2010). Here, serotonin excites the GABAergic neurons of the TRN (Pape & McCormick, 1989; McCormick & Wang, 1991). TRN input strongly inhibits medial geniculate body (MGB) neurons in both anesthetized and conscious animals (X. J. Yu et al., 2009). This means that salicylate, by blocking 5-HT fibers and activating TRN, would therefore disinhibit this inhibitory TRN response (Guillery & Sherman, 2002). Accordingly, salicylate would activate MGB through disinhibition.

Using functional magnetic resonance imaging (fMRI) and voxel-based morphometry in tinnitus patients, the highest degree of hyperactivity was found in the NAc (Leaver et al., 2011), which was suggested as being the result of reduced functional output of the ventromedial prefrontal cortex (vmPFC) in tinnitus patients (Leaver et al., 2011). Activation of the NAc would lead to increased inhibition of TRN neurons, and thus results in increased inhibition of MGB neurons. TRN-induced inhibition of the MGB was suggested to participate in a 'noise-cancellation' process that during tinnitus fails to turn off a typically occurring 'noise' (Rauschecker et al., 2010). It remains to be clarified how the predicted *stimulating* salicylate-induced effect on MGB through the TRN (Guillery & Sherman, 2002), and the contrasting presumptive *inhibitory* effect on the MGB through the TRN (Rauschecker et al., 2010), influence cortical hyperactivity during tinnitus through alteration of thalamocortical input.

Now the question arises of how limbic and paralimbic pathways can be activated during tinnitus. Following the hypothesis that subcortical hyperactivity during tinnitus may occur in the DCN independently of the cochlea (Kaltenbach, 2011), a selective activation of nonlemniscal pathways may be a likely consequence. This would explain recent findings of hyperactivity in the dorsal cortex of the inferior colliculus (DCIC) rather than in the central nucleus of the inferior colliculus (CIC) (Holt et al., 2010). The major sources of input to the dorsal part of the MGB are from nonlemniscal parts of the IC, the DCIC and external cortex of the inferior colliculus (ECIC) that in turn receive ascending information from the (dorsal nucleus of the lateral lemniscus [DNLL]) (Malmierca & Merchán, 2004). The multisensory cells of the MGB project to the amygdala (Doron & Ledoux, 1999; Kuwabara & Zook, 2000; for review see Malmierca & Merchán, 2004). Thus, through nonlemniscal pathway activation, hyperactivity independent of sound-driven signals could activate emotional pathways and the cortex.

A predicted modulation of tinnitus strength through nonauditory factors such as the limbic system (Møller, 2003; Zenner et al., 2006; Jastreboff, 2007) or limbic and

paralimbic system (Rauschecker et al., 2010) may thus be regarded in the context of altered thalamocortical input.

Hypothesis IV: Tinnitus is likely to correlate with an altered serotonergic and GABAergic activity in limbic and paralimbic structures. Considering the open question of subcortical activity discussed in the preceding text, to what extent an "emotional neural amplifier" alters the excitability of the auditory cortex, and thus tinnitus, remains elusive.

4 Auditory Cortex

4.1 Molecular Aspects of Tinnitus at the Level of the Auditory Cortex

Physiological studies reported hyperactivity and synchronous firing rates as an electrophysiological response of the primary auditory cortex (A1) of animal models of tinnitus (Eggermont, 2006, 2008; Lobarinas et al., 2008). There are currently two views on how cortical hyperactivity is generated during tinnitus.

Contrast enhancement caused by discontinuities in the balance of excitation and inhibition across the edge of normal hearing is suggested to contribute to tinnitus (Rauschecker et al., 2010; Roberts et al., 2010). This hypothesis presents the classic view that suggests that subcortical hyperactivity after reduced (GABAergic/glycinergic) lateral inhibition is a correlate of tinnitus. Reduced lateral inhibition, however, would put the activity peaks present during tone perception in the auditory cortex at the transition border of cochlear-deprived frequencies (Gerken, 1996).

As an alternative to this hypothesis, abnormal neural activity was predicted to be generated in tonotopic deprived frequency regions caused by hearing impairment (Kiang et al., 1969; Llinás et al., 2005; König et al., 2006). In line with this latter hypothesis, tinnitus patients report the pitch of their perceived tinnitus tone in frequency regions where hearing is impaired, and not at the transition border (Noreña et al., 2003; König et al., 2006).

Until now, no convincing molecular event can explain the observations made in tinnitus subjects, which means that it is unknown how in the sensory-deprived region cortical hyperactivity is generated after cochlear damage.

Reduced thalamocortical input recognized in field potential measurements after acoustic trauma (Tan et al., 2007) has been suggested to be linked to reduced Arc/Arg3.1 levels. Arc/Arg3.1 has emerged as an attractive candidate effector molecule/immediate early gene product (Link et al., 1995; Lyford et al., 1995; for a review see Bramham et al., 2008). Its induction correlates with experience-induced changes in synaptic activity (Guzowski et al., 2000; Plath et al., 2006; Shepherd et al., 2006).

Arc/Arg3.1 transcription is induced extremely rapidly, enabling, through the detection of Arc/Arg3.1 mRNA by in situ hybridization, acquisition of information about altered synaptic activity. Accordingly, increased Arc/Arg3.1 mRNA levels are seen during novelty exposure of the hippocampus, during acquisition of long-term fear memory in the amygdala, or after intense sensory experience after sensory deprivation in the somatosensory cortex (Guzowski et al., 1999; Ramírez-Amaya et al., 2005; Tagawa et al., 2005; for a review see Bramham et al., 2008). New studies analyzing spontaneous miniature excitatory postsynaptic potentials (mEPSPs) indicate that increases in Arc/Arg3.1 protein are associated with enhanced endocytosis of surface AMPA receptors that leads to reduced synaptic AMPA receptor responses (Ramírez-Amaya et al., 2005; Rial Verde et al., 2006). In contrast, neurons in Arc/Arg3.1 knockout animals exhibit markedly reduced endocytosis, increased steady-state surface AMPA receptor levels and an increased amplitude of spontaneously evoked mEPSCs (Rial Verde et al., 2006; Shepherd et al., 2006; Turrigiano, 2007). Reduced AMPA receptor trafficking is a direct molecular correlate of deprivation phenomena (Carroll et al., 1999; Heynen et al., 2003), including whisker deprivation (Allen et al., 2003).

Accordingly, an Arc/Arg3.1-mediated increase in glutamatergic sensitivity of pyramidal neurons in cortical layers II/III was described after visual deprivation linked to increased compensating synaptic strength (Goel & Lee, 2007). The response behavior appears to mirror that of increased glutamatergic sensitivity of pyramidal neurons in the auditory cortical layers II/III after auditory trauma, a phenomenon linked also to increased synaptic strength (Kotak et al., 2005). Whether, similarly to the visual system, Arc/Arg3.1 is enhanced under this auditory deprivation paradigm needs to be investigated in further studies.

Recent findings report of an increase in basic mEPSCs in pyramidal neurons of the cortex after Arc/Arg3.1 deletion (Gao et al., 2010) the reduced level of Arc/Arg3.1 in the glutamatergic pyramidal cells of layers II-–VI in the frequency-deprived regions of the AC in tinnitus animals may thus mirror basically enhanced mEPSCs, or even with epileptic-like highly synchronized network activity, as has been shown for Arc/Arg3.1 knockout mice (Peebles et al., 2010).

It has been demonstrated that high synchronization of neuronal activity in the sensory-deprived frequency regions of the A1 is a correlate of tinnitus (Eggermont, 2003; Saunders, 2007; Eggermont, 2008). The observed decline of Arc/Arg3.1 in the AC after acoustic trauma and salicylate treatment (Tan et al., 2007; Panford-Walsh et al., 2008) could therefore serve as an attractive molecular correlate to explain enhanced mEPSCs and increased synchronization with frequency-deprived regions of the AC in tinnitus subjects.

Hypothesis V: A decline in Arc/Arg3.1 may be considered as a molecular correlate that could be responsible for synchronized network activity in the auditory cortex by inducing basically enhanced mEPSCs. It remains elusive if hearing loss with and without tinnitus exhibits differences in cortical Arc/Arg3.1 levels.

5 Interaction Between the Brain and the Periphery

5.1 Bidirectional Feedback Response Between Central and Peripheral Brain Areas in the Context of Tinnitus

Considering the likeliness of peripheral deafferentation together with central contributions (emotional neural amplifier) (Rauschecker et al., 2010) to the generation and manifestation of tinnitus, a crucial future task will be to identify the presumptive bidirectional interaction between the peripheral organ and the brain.

Activation of the olivocochlear system, which originates in the brain stem and terminates in the cochlea (Warr & Guinan, 1979; White & Warr, 1983) and cochlear nucleus (Benson & Brown, 1990; Brown, 1993; Benson et al., 1996), is well known to have a suppressive effect on sound-evoked and spontaneous cochlear neural output (Guinan & Gifford, 1988; Rajan, 1988). Recent findings demonstrated that stimulation of the olivocochlear bundle (OCB) leads to strychnine-sensitive suppression of the trauma-induced enhanced spontaneous firing rate in the IC (Mulders et al., 2010; see also Robertson and Mulders, Chapter 6). In contrast, OCB stimulation had only small effects on spontaneous firing in the cochlear nucleus (CN) (Mulders et al., 2010). Therefore, an intrinsic circuitry between the CN and IC was suggested that, in addition to the peripheral efferent effect, influences the OCB-mediated spike rate in the IC (Mulders et al., 2010). While the strychnine sensitivity of this effect was discussed in the context of an effect of OCB fibers terminating onto cochlear OHCs as predicted from electrical stimulation (Liberman & Brown, 1986; Dallos et al., 1997), novel data describing the expression of glycine receptors at the level of IHCs (Dlugaiczyk et al., 2008) may lead to hypothesize that hyperactivity in the IC after auditory trauma may also be influenced by efferent glycinergic feedback at the level of the IHCs. Also stress, known to influence tinnitus responsiveness dramatically (Section 3.3.2), may influence central activity patterns after auditory trauma through efferent feedback on auditory fibers (Knipper et al., 2010).

An fMRI study revealed that higher cortisol levels were associated with a stronger amygdala response to emotional stimuli (Wolf, 2009), emphasizing the correlated activation of the HPA axis and amygdala activity during stress responses. Activation of the HPA axis is likely to influence lateral efferent feedback projections. The hypothesis is based on dynorphin and enkephalin-like opioids that are codistributed within lateral efferent brain stem nuclei. Also descending fiber bundles, lateral efferent terminal varicosities as well as inner and outer spiral bundles in the cochlea of species such as the guinea pig and rat were found to be enkephalin and dynorphin positive (Abou-Madi et al., 1987; Altschuler et al., 1988; Jongkamonwiwat et al., 2003).

Accordingly, a stress-induced release of opioid peptides, specifically dynorphins from lateral efferent terminals in the auditory periphery, has been suggested to be involved in tinnitus induction, due to its potentiation of excitatory effects on NMDA receptors (for a review see Sahley & Nodar, 2001). Stress-induced release of opioid peptides occurred, for example, in response to intense and presumably stressful

wideband noise leading to enhanced levels of [Met5]enkephalin-like opioid peptides in guinea pig perilymph (Drescher et al., 1983; Drescher & Drescher, 1985). Together with localization of opioid receptors in the lateral olivocochlear complex and potential activity on NMDA receptors (for review see Sahley & Nodar, 2001; Sahley et al., 2008), the finding justifies the assumption of a more direct impact of stress responses on the physiology of auditory nerve activity of hearing impaired specimens with tinnitus, but perhaps also of hearing impaired animals without tinnitus.

Hypothesis VI: The efferent system is a likely candidate to influence hyperactivity responses in the central auditory pathways after auditory trauma. It remains to be clarified in future studies to which extent altered efferent activity influences brain responses after hearing loss without as well as with tinnitus. More effort to understand the molecular basis of the link between altered neuronal activity and stressors is required, in particular in the context of the predicted role of '"neural amplifiers" that influence tinnitus.

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
A1	primary auditory cortex
AC	auditory cortex
AM-111	inhibitor of c-Jun N-terminal kinase-mediated apoptosis
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPA R	AMPA receptor
AN	auditory nerve
AP	action potential
Arc/Arg3.1	activity-regulated cytoskeleton-associated protein
AVCN	anteroventral cochlear nucleus
BDNF	brain-derived nerve growth factor
CIC	central nucleus of the inferior colliculus
CN	cochlear nucleus
DCIC	dorsal cortex of the inferior colliculus
DCN	dorsal cochlear nucleus
DNLL	dorsal nucleus of the lateral lemniscus
DPOAE	distortion product otoacoustic emissions
ECIC	external cortex of the inferior colliculus
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
$GABA_A$ receptor	ionotropic GABA receptor; benzodiazepine receptor
GAD	glutamate decarboxylase or glutamic acid decarboxylase
GluR	glutamate receptors
GlyR	glycine receptor chloride channel
HPA axis	hypothalamic-pituitary-adrenal axis
IC	inferior colliculus

IHC	inner hair cell
JNK	c-Jun N-terminal kinase
mEPSC	excitatory postsynaptic current
mEPSP	miniature excitatory postsynaptic potential
MGB	medial geniculate body
NAc	nucleus accumbens
NMDA	N-methyl-d-aspartate
NMDA R	NMDA receptor
OCB	olivocochlear bundle
OHC	outer hair cell
PN	projecting neurons
PVCN	postero ventral cochlear nucleus
SR	spontaneous (discharge) rate
TRN	thalamic reticular nucleus
TTX	tetrodotoxin
VCN	ventral cochlear nucleus
vmPFC	ventromedial prefrontal cortex

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Chapter 4
The Cochlea and the Auditory Nerve as a Primary Source of Tinnitus

Régis Nouvian, Michel Eybalin, and Jean-Luc Puel

1 Introduction

Tinnitus, the perception of sound in the absence of external noise, degrades the quality of life, extending from irritability, stress, and anxiety to severe depression and suicide. The increase in human life span in industrialized countries calls for the development of new therapies for tinnitus. Indeed, tinnitus is most often associated with presbycusis (or age-related hearing loss) and noise-induced hearing loss. A distribution histogram shows that almost 12% of men between the ages of 65 and 74 experience tinnitus (see Fig. 1A in Lockwood et al., 2002). Although hearing aids may restore to some extend hearing capabilities, they are of little help for tinnitus, which is the major complaint of presbycusis patients. Yet, the exposure of the population to multiple loud noise sources (at work or in public places) leads to an early onset of hearing disorders such as tinnitus. For example, 76% of the disc jockeys who have worked in nightclubs 3 nights a week for 6 years suffer from tinnitus (Potier et al., 2009). However, the highly heterogeneous etiology of tinnitus precludes the generation of a unique "universal" animal model of tinnitus and raises a major biomedical challenge. In addition to presbycusis and noise-induced hearing loss, tinnitus is associated with Ménière's disease. Other, less frequent origins include exposure to ototoxic drugs (antibiotics, nonsteroidal anti-inflammatory drugs, and chemotherapeutic agents), autoimmune processes, or infectious diseases

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(Nicolas-Puel et al., 2002). Extremely rare is somatic tinnitus triggered by voluntary or external manipulations of the jaw, movements of the eyes, or pressure applied to head and neck regions (Shore et al., 2007). Finally, the identification of tinnitus generator sites is crucial to (1) decipher the cellular and molecular tinnitus mechanisms and (2) engineer future therapies. Although several studies report that changes in central auditory structures cause tinnitus (for review see Roberts et al., 2010), others argue for peripheral (i.e., cochlea and auditory nerve) origin (Guitton et al., 2003, 2005; Ruel et al., 2008a). This chapter proposes that the auditory nerve is a potential tinnitus generator through recruitment of *N*-methyl-D-aspartate (NMDA) receptors at the first auditory synapse. In addition, the review proposes alternative mechanisms for tinnitus generation within the cochlea as well as future therapies that can be envisioned to treat tinnitus.

2 The Cochlear NMDA Receptors Hypothesis

In common with other sensory systems, a basal level of spontaneous activity (unsynchronized) is present within the auditory system, even in absence of noise. Therefore, any situation that increases spontaneous activity levels along the ascending auditory pathway can theoretically result in tinnitus (Roberts et al., 2010). This may occur when the activity of ion channels governing input and excitability of auditory synapses is altered. In the cochlea, excitation of afferent auditory fibers relies on glutamate release from inner hair cells (IHCs; Fig. 4.1). IHC synapses are characterized by an electron-dense body at each active zone, the synaptic ribbon, which tethers a halo of synaptic vesicles and is itself anchored to the plasma membrane (for reviews see Nouvian et al., 2006; Matthews & Fuchs, 2010). In response to sound stimulation, IHCs depolarize, thereby allowing calcium influx through Ca_v 1.3 voltage-gated calcium channels in the vicinity of synaptic ribbons. This calcium rise triggers the fusion of glutamate-filled synaptic vesicles to the plasma membrane, leading to transmitter release onto auditory nerve terminals (Parsons et al., 1994; Moser & Beutner, 2000). In the absence of sound, spontaneous release operates at lower frequency and drives the spontaneous activity of auditory fibers (Glowatzki & Fuchs, 2002).

2.1 NMDA Receptors and Tinnitus: The Salicylate-Induced Tinnitus Model

Aspirin and its active component salicylate have long been known to reliably cause hearing loss and tinnitus in humans that recover after treatment is stopped. While salicylate-induced hearing loss has been attributed to the reduction of outer hair cell (OHC) electromotility (Dieler et al., 1991; Shehata et al., 1991; Tunstall et al., 1995), the mechanism underlying salicylate-induced tinnitus has remained elusive

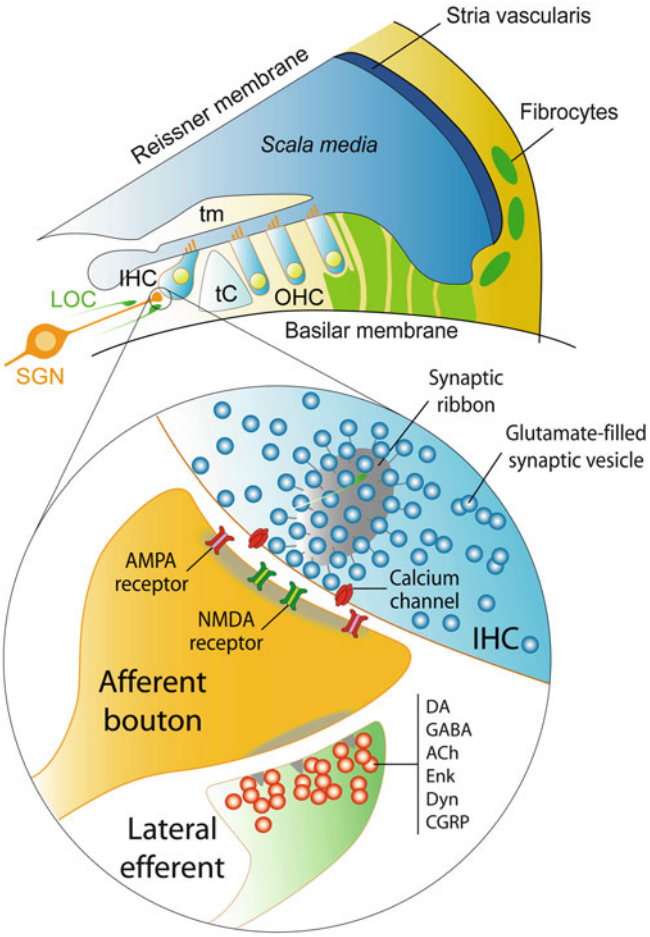

Fig. 4.1 Schematic cross section through the cochlear epithelium depicting a ribbon synapse between an inner hair cell and an afferent terminal bouton and the lateral olivocochlear feedback onto the afferent terminal. While sound encoding relies on the activation of AMPA receptors that populate the postsynaptic density of the afferent terminal, the NMDA receptor recruitment may favor tinnitus occurrence. The spiral ganglion neurons excitability is under the control of neurotransmitters/neuromodulators contained in lateral efferent terminals. tC, tunnel of Corti; OHC, outer hair cell; IHC, inner hair cell; tm, tectorial membrane; LOC, lateral olivocochlear component; SGN, spiral ganglion neuron

during decades. The salicylate-induced tinnitus model has thus been widely used to decipher (1) the location of the tinnitus generator, (2) the molecular and cellular mechanisms of tinnitus, and (3) the consequence of tinnitus from the cellular to the system level.

The systemic administration of salicylate alters the auditory neurons activity along the ascending auditory pathway (from the auditory nerve to the cortex; for review see Boettcher & Salvi, 1991; Cazals, 2000; Eggermont & Roberts, 2004).

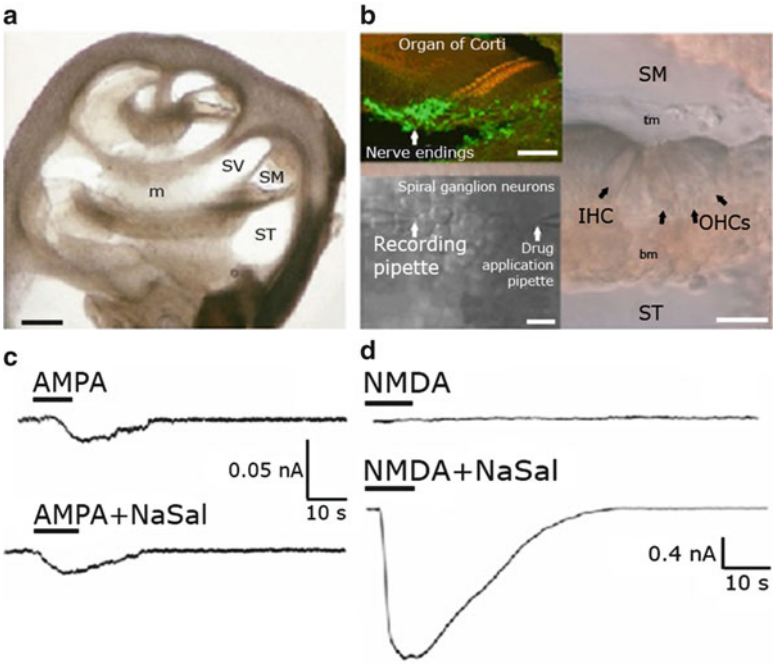

Fig. 4.2 Patch-clamp recordings of auditory neuron somata from cochlear slices. (**A**, **B**) Cochlear slices from neonatal rat. Scale bars: 500 μm (**A**), 20 μm (**B**). bm, basilar membrane; t, tectorial membrane. (**B**, upper panel) Confocal immunolocalization of hair cells (red, rhodamine phalloidin) and nerve terminals (green, neurofilament). Scale bar: 150 μm. (**B**, lower panel) Optical observation of the recording micropipette positioned in the spiral ganglion area. Scale bar = 20 μm. (**C, D**) Current responses of voltage-clamped cochlear spiral ganglion neurons induced by (**C**) 1 mM AMPA and 1 mM AMPA + 5 mM sodium salicylate and (**D**) by 1 mM NMDA and 1 mM NMDA + 5 mM sodium salicylate. (Adapted from Ruel et al., 2008a)

Therefore, any auditory nuclei or neuronal assembly can be involved in the salicylate-induced tinnitus observed with behavioral paradigms (Turner, 2007). Among the pleiotropic effects of salicylate, glutamate receptors modulation is an attractive target to modify input and excitability of auditory neurons (Peng et al., 2003). Glutamate release from IHCs yields excitatory postsynaptic currents through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation (Glowatzki et al., 2008). However, the contribution of the others glutamate-gated ion channels, the NMDA and kainate receptors, has never been firmly established at the first auditory synapse (Ruel et al., 2007), despite the fact that NMDA receptors with NR2B subunits are present at this synapse (Ruel et al., 2008a).

Recently, patch-clamp recordings and two-photon calcium imaging on cochlear slices from postnatal rats (Fig. 4.2A and B) were used to demonstrate the salicylate effects on spiral ganglion neurons. Salicylate induced no potentiation of the current elicited by AMPA (Fig. 4.2C). Conversely, although NMDA alone induced no

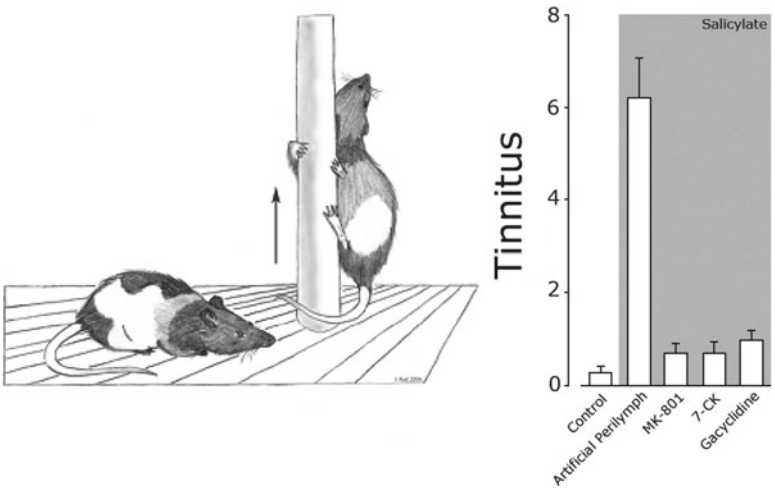

Fig. 4.3 Behavioral paradigm to assess the occurrence of tinnitus in rats. Once conditioned, animals received daily intraperitoneal injections of saline alone or containing 300 mg/kg of sodium salicylate for 4 days. The injections were performed 2 hours before the behavioral measurements. Involvement of cochlear NMDA receptors in behavioral responses (score and false positive responses) was investigated by applying antagonists (10 μM MK-801, 50 μM 7-chlorokynurenate, 7-CK, or 50 μM gacyclidine) into the fluid of the cochlea via a gelfoam placed on the round window membrane of both ears

detectable current, a large inward current was observed when salicylate was co-applied with NMDA (Fig. 4.2D). Morevover, both salicylate and arachidonate (a cyclooxygenase substrate) enabled calcium influx into spiral ganglion neurons through NMDA receptor activation (Ruel et al., 2008a). Accordingly, NMDA receptors antagonists blocked the spontaneous rate activity increase induced by an intracochlear perfusion of salicylate in adult guinea pigs (Ruel et al., 2008a). Consistently with the cyclooxygenase inhibitor role of salicylate (Vane et al., 1998), the arachidonate content increased in the whole guinea pig cochlea poisoned with salicylate (Ruel et al., 2008a). Altogether, these results suggest the following cascade: salicylate inhibits cochlear cyclooxygenase leading to an increase in arachidonate content. Arachidonate then enables NMDA receptors activation (Casado & Ascher, 1998), which causes a robust increase of the auditory fiber firing rate. Within this framework, the auditory fiber spontaneous activity increase is interpreted as an incoming sound by the central nervous system (CNS). This hypothesis has been validated using an active avoidance behavioral paradigm in rats conditioned to perform a motor task (to jump a climbing pole) when exposed to a 10-kHz tone (Fig. 4.3). The number of correct responses to sound (score) and the number of responses without sound (false positives) were counted. Whereas salicylate increased the number of avoidance responses in the absence of external sound (indicating tinnitus perception as false positives), the delivery of NMDA receptors antagonists into the cochlea reduced the number of false positives (Guitton et al., 2003).

Altogether, these data demonstrate that (1) the cochlear NMDA receptors activation contributes substantially to salicylate-induced tinnitus and (2) primary auditory neurons hyperexcitability favors tinnitus. However, one may argue that salicylate-induced tinnitus might not faithfully recapitulate human tinnitus in pathological conditions. Alternatively, the recruitment of NMDA receptors at the IHC afferent synapse during pathological conditions may lead to tinnitus.

2.2 NMDA Receptors and Tinnitus: The Noise-Induced Tinnitus Model

Tinnitus has been widely associated with noise trauma. The multiple deleterious effects of noise injury on the cochlear structure and function impede the identification of a single mechanism responsible of noise-induced tinnitus. However, some features resulting from noise trauma can be interpreted in the framework of the cochlear NMDA receptors hypothesis. While glutamate enables fast synaptic transfer, high glutamate concentration within the synaptic cleft leads to excitotoxicity (Puel, 1995). In response to sound overstimulation (noise trauma), IHCs massively release glutamate onto terminals of afferent dendrites (Puel et al., 1998). This excessive glutamate release saturates membrane glutamate transporters on supporting cells, inducing swelling and destruction of afferent terminals (Fig. 4.4). During the following days, a fraction of afferent dendrites recovers from this excitotoxic injury and connects again IHCs (Puel et al., 1995; Kujawa & Liberman, 2009, Fig. 4.4). In situ hybridization demonstrated that this reinnervation is associated with increased levels of mRNA coding the NR1 subunit of NMDA receptors in spiral ganglion neurons (Puel et al., 1995). Consistently, the perfusion of a NMDA receptors antagonist into the cochlea delayed both the reformation of synapses and the restoration of hearing (d'Aldin et al., 1997). It is therefore tempting to speculate that NMDA receptor activation during IHC reinnervation promotes a different auditory neurons firing pattern (increase/decrease or burst firing), which remains to be elucidated. An incomplete recovery or an aberrant neo-synaptogenesis may thus favor long-term recruitment at the synapse and contributes to noise-induced tinnitus, as shown for salicylate-induced tinnitus (Ruel et al., 2008a). If this hypothesis is valid, NMDA antagonist delivery into the cochlea constitutes a translational step to treat tinnitus resulting from sound overexposure.

2.3 NMDA Receptors and Tinnitus: Clinical Evidence

Cochlear NMDA receptors as a correlate to the presence of tinnitus has been probed in a compassionate clinical trial on patients with unilateral deafness associated with tinnitus (Wenzel et al., 2010). Administration of gacyclidine, a noncompetitive NMDA receptor antagonist, into the round window niche relieves tinnitus as reported from subjective criteria. However, the tinnitus perception came back,

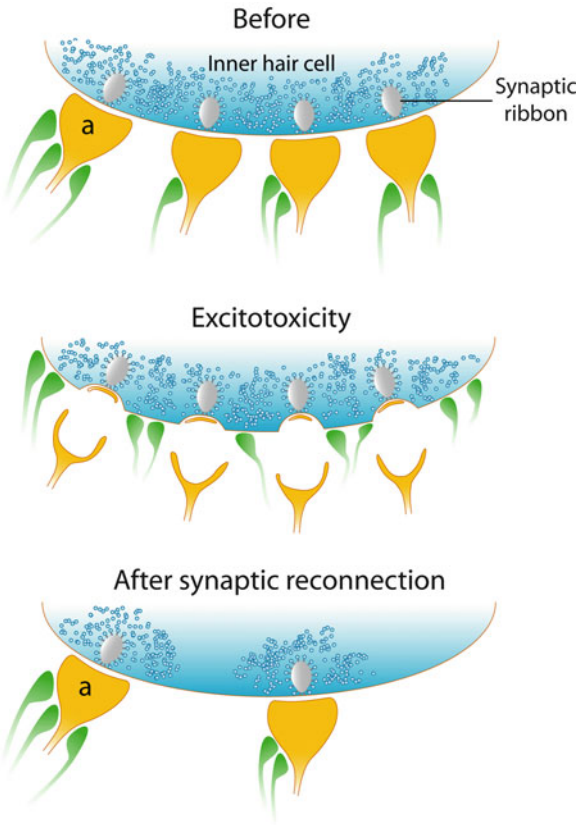

Fig. 4.4 Schematic showing afferent ribbon synapse loss after excitotoxicity. Each cochlear neuron is excited by a single glutamatergic synapse with a single IHC (top). For clarity, only four synapses are represented. A massive glutamate release during noise trauma leads to afferent boutons swelling (middle) followed by a 50% loss of synaptic ribbons and afferent fibers (bottom). *a*, type I afferent fiber

sometimes worse, several days after the end of the perfusion. Albeit this study supports the cochlear NMDA receptor hypothesis, the rather small number of cases (four of six were positive to the gacyclidine treatment) calls for larger clinical trials. In addition, a totally implantable system delivering drugs onto the round window is required to circumvent the transient effects observed in the study.

3 Alternative Cochlear Sites for Tinnitus Generation

3.1 Does the Lateral Olivocochlear Innervation Favor Tinnitus?

The cochlear function is under the regulation of the olivocochlear innervation, which comprises two subsystems: a medial olivocochlear component (MOC) originating from medial nuclei of the superior olivary complex and a lateral olivocochlear component (LOC) originating from the lateral superior olive (Guinan, 2006).

The MOC system projects onto OHCs and the LOC component projects onto primary auditory neurons dendrites beneath IHCs (Fig. 4.1). Whereas MOC terminals likely use acetylcholine and γ-aminobutyric acid (GABA) as neurotransmitters, LOC efferent terminals express dopamine, acetylcholine, GABA, enkephalins, dynorphins, and calcitonin gene-related peptide (CGRP) as neurotransmitters/neuromodulators (Eybalin, 1993). Acetylcholine release from MOC terminals hyperpolarizes OHCs through the coupling of α9–α10 nicotinic receptors to SK2 potassium channels (for review see Wersinger & Fuchs). Therefore, the MOC system activation prevents the OHC electromotile activity resulting in threshold increases and provides a protection mechanism from acoustic injury (Puel et al., 1988; Maison et al., 2002). The large number of neurotransmitters identified in LOC efferent terminals has hampered understanding of the LOC system function, although a role in neural excitability control has been proposed (Puel, 1995). Pharmacological experiments using acetylcholine, CGRP, and dynorphin support excitatory function of the LOC, while an inhibitory action is achieved by intracochlear applications of GABA, dopamine, or dopamine transporter inhibitor (Felix & Ehrenberger, 1992; Ruel et al., 2001, 2006). Interestingly, intracochlear applications of dopaminergic antagonists strongly increased the basal activity of low spontaneous rate auditory nerve fibers (Ruel et al., 2001, 2006; Fig. 4.5A). This experiment indicates a dopamine tonic release from olivocochlear terminals onto auditory nerve fibers. In addition, the increase in firing rate was immediately followed by a complete reduction of high spontaneous rate fibers spiking (Fig. 4.5B). The mechanism underlying this postexcitatory inhibition was investigated by processing cochleae for electron microscopy at the end of the recording sessions. The ultrastructural examination of the cochleae perfused with the dopamine receptor antagonists revealed that, while some auditory dendrites terminals connected to IHCs were swollen, small-sized dendritic terminals remained morphologically intact (Ruel et al., 2001, Fig. 4.5C and D). Although there are no direct arguments, one may assume that small-sized intact boutons correspond to low spontaneous rate fibers in the auditory nerve, and swollen terminals to high spontaneous rate fibers, which are more sensitive to excitotoxicity. How do these experiments relate the LOC to a potential tinnitus generator? First, the spontaneous firing rate increase may be interpreted as an incoming sound by the CNS. Then, the alterations in auditory dendrite terminals seen in electron microscopy recall those observed after noise trauma. Excitotoxicity may thus occur at the first auditory synapses after administration of dopaminergic antagonists. In this scenario, an expected synaptic repair will promote NMDA receptor activation, which would in turn favor a new pattern of auditory fiber activity.

3.2 Are Inner Hair Cells Involved in Tinnitus Generation?

The auditory fiber firing rate is driven by glutamate release from IHCs. Despite no direct proof has been reported for the involvement of transmitter release into tinnitus perception, the IHC presynatic active zone would be the most appropriate structure

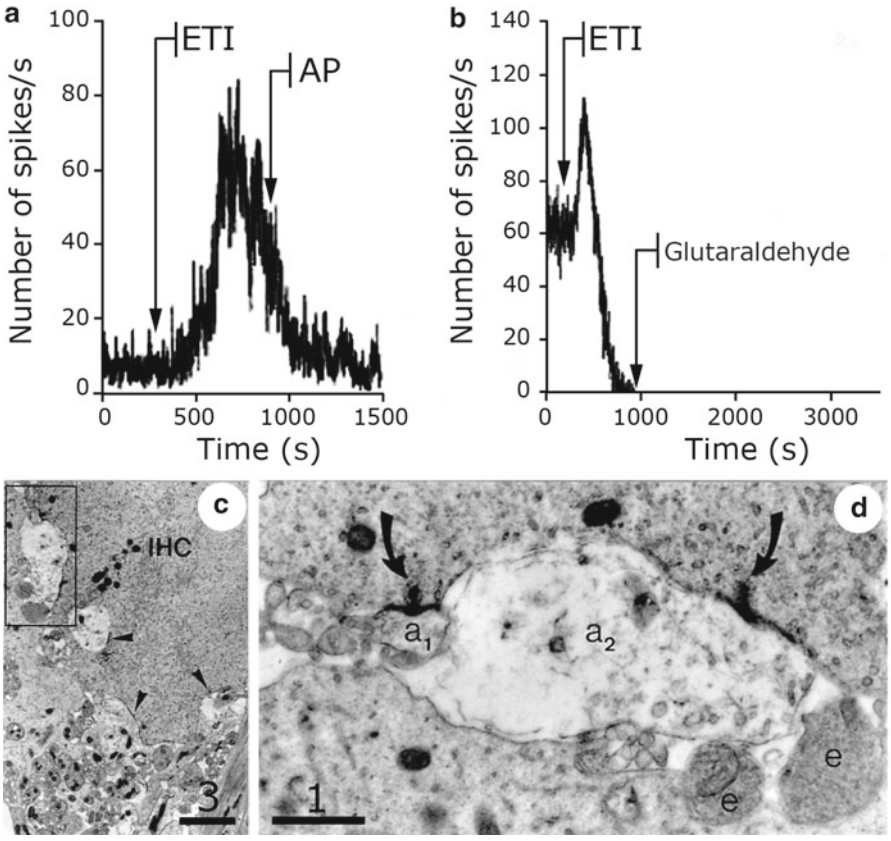

Fig. 4.5 (**A**) A 10-min perfusion of the selective D2 antagonist eticlopride (ETI, 50 μM) induced a strong increase of the firing rate of a low spontaneous firing rate auditory nerve fiber. The fiber coded for 12 kHz with a 12 spikes/s spontaneous firing rate and a 35-dB sound pressure level (SPL) threshold at the characteristic frequency (Q10 dB = 3). The eticlopride effect was reversed by a perfusion of artificial perilymph (AP). (**B**) A similar 10-min perfusion of 50 μM eticlopride (ETI) elicited a fast transient increase of the firing rate of a high spontaneous rate fiber followed by a marked firing reduction. The nerve fiber coded for 9 kHz with a 68 spikes/s spontaneous rate activity and a 12 dB SPL threshold at the characteristic frequency (Q10 dB = 6). (**C, D**) Electron microscopy of an IHC base fixed as indicated in **B**. (**C**) Some afferent dendrites are swollen (arrowhead). The boxed area in (**C**) is enlarged in (**D**). It shows two normal synaptic ribbons (curved arrows) facing an intact dendrite (*a1*) on the left and a swollen dendrite (*a2*) on the right that is contacted by two vesiculated lateral efferent terminals (*e*). Scale bars = 3 μm (**C**); 1 μm (**D**). (Adapted from Ruel et al., 2001)

to elicit changes in auditory fiber firing rate, thus favoring tinnitus. Calcium imaging in hair cells has revealed localized microdomains with elevated [Ca^{2+}] (referred to as calcium hotspots), arising from synaptic calcium influx (Issa & Hudspeth, 1994, 1996; Tucker & Fettiplace, 1995; Zenisek et al., 2003). It has been suggested that the high calcium microdomains heterogeneity within a single IHC governs the spectrum of auditory neurons firing rate (Frank et al., 2009; Meyer et al., 2009).

Therefore, any change in calcium signaling at the IHC active zone would influence the rate behavior of auditory fibers. Interestingly, NMDA receptors, which are calcium permeable, have been shown to be localized at IHC synapses in postsynaptic densities and presynaptic active zones, in close vicinity to synaptic ribbons (Ruel et al., 2008a). However, functional evidence for presynaptic NMDA receptors is still lacking.

IHCs can also be targets of LOC regulation after an excitotoxicity. At the same time that auditory dendrites terminals swell and synapses with IHCs disrupt, the LOC undergoes a synaptic plasticity-like process. Transmission electron microscopic examination showed that LOC terminals synaptically connected IHCs during the period of auditory dendrite regrowth (Puel et al., 1995). This LOC rewiring may therefore alter IHC excitability (excitation or inhibition), leading to modified activities at the active zones. Here again, future experiments are needed to demonstrate that the IHC membrane potential is under the control of LOC terminals after excitotoxicity.

4 Summary

Addressing future therapies for tinnitus requires deciphering its molecular mechanisms. The first auditory synapse has been shown to be responsible for deafness (Yasunaga et al., 1999; Kim et al., 2004; Delmaghani et al., 2006; Ruel et al., 2008b; Baig et al., 2011). In addition, the NMDA receptor contribution to salicylate-induced tinnitus pinpoints the auditory synapse as a potential source of peripheral tinnitus. Therefore, NMDA receptors are attractive targets to design therapeutics. However, the systemic administration of substances acting on NMDA receptors would favor their binding to brain receptors before they reach the cochlea, likely causing dramatic side effects. Alternatively, NMDA antagonists delivery through the round window membrane provides an interesting clinical perspective to circumvent unwanted side effects. Indeed, drug delivery systems to apply molecules onto the round window membrane are already commercially available (Silverstein Microwick™, Summit Medical, Inc., St-Paul MN; Intraear™ Durect Corp., Cupertino, CA). These drug delivery systems enable gentamicin-induced labyrinth destruction in patients with vertigo caused by Menière's disease. However, since the first clinical trial indicated that an efficient tinnitus therapy requires a long-term application of NMDA antagonists (Wenzel et al., 2010), the development of a totally implantable drug delivery system is therefore mandatory to achieve a successful local tinnitus therapy.

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Chapter 5
Dorsal Cochlear Nucleus: Somatosensory–Auditory Interactions in Tinnitus

Susanne Dehmel, Seth D. Koehler, and Susan E. Shore

1 Introduction

In normal individuals, phantom auditory sensations like tinnitus can develop during head, neck, and jaw muscle contractions (Levine et al., 2003). In more than two thirds of people with chronic tinnitus, active and passive manipulations of these regions, such as jaw clenching or tensing the neck muscles, can alter the loudness, pitch, and location of the tinnitus (Pinchoff et al., 1998; Levine, 1999), and tinnitus can occur after somatosensory insults (Rubinstein et al., 1990). These observations led to the definition of a "somatic tinnitus" syndrome (Levine et al., 2003) in which an imbalance of bimodal somatosensory–auditory integration was hypothesized as its underlying cause (Levine, 1999; Shore et al., 2007). After noise-induced tinnitus, somatic tinnitus is the second most common type of tinnitus (Eggermont, 2005).

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2 Correlates of Tinnitus in the Cochlear Nucleus

Significant work has been done in cats and rodents to identify physiological, molecular, and anatomical markers for tinnitus in the cochlear nucleus (CN). Tinnitus correlates have been identified as changes that follow the types of hearing damage known to induce tinnitus in humans, such as those caused by ototoxic drug administration, narrowband or impulse noise-exposure, or somatic insults. Because the incidence of tinnitus after hearing damage is highly variable, behavioral measures of the presence and nature of the damage-induced tinnitus have been used to confirm that these changes are indeed correlates of tinnitus and not only a result of hearing damage (Jastreboff et al., 1988; Brozoski et al., 2002; Turner et al., 2006).

2.1 Physiological Correlates of Tinnitus in the CN

2.1.1 Tonotopically Restricted Spontaneous Hyperactivity After Hearing Damage

Cochlear damage, known to result in tinnitus, induces increased spontaneous firing rates (SFRs) in neurons in the dorsal and ventral CN (DCN; VCN) (Kaltenbach & McCaslin, 1996; Bledsoe et al., 2009). Noise and cisplatin, but not salicylate, exposure induce hyperactivity in the DCN (Kaltenbach et al., 2002, 2004; Wei et al., 2010). Increased SFR in the DCN is observed primarily in fusiform cells (Fig. 1A and B), the principal output neurons of the DCN (Brozoski et al., 2002; Shore et al., 2008; Finlayson & Kaltenbach, 2009), but may also be found in the inhibitory interneurons, cartwheel cells (see Section 5.2.1.2). Elevated SFR that follows hearing damage is usually confined to a restricted region of the tonotopic axis related to the region of cochlear damage (Fig. 5.1C) and is maximal at frequencies above the traumatizing frequency (Kaltenbach & Godfrey, 2008). This parallels results of psychophysical studies in humans in which the tinnitus frequency correlates with the edge frequency of the audiogram, the frequency with the severest hearing loss or the frequency range of the hearing loss (Eggermont & Roberts, 2004; Schaette & Kempter, 2009; Moore et al., 2010). One study reported tinnitus at a frequency below the exposure frequency. The tinnitus was accompanied by elevated sound-evoked rates in response to the tinnitus frequency and best-frequency tones (Brozoski et al., 2002). The increased SFR shown in Figure 5.1 has a peak along the tonotopic axis of the DCN in tone-exposed animals with evidence of tinnitus (Kaltenbach et al., 2004). The profile of increased SFR is also wider than the profile for the response to sound, consistent with a narrow or wideband, rather than a pure tone tinnitus percept.

Elevated SFRs develop at different rates depending on the auditory structure (e.g., more rapidly in VCN than in DCN) (Kaltenbach & Afman, 2000; Bledsoe et al., 2009) and may reflect mechanisms that change over time because elevations in DCN SFRs survive cochlear ablation (Zacharek et al., 2002) but those in inferior colliculus (IC) do not (Mulders & Robertson, 2009).

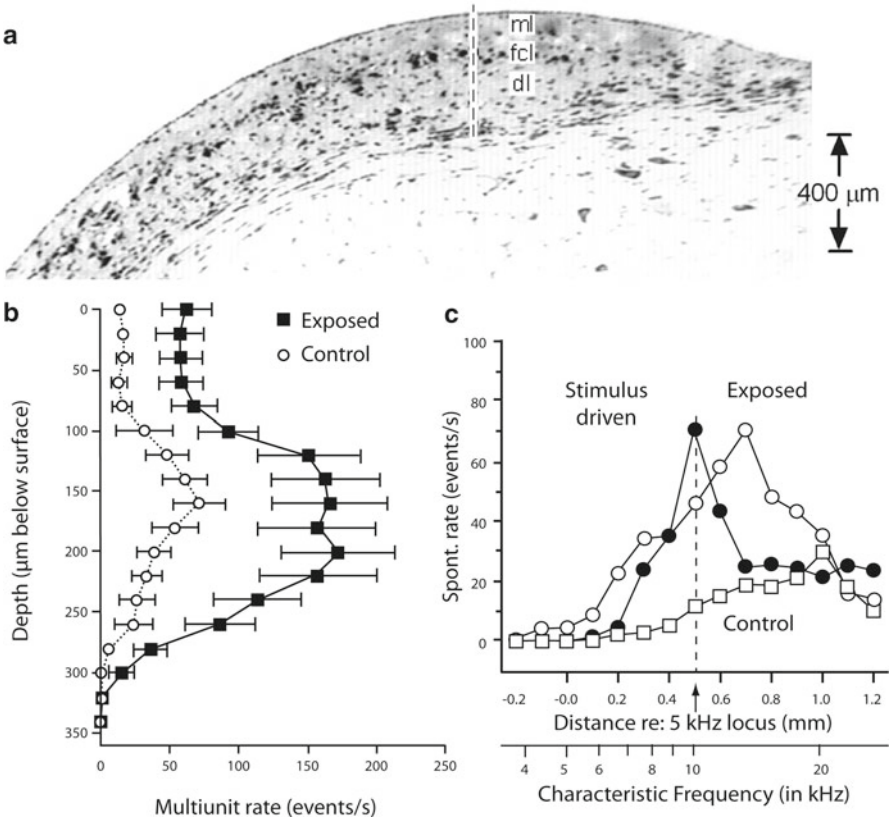

Fig. 5.1 Multiunit SFRs are elevated in tone-exposed animals in the fusiform cell layer at points in the tonotopic axis above the exposure tone. (**A**) Transverse section showing the DCN fusiform cell layer. fcl, fusiform cell layer; ml, molecular layer; dl, deep layer. (**B**) Activity profile of control and exposed animals along a vertical penetration through the DCN; exposure sound was a 10 kHz tone, 115 dB sound pressure level (SPL) for 4 hours. SFR was measured 5–6 days after the exposure. (C) SFRs of noise-exposed (open circles) and control animals (squares) are compared to stimulus-driven rates (10 kHz, 20 dB sensation level) for control animals (filled circles). The dashed line and arrow labels the tonotopic locus of the exposure tone frequency. (**A**, **B**: From Finlayson and Kaltenbach, 2009.) (**C**: From Kaltenbach and Godfrey, 2008.)

2.1.2 Increased Bursting Activity

After noise exposure, increased burst firing (Fig. 5.2) has been identified in DCN that could account for about 50% of SFR increases seen in this structure (Finlayson & Kaltenbach, 2009). Although this suggests increased SFRs in cartwheel cells, which fire complex spikes under normal conditions, it is not clear whether the increased bursting corresponds to increased cartwheel cell activity or increased burst firing in fusiform cells.

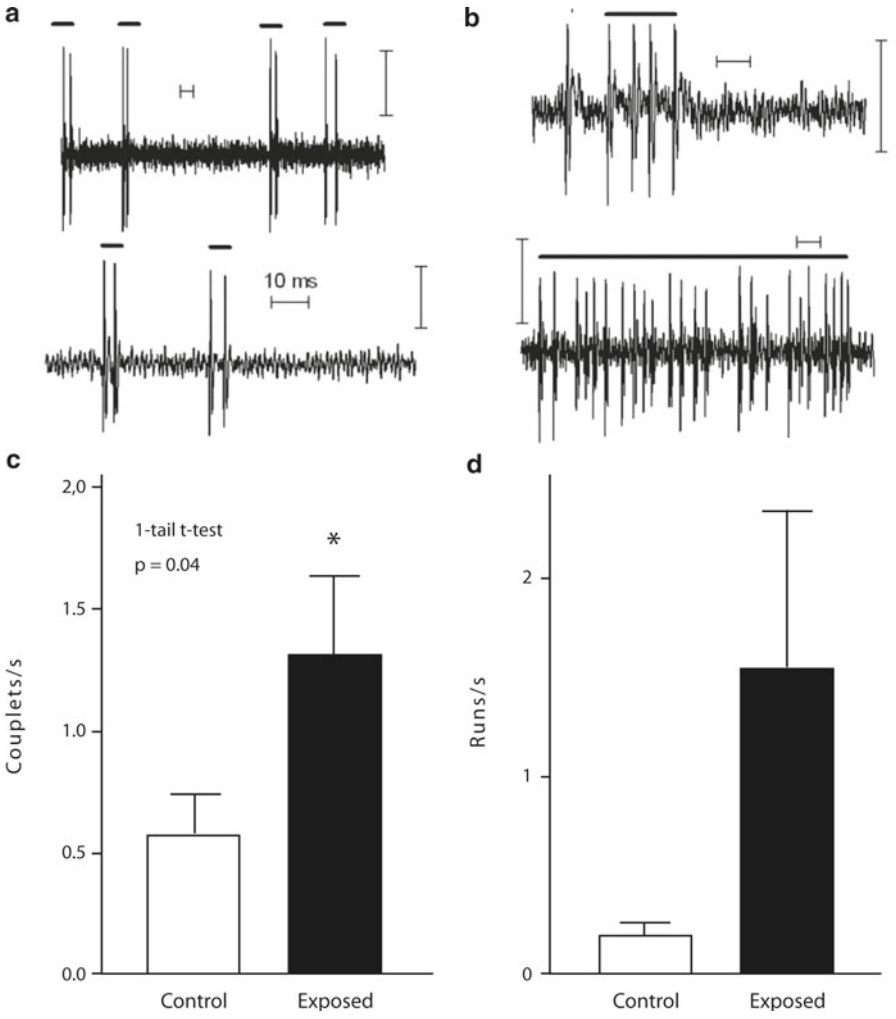

Fig. 5.2 Noise-exposure induces increased bursting activity in the DCN. Spike trains of exposed animals show bursting in the form of couplets (spike pairs, **A**) or in runs (3–5 or up to 10 spikes per run (**B**). Couplets and runs are marked by horizontal bars above the trace. Horizontal scale bars = 10 ms; vertical scale bar = 50 μV (**A**, **B**). The rate of couplets (**C**) and run occurrences (**D**) was increased in exposed compared to control animals. (From Finlayson and Kaltenbach, 2009.)

2.1.3 Increased Neural Synchrony

Of the three types of neural activity proposed as tinnitus correlates (increased SFR, neural synchrony, and bursting activity), changes in neural synchrony in auditory pathways (Seki & Eggermont, 2003) correspond most closely to the frequency profile of hearing loss and tinnitus (Norena et al., 2002; Roberts et al., 2008). Increased neural synchrony in the hearing loss regions in auditory cortex and IC corresponds well

with the tinnitus spectrum (Bauer et al., 2008). Elevated synchrony has also been shown in DCN in vitro after narrowband noise exposure (O'Donahue et al., 2010). Because synchrony can be transmitted with high fidelity from one brain center to another (Masuda & Kori, 2007; Takahashi et al., 2009), the increased synchrony shown in IC and cortex might be initiated in the DCN. Elevated SFRs may play a crucial role by providing a substrate for increased synchronous activity, but synchrony may be the neural correlate of tinnitus in the DCN that is more likely to impact postsynaptic targets and recruit IC and cortical neurons into a tinnitus percept.

2.2 *Anatomical and Molecular Correlates of Tinnitus in the DCN*

Increased SFRs in DCN fusiform cells likely reflect a shift in the balance of excitation and inhibition as a result of diminished inhibitory or enhanced excitatory neurotransmission (see Section 5.3 on somatosensory influence) after auditory nerve deafferentation (Wang et al., 2009; Zeng et al., 2009; Dong et al., 2011). Impairment of glycinergic inhibitory neurotransmission after noise exposure (Wang et al., 2009) could unmask areas of increased SFR. Glycine receptor (GlyR) α_1 decreases in DCN have been shown in rats with behavioral evidence of tinnitus while the anchoring protein, gephyrin, increased, suggesting changes in intracellular receptor trafficking some months after traumatic sound. Consistent with decreased α_1 subunit protein levels, strychnine binding studies show tinnitus-related decreases in the number of GlyR binding sites (Fig. 5.3). Tinnitus-associated hearing damage also induces changes in serotonergic, endocannabinoid and nitric oxide transmission. Serotonergic neurons in the dorsal raphe nucleus that project to the CN are more active after tinnitus induction by salicylate (Thompson & Thompson, 2001; Caperton & Thompson, 2011). In VCN salicylate models of tinnitus, endocannabinoid receptors are down-regulated (Zheng et al., 2007) whereas nitric oxide synthase is up-regulated (Zheng et al., 2006). There is no change in either of these receptor systems in the DCN in salicylate models, but it is not known how these neurotransmitter systems are affected in a noise-exposure model of tinnitus.

2.3 *Theoretical Role of the DCN in Tinnitus*

The presence of tonotopically restricted hyperactivity, bursting activity, and elevated neural synchrony in this early brainstem nucleus indicate that the DCN could convey already formed neural patterns representing tinnitus to higher auditory nuclei such as IC and auditory cortex. Several mechanisms have been proposed by which the DCN develops tinnitus correlates after deafferentation. One possibility is homeostatic plasticity that results after inner or outer hair cell loss (Schaette & Kempter, 2009) and increases the excitability of deafferented neurons. As described in Section 5.2.2, a reduction in glycinergic neurotransmission could lead to an unmasking of

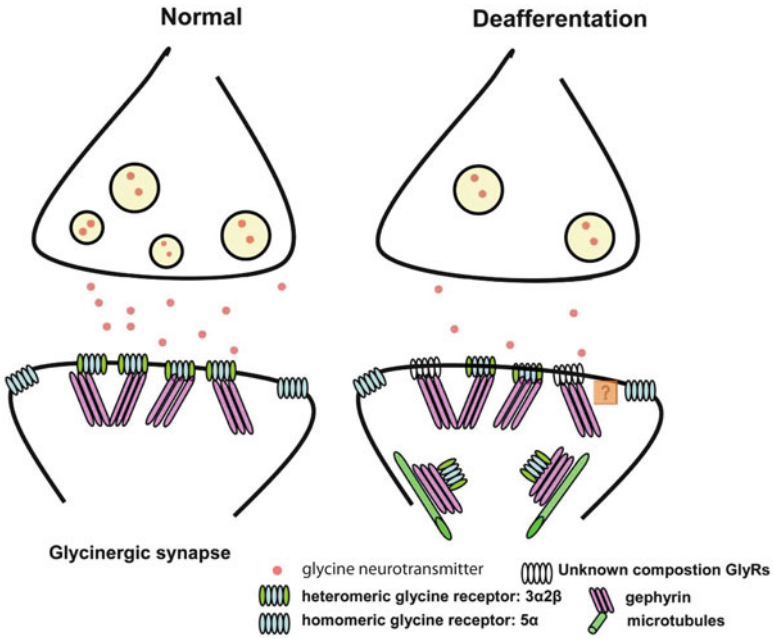

Fig. 5.3 Plastic changes in glycinergic synapses over fusiform cells in DCN after sound exposure. Glycine released from presynaptic terminals acts on postsynaptic heteromeric and extrasynaptic homomeric GlyRs under normal conditions (left). Gephyrin is an anchoring protein that directly interacts with the large intracellular loop of GlyR subunits. After sound overexposure and consequent peripheral auditory deafferentation, there is less glycine release from presynaptic terminals to fusiform cells in DCN (right). As a compensatory response, postsynaptic membrane GlyR decreases or receptor composition changes, or both. Gephyrin may also serve as the intracellular retrograde transport adapter that links GlyRs with the microtubule-dependent dynein motor complex to remove abnormal functional GlyRs from postsynaptic membrane. (From Wang et al., 2009.)

excitatory activity. Alternative or complementary explanations involve upregulation of excitatory inputs and alterations in their receptors. The somatosensory innervation of the CN and its upregulation after cochlear damage is one example of this type of neuroplasticity, as discussed in Section 5.3.

3 Role of Somatosensory Innervation of the CN in the Generation and Modulation of Tinnitus

The functional connection between the somatosensory and auditory systems is exemplified in the observations that tinnitus patients can modify their tinnitus with somatic maneuvers and that tinnitus can be produced by somatosensory insults. However, this connection is also apparent in subjects without tinnitus in whom proprioceptive and tactile input can influence sound-source lateralization and speech

and sound-level perception (Lewald et al., 1999; Schurmann et al., 2004; Ito et al., 2009). In addition, responses to jaw protrusion have been observed along the auditory pathway in a functional magnetic resonance imaging (fMRI) study (Lanting et al., 2010). Bimodal interactions between the somatosensory and auditory systems occur as a result of their extensive anatomical connections at all levels of the auditory pathway (Dehmel et al., 2008). At the outset, innervation of the CN by somatosensory ganglia and brainstem nuclei (see Section 5.3.1) that convey somatosensation from the head and neck, as well as multisensory responses recorded from DCN neurons (see Section 5.3.2), are consistent with somatosensory inputs to the DCN playing a role in tinnitus pathology.

3.1 Somatosensory Innervation of the CN

3.1.1 Somatosensory Innervation from the Dorsal Root Ganglion and Trigeminal Ganglion to the CN

The dorsal root ganglion (DRG) of the spinal nerve at the C2/7/8 level and the trigeminal ganglion (TG) contain the primary somatosensory neurons that project to the CN (Pfaller & Arvidsson, 1988; Shore et al., 2000; Zhan et al., 2006). The DRG is the origin of the spinothalamic pathway and the dorsal column–medial lemniscal system. The first pathway mediates itch, crude touch, temperature, and pain; and the latter carries proproceptive and fine touch information to the dorsal column nuclei, nucleus cuneatus, and nucleus gracilis, which receive their input from the head (pinna), neck, shoulders, *upper* trunk and limbs, and from the *lower* trunk and limbs respectively. DRG neurons terminate on primary dendrites of unipolar brush cells and the distal dendrites of granule cells located predominantly in the subpeduncular corner (between the anterior VCN and the inferior cerebellar peduncle) and lamina of the granule cell domain (GCD), which includes the shell region and the fusiform cell layer of the DCN (Pfaller & Arvidsson, 1988; Zhou & Shore, 2004; Zhan et al., 2006).

TG neurons that project to the CN innervate the vocal tract/intraoral structures such as tongue muscles, jaw, and the temporomandibular joint and project to the brainstem trigeminal sensory complex, which contains the spinal trigeminal nucleus (Sp5) (Romfh et al., 1979; Nazruddin et al., 1989; Takemura et al., 1991). TG projections to the CN consist of thin fibers and *en passant* boutons terminating mainly on CN granule cells but also on large cells in magnocellular regions of the VCN (Shore et al., 2000).

3.1.2 Somatosensory Innervation from the Sp5 and Dorsal Column Nuclei

Sp5 and the dorsal column nuclei contain the secondary neurons of the somatosensory pathways that project to the CN. The distribution of CN-projecting neurons in Sp5 in Figure 5.4A–C suggests that they carry mainly non-nociceptive information

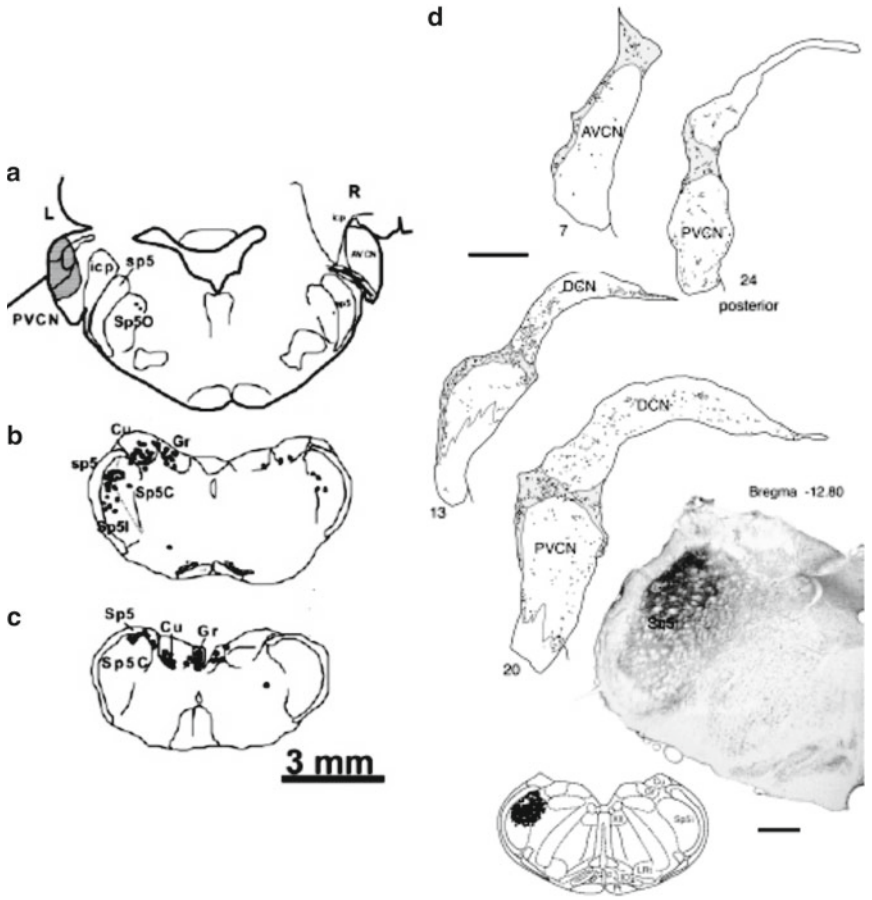

Fig. 5.4 The caudal and intermediate parts of the Sp5 innervate the ipsilateral granule cell domain, deep DCN and magnocellular VCN. (**A**) The shaded area represents the fluorogold injection site. (**B**, **C**) Each dot represents a retrogradely labeled neuron after injection of fluorogold into the CN in one animal. Drawings are made from serial transverse sections from rostral (**A**) to caudal (**C**). (**D**) The photo and drawing of the anterograde tracer (biotinylated dextran amines) injection site in the Sp5 is shown on the lower right. Each dot represents a labeled terminal, which mostly concentrate in the GCD and deep DCN. Scale bars = 0.5 mm. AVCN, anteroventral cochlear nucleus; Cu, cuneate nucleus; DCN, dorsal cochlear nucleus; Gr, gracile nucleus; icp, inferior cerebellar peduncle; IO, inferior olive; LRN, lateral reticular nucleus; Pt, pyramidal tract; PVCN, posteroventral cochlear nucleus; Sp5, spinal trigeminal nucleus; sp5, spinal trigeminal tract; Sp5C, pars caudalis of Sp5; Sp5I, pars interpolaris of Sp5; XII, hypoglossal nucleus. (**A–C**: From Zhou and Shore, 2004; **D**: From Haenggeli et al.,2005.)

(Zhou and Shore, 2004; Shore and Zhou, 2006). Sp5 terminal endings are scattered across the entire CN (Fig. 5.4D), making synaptic contacts with granule cells or large principal cells (Wolff & Kunzle, 1997; Haenggeli et al., 2005). Dorsal column projection neurons from the cuneate and gracile nuclei terminate as mossy fibers

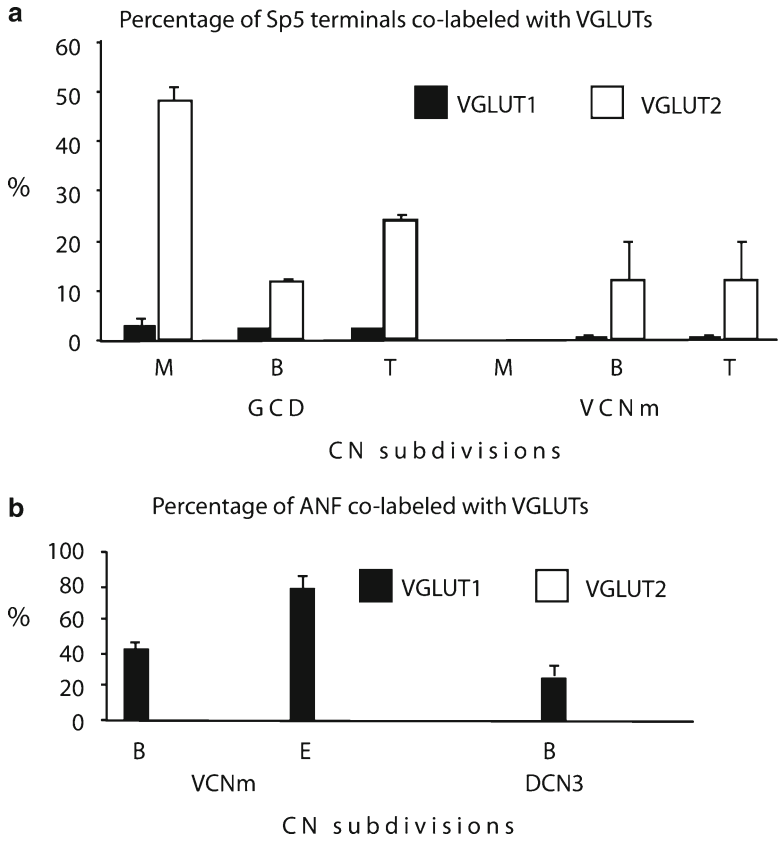

Fig. 5.5 Auditory nerve fiber endings colable with VGLUT1 and endings from the spinal trigeminal nucleus mainly colable with VGLUT2. (**A**) About 50% of MFs and 12% of small Sp5 boutons colabeled with VGLUT2. Very few Sp5 MFs colabeled with VGLUT1 (paired *t*-test, p 0.05). (**B**) In contrast, many labeled ANFs (79.5% of endbulb-like terminals and 43.0% of bouton terminals) colocalized with VGLUT1 in the VCNm as well as in the DCN3 (26.0%). Neither ANF endbulb-like terminals nor small boutons were colocalized with VGLUT2. Bars represent mean and SEM. M, mossy fibers; B, boutons; T, total (M and B); E, endbulb-like terminals; GCD, granule cell domain; VCNm, magnocellular VCN; DCN3, deep DCN. (From Zhou et al., 2007.)

and small boutons mainly on granule cells in the GCD (Itoh et al., 1987; Weinberg & Rustioni, 1987; Wright & Ryugo, 1996).

Vesicular glutamate transporters (VGLUT) have been used as markers for glutamatergic projections and the two subtypes VGLUT1 and VGLUT2 show different distributions in the CN (Kaneko et al., 2002). VGLUT1 is expressed primarily in the magnocellular regions of the VCN, the deep layer of the DCN, and the molecular layer of the DCN, whereas the most intense VGLUT2 labeling is found in the GCD. Auditory nerve fibers (Fig. 5.5A) exclusively colabel with VGLUT1 (Zhou et al., 2007; Zeng et al., 2009); in contrast, somatosensory inputs (Fig. 5.5B) from cuneate nucleus and Sp5 colabel primarily with VGLUT2 (Zeng et al., 2011). This raises the

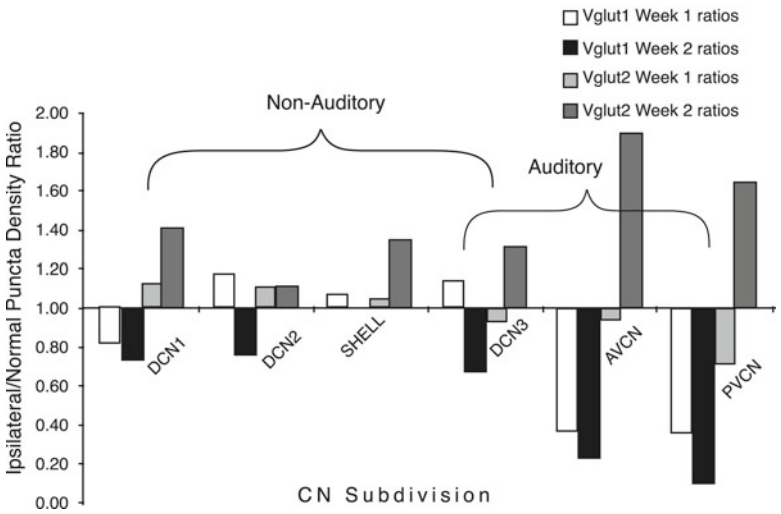

Fig. 5.6 The number of VGlut2-positive terminals increases in the CN after unilateral deafening with kanamycin injections. The ratio of VGLUT immunoreactivity between deafened and normal animals is shown. A ratio above 1 indicates an increase in puncta density after deafening, a ratio below 1 indicates a decrease. At 1 and 2 weeks after deafness, VGLUT1 is decreased in VCNm (AVCN and PVCN) and DCN3, reflecting the large reduction of VIIIth nerve terminals. In contrast, VGLUT2 is elevated above normal in DCN1, DCN2, and the Shell region at 1 week after deafness and is elevated in all regions by 2 weeks. DCN 1, 2, 3, molecular, fusiform, and deep layers of DCN; shell, shell region; DCN, AVCN, and PVCN, dorsal, anteroventral, and posteroventral cochlear nucleus. (From Zeng et al., 2009.)

possibility of functional differences in the roles of VGLUT1 versus VGLUT2 in synaptic excitation (Gras et al., 2002; Varoqui et al., 2002; Fremeau et al., 2004). Animal models show correlations between changes in VGLUT2 expression with disorders characterized by hyperexcitability such as neuropathic pain and epilepsy (Wallen-Mackenzie et al., 2010). Paralleling those findings VGLUT2 might also play a role in the development of tinnitus after deafening: plastic changes after unilateral deafening lead to significantly increased numbers of VGLUT2-positive puncta in regions of the CN that receive somatosensory inputs, suggesting that increased glutamatergic, nonauditory inputs might underlie hyperexcitability resulting in tinnitus (Fig. 5.6).

The presence of mossy fiber inputs from Sp5 and cuneate nucleus in the CN GCD suggests that these connections induce synaptic plasticity. Evidence for this comes from cerebellar mossy fibers, which adjust synaptic strength by modulating their neurotransmitter release (Sola et al., 2004). Short- and long-term plasticity has also been shown for mossy-fiber synapses in the hippocampus (McBain, 2008; Chen et al., 2010). Adjustable somatosensory mossy fiber inputs to the CN GCD could interact with increased numbers of somatosensory mossy fibers to modulate CN output activity and contribute to neuroplastic changes after auditory deafferentation, which may lead to tinnitus.

3.2 Somatosensory–Auditory Integration in the DCN

3.2.1 Dorsal Column and Trigeminal Stimulation Effects on Spontaneous and Sound-Evoked DCN Responses

Electrically stimulating the medullary somatosensory nuclei (MSN, dorsal column nuclei and Sp5 combined) primarily inhibits spontaneous activity in DCN fusiform and giant cells (Young et al., 1995; Davis et al., 1996). The influence of dorsal column stimulation on sound-evoked responses of DCN chopper neurons was first investigated by Saade et al. (1989), who showed either a facilitating or suppressing bimodal interaction depending on the delay between the auditory and somatosensory stimuli. Dorsal column stimulation affected the early temporal characteristics of sound-evoked responses of most DCN principal cells by increasing the latency of tonic and pauser responses, converting the latter to buildup responses (Fig. 5.7 A and B). Rate changes for the remainder of the response were seen in 30% of the units, which mostly resulted in rate enhancement (Fig. 5.7 C). Half of the recorded cartwheel cells also showed rate decreases. In contrast, only a few vertical cells showed slight rate decreases (Kanold et al., 2011).

Electrically stimulating the TG evoked responses in 29% of DCN fusiform cells (Shore, 2005). In contrast to the mainly suppressing effect of dorsal column stimulation, a similar number of units were excited (i.e., showed purely excitatory responses or excitatory responses followed by inhibition) and inhibited (Fig. 5.8). In contrast to stimulation of primary neurons in the TG, Sp5 stimulation exerted a predominantly excitatory effect on SFRs of pauser-buildup, buildup, and chopper neurons (52% excitatory responses vs. 17% inhibitory or excitatory–inhibitory responses; Koehler et al., 2011).

Preceding sound stimulation with electrical stimulation of the TG resulted in bimodal suppression in the majority of units (60% suppression vs. 18% enhancement, Fig. 5.9). In contrast to the dominance of bimodal suppression during TG stimulation, effects of Sp5 stimulation during bimodal integration were equally suppressive (41%) and enhancing (38%), even though the effect of Sp5 stimulation alone was predominantly excitatory (Koehler et al., 2011). However, these patterns were segregated according to their sound-evoked response type; chopper units showed only bimodal enhancement whereas buildup units showed only bimodal suppression. Sp5 stimulation can also alter the *timing* of sound-evoked responses, by increasing or decreasing the regularity of firing and the latency of the auditory response, which is manifest as a change in the amount of chopping and the consistency of the first interspike interval (Fig. 5.10). Evidence described here, that neurons in the spinal trigeminal and dorsal column nuclei can change neural responses to sound in the DCN, suggests that somatosensory inputs to DCN can modulate or generate increased SFRs after hearing damage that are neural correlates of tinnitus.

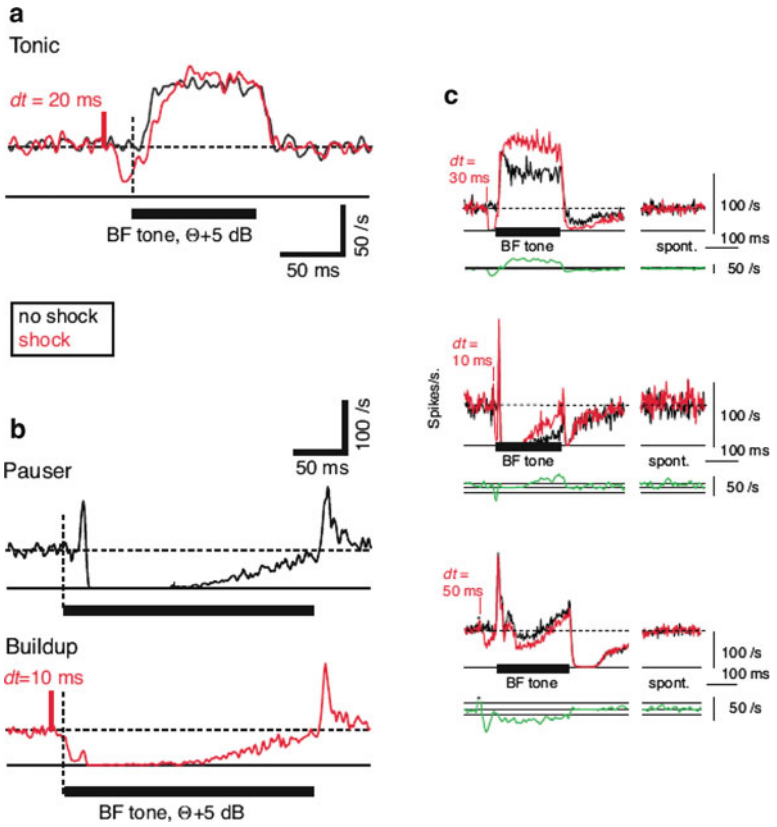

Fig. 5.7 Electrical stimulation of the dorsal column increases the latency of acoustic responses and enhances or suppresses the discharge rate for the later response components. PSTHs for the acoustic response (black) are compared to the acoustic response preceded by an electric shock to the dorsal column (red). Dt represents the time interval. The duration of the acoustic stimulus is marked by the black horizontal bar. The spontaneous rate is labeled as a dashed line. With dorsal column stimulation, the first spike is delayed in the tonic response (**A**) and the pauser is converted to a buildup response (**B**). (**C**) Examples for units in which the rate during the remainder of the response is influenced by dorsal column stimulation. In most units this influence was seen as rate enhancement (top two examples); in others a suppression was observed. Rate differences (with-shock minus no-shock) are plotted as green traces, horizontal lines show mean ±1 SD from the spontaneous rate. Significant rate changes are present where the rate differences are outside the ± 1SD area. (From Kanold et al., 2011.)

3.2.2 Role of Somatosensory–Auditory Integration in the DCN in Tinnitus

In species with movable pinna, inputs from the dorsal column that encode pinna movements may be used to cancel spectral changes due to pinna movements, in order to distinguish spectral changes due to sound source movements for sound

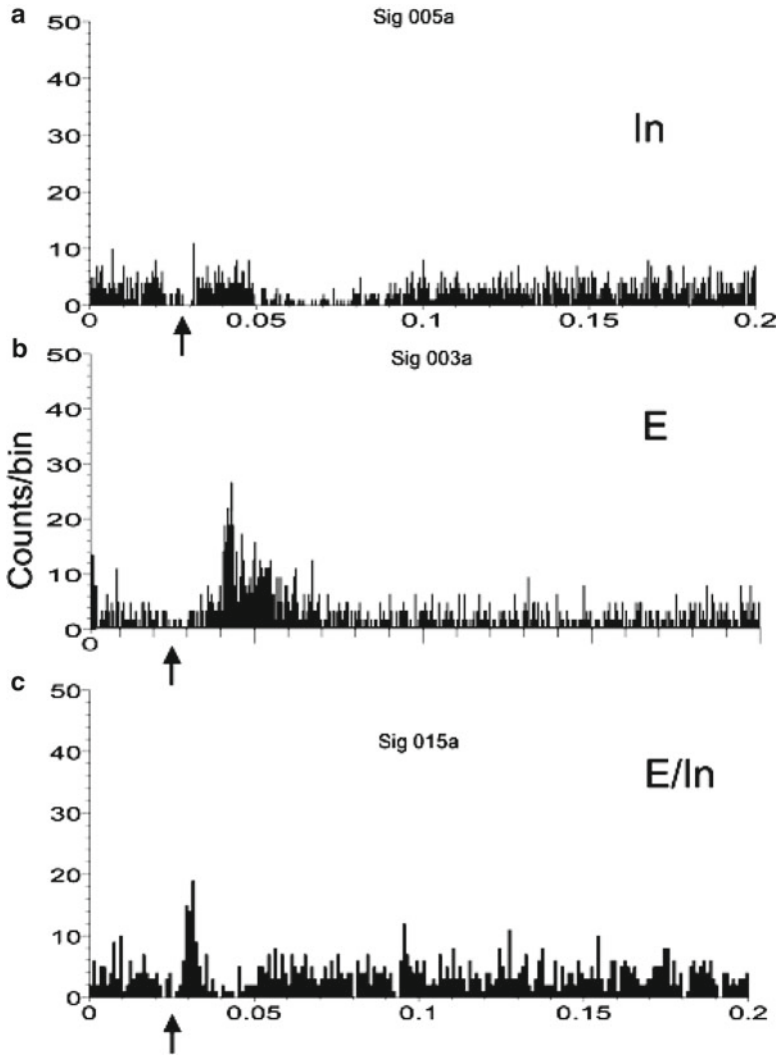

Fig. 5.8 Fusiform cells in the dorsal cochlear nucleus show inhibitory (In), excitatory (E), and mixed excitatory–inhibitory (E/In) responses to trigeminal ganglion stimulation. The arrow indicates the time of trigeminal ganglion stimulation with 80 μA. PSTHs are averaged for 200 presentations, bin width, 1 ms. (**A**) The inhibitory response has a latency of 20 ms and lasts for approximately 70 ms. (**B**) The latency of the excitatory response is approximately 15 ms and lasts for around 25 ms. (**C**) Example for an E/In type response, in which the excitation is followed by inhibition lasting approximately 20 ms. (From Shore, 2005.)

localization in the vertical plane (May, 2000; Oertel & Young, 2004). In humans, sound source lateralization can be altered by somatosensory input from the dorsal column during stimulation of the neck muscles (Lewald et al., 1999). This might explain cases in which the tinnitus location changes with somatic maneuvers

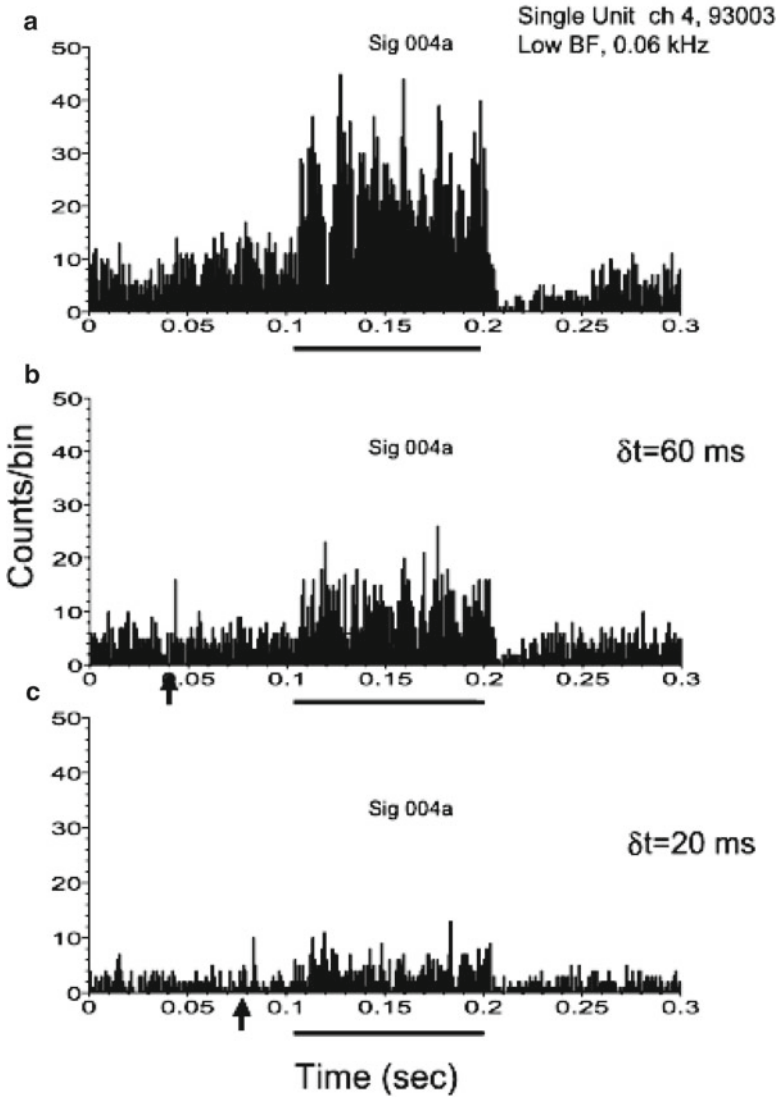

Fig. 5.9 Trigeminal stimulation differentially suppresses responses to broadband noise (BBN) depending on the temporal gap (dt) between the two bimodal stimuli. Poststimulus time histograms of responses from one single unit to combined trigeminal and acoustic stimulation (80 μA+30 dB SPL BBN) are shown. (**A**) BBN alone. (**B**) Trigeminal stimulation precedes BBN by 60 ms. (**C**) Trigeminal stimulation precedes BBN by 20 ms. Suppression is greatest at small dt values. Arrow shows onset of trigeminal stimulation; bar below PSTH shows onset and duration of BBN. Bin width, 1.0 ms. (From Shore, 2005.)

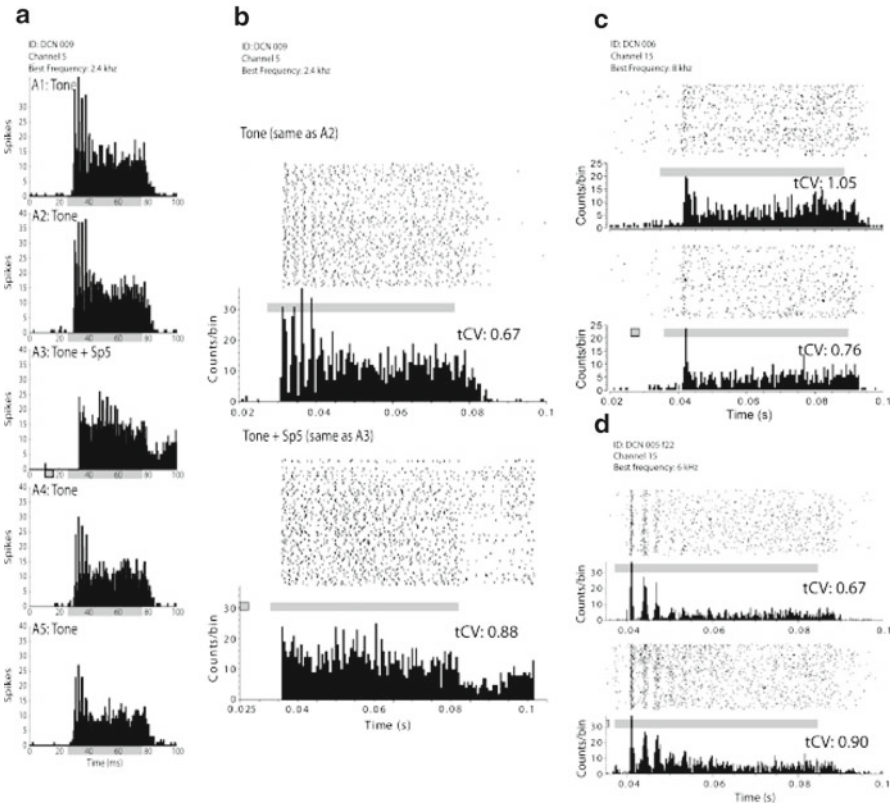

Fig. 5.10 Spinal trigeminal nucleus (Sp5) stimulation changes firing rate and regularity in dorsal cochlear nucleus (DCN) fusiform cells. Firing rate is suppressed and regularity of the acoustic response is decreased when sound is preceded by Sp5 stimulation. (**A**, **A1**, and **A2**) Identical responses of a chopper unit response to BF tones are shown before bimodal stimulation. (**A3**) Bimodal response showing suppressive integration. (**A4** and **A5**) Partially recovered acoustic responses at 5 and 10 minutes after the collection of bimodal responses. (**B**) Raster plot and PSTH of a chopper unit response to BF tones (top, same as **A2**) and BF tones preceded by Sp5 stimulation (bottom, same as A3). (**C**) Raster plot and PSTH of a pauser unit response to BF tones (top) and BF tones preceded by Sp5 stimulation (bottom). (**D**) Raster plot and PSTH of a chopper unit response to BF tones (top) and BF tones preceded by Sp5 stimulation (bottom). Each PSTH is composed of 200 trials. In each raster plot, each point represents a spike and each row represents a single stimulus trial. The bottom row is the first trial. Solid gray bars indicate the duration of the acoustic stimulus. Gray bars with black borders indicate the duration of electrical stimulation of Sp5. The average value of the transient coefficient of variation (tCV) is indicated above each response in (**B**), (**C**), and (**D**). (From Koehler et al., 2011.)

(Levine, 1999). Another proposed role of somatosensory inputs is to emphasize novel sounds by filtering out self-generated sounds such as vocalizations and respiration from external auditory signals (Bell et al., 1997). The bimodal suppressive effects of the dorsal column, Sp5 and TG inputs to CN, could serve this function. The rate changes during bimodal somatosensory–auditory stimulation could explain

why somatosensory maneuvers of face/head/neck regions can evoke tinnitus or modulate the perceived loudness of an existing tinnitus in humans (Pinchoff et al., 1998; Sanchez et al., 2002; Levine et al., 2003). Alterations in fine temporal structure of sound-evoked responses by Sp5 stimulation (Koehler et al., 2011) may explain why patients are able to alter their tinnitus pitch and quality in addition to its loudness. However, for both dorsal column and trigeminal pathways (Shore, 2005; Kanold et al., 2011), the strength and sign of bimodal integration depend on the stimulus timing for both modalities, which would vary depending on the context in a natural environment.

3.2.3 Plasticity of Somatosensory and Bimodal Responses After Noise Damage and Their Role in Tinnitus Pathogenesis

Multisensory neurons have the propensity for receiving cross-modal compensation after sensory deprivation (Allman et al., 2009). A strengthening of the somatosensory, excitatory drive to principal cells and inhibitory interneurons in the DCN could result from the increase in VGLUT2-positive terminals in regions receiving somatosensory input after cochlear damage, in contrast to, and perhaps in consequence of the decrease in VGLUT1-positive auditory nerve terminals (Fig. 5.6). It is therefore not surprising that DCN neurons are more responsive to trigeminal stimulation in noise-damaged guinea pigs. Guinea pigs with noise-induced hearing loss demonstrated significantly lower thresholds, shorter latencies and durations, and increased response amplitudes to TG stimulation than normal animals. Further, the number of units exhibiting bimodal integration, as well as the degree of integration, was enhanced after noise damage (Shore et al., 2008). Together with a higher proportion of inhibitory unimodal responses, bimodal integration was mainly suppressive in the noise-damaged animals, suggesting that projections from the TG to the CN are increased or redistributed to favor inhibitory interneurons, or both, after hearing loss (Shore et al., 2008). For Sp5, this redistribution appears to favor excitatory neurons because bimodal *enhancement* predominates after noise damage (Dehmel et al., 2012).

The idea that an altered balance between auditory nerve and somatosensory inputs could result in tinnitus is exemplified by the finding that increased SFRs after noise exposure are confined to those DCN fusiform cells that show an *excitatory* response to trigeminal stimulation (Fig. 5.11 A and B). This suggests that tinnitus

Fig. 5.11 (continued) Units that were inhibited by trigeminal stimulation and units that did not respond to trigeminal stimulation did not show increased SFR after noise damage. (From Shore et al., 2008.) (**C**) fMRI responses (†) to sound and somatosensory stimulation are seen along the auditory pathway. Responses to somatosensory stimulation are enhanced in tinnitus subjects in the CN (right) and IC (left) (*). Region of interest responses (percent signal change from baseline) are shown for response to sound, jaw protrusion, and both conditions in control subjects (white box plots) and tinnitus subjects (gray box plots). Multisensory integration (int) is defined as the difference between the multisensory condition and the sum of the unisensory condition. Box plots show the smallest observation, 25th, 50th, and 75th percentile, and largest observation. IC, inferior colliculus; CN, cochlear nucleus. (**A**, **B**: From Shore et al., 2008.). (**C**: From Lanting et al., 2010.)

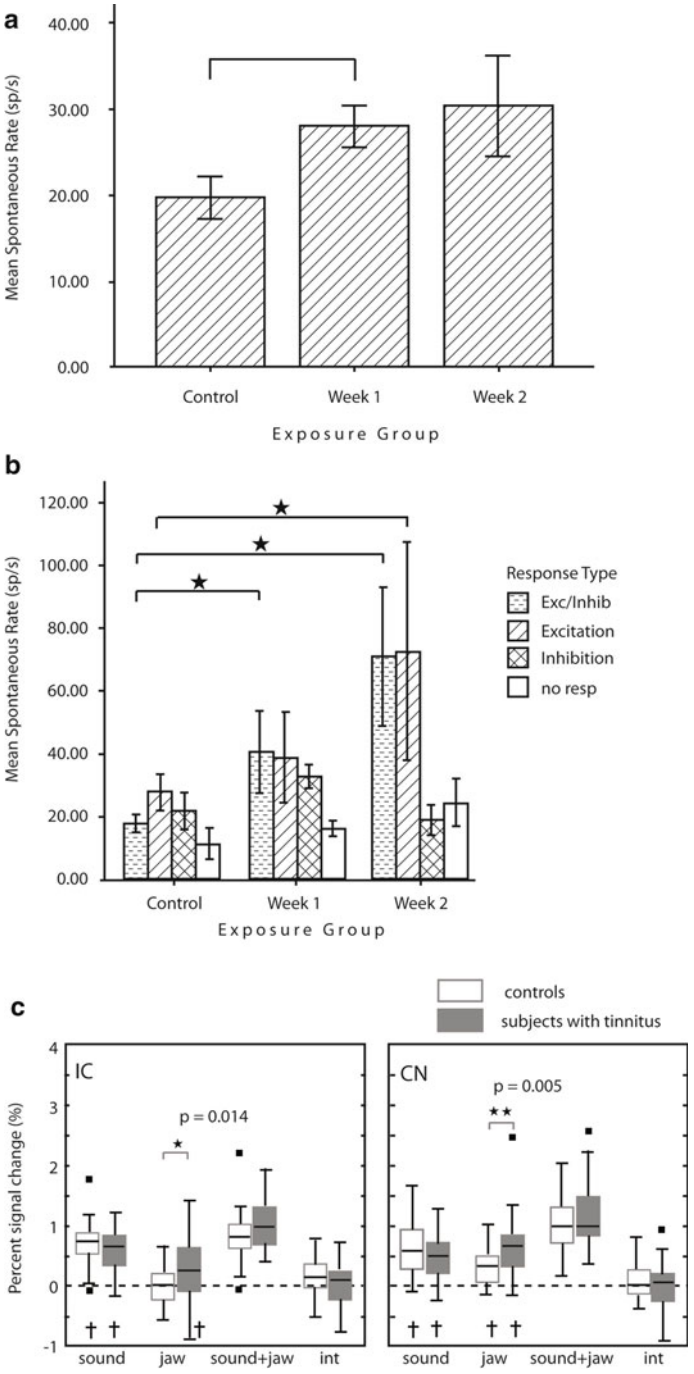

Fig. 5.11 (**A**) Mean spontaneous firing rates (SFRs) for dorsal cochlear nucleus single units at 1 and 2 weeks after noise exposure at 120 dB SPL. SFR is significantly higher at 1 week after exposure (Bonferroni-adjusted comparison; $*p<0.05$). (**B**) The distribution of SFRs by responses to trigeminal stimulation indicates that only units that are activated by trigeminal stimulation (those that display excitatory and excitatory/inhibitory responses) showed increased SFRs after noise exposure.

may be generated by a restricted group of neurons (Bauer et al., 2008; Finlayson & Kaltenbach, 2009). Consistent with the strengthened somatosensory inputs to the CN shown by Zeng et al. (2009) and Shore et al. (2008), fMRI results showed that jaw movements evoked more activity in the CNs of tinnitus subjects than in non-tinnitus subjects (Fig. 11 C).

Increased SFRs in fusiform cells may also result from changes in synaptic plasticity at parallel fiber–fusiform cell synapses and parallel-fiber cartwheel cell synapses (Fujino & Oertel, 2003; Tzounopoulos et al., 2004, 2007). Activation of the granule cell–cartwheel cell network by paired tones can lead to a plasticity-dependent reduction in the response to that sound in a DCN circuit model (Roberts et al., 2006) while pinna stimulation can lead to a reduction in DCN SFR for minutes (Zhang & Guan, 2008).

4 Summary

The concept of somatic tinnitus is derived from observations that tinnitus can be evoked or modified by somatic maneuvers, and that tinnitus can develop acutely after somatic insults to the face, head or neck. Extensive morphological and physiological evidence suggests that somatosensory–auditory interactions in the DCN play an important role in somatic tinnitus. The role of the somatosensory–auditory interactions in the normal system in the suppression of self-generated sounds during processing of external sound signals or cancellation of body movements during sound-source localization is still hypothetical. However, there is accumulating evidence that plastic changes triggered by insults to either the somatosensory or auditory input pathways to the DCN lead to compensatory shifts in the balance of excitation and inhibition. This imbalance is reflected in the upregulation of glutamatergic inputs from somatosensory pathways after deafening, the increased sensitivity of DCN neurons to somatosensory stimuli, and, as a consequence, the increased SFRs of a restricted group of neurons that are excited by those somatosensory inputs. Accompanying downregulation of glycinergic transmission would further shift this balance toward excitation. This increased sensitivity to somatosensory inputs has been verified in an imaging study with tinnitus patients.

Increased SFRs in the DCN have been repeatedly demonstrated in animal models after auditory system damage that causes tinnitus, leading to the notion of increased SFR as a neuronal correlate of tinnitus. However, the correspondence in animal and human models between behaviorally verified tinnitus spectra and auditory insults with the sites of increased SFR needs further exploration. These details are important for developing tinnitus treatments in animal models using physiologically and morphologically based markers of treatment efficacy. Tinnitus correlates of changes in temporal firing properties such as synchrony have been less extensively studied in the DCN, however this might be an important correlate that effectively triggers increased input activity to higher stages of the auditory pathway. In this context, studies showing that somatosensory inputs alter the timing of sound-evoked responses as well as firing rates of DCN neurons are important. How the somatosensory influence on spike timing is altered in animals with behaviorally

confirmed tinnitus will provide insight into the importance of DCN spike-timing in tinnitus. The somatosensory influence on spike rate and timing shown in animal experiments is mirrored in the ability of patients to modify the pitch as well as the loudness of their tinnitus by somatic maneuvers.

Assuming that tinnitus can develop from an imbalance of somatosensory–auditory processing, the segregation of both pathways by their specific VGLUT transporters in the CN would be a starting point for tinnitus treatment (see also Langguth et al., Chapter 11). This would require the development of subtype-specific pharmaceuticals for each VGLUT, which has been recognized as an important tool for treating various neurological disorders, but is not yet available. Another outstanding question concerns the role of synaptic plasticity in tinnitus development and whether this plasticity can be counteracted or even be reset using specific stimulation strategies to rebalance the bimodal integration in the auditory system. Often overlooked is the bidirectional connection of the DCN with the VCN and the more rapidly occurring increases in VCN SFR after cochlear damage. This highlights the VCN as a potentially important structure to be explored as a site of tinnitus pathogenesis.

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Abbreviations

DCN	dorsal cochlear nucleus
DRG	dorsal root ganglion
fMRI	functional magnetic resonance imaging
GCD	granule cell domain
IC	inferior colliculus
MSN	medullary somatosensory nuclei
SFR	spontaneous firing rate
SP5	spinal trigeminal nucleus
Sp5	spinal trigeminal tract
TG	trigeminal ganglion
VCN	ventral cochlear nucleus
VGLUT	vesicular glutamate transporter

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Chapter 6
The Inferior Colliculus: Involvement in Hyperactivity and Tinnitus

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1 Introduction

This chapter addresses several broad issues regarding the role of the inferior colliculus (IC) in tinnitus:

1. What are the changes in neural activity in the IC that accompany treatments known to induce tinnitus? (Section 6.2)
2. When the precipitating cause is cochlear trauma, how do changes in neural activity in the IC relate to the peripheral functional changes? (Section 6.3)
3. Are these changes intrinsically generated in the IC, or driven by abnormal activity elsewhere in the auditory pathway? (Section 6.4)
4. What is the evidence that abnormal neural activity in the IC is the cause of the tinnitus percept? (Sections 6.2, 6.3, 6.4)

1.1 Overview

The search for neural substrates of tinnitus involves investigation of many levels of the auditory pathways. The vast majority of neural information emanating from all lower brainstem centers passes through the IC en route to the thalamus and cortex,

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although there is evidence for the existence of a direct projection from lower brainstem to auditory thalamus (Anderson et al., 2006).

It is therefore of considerable interest to learn whether changes occur in the functioning of the IC as a result of treatments that are known to induce tinnitus. The importance of studies of the IC for elucidating the nature and location of neural events generating tinnitus can perhaps be illustrated by the following theoretical examples. There has been substantial effort devoted to characterizing changes in neural activity in the lower brain stem nucleus, the dorsal cochlear nucleus (DCN), and in the higher level auditory cortex (AC). A failure to find comparable alterations in neural behavior in the IC would, in theory, call into question the DCN as a contributor to tinnitus, and would implicate other areas instead, such as the AC and thalamus, as the main source of abnormal activity giving rise to the tinnitus percept. On the other hand, a demonstration that changes occur in the IC that are similar in broad respects to those seen in the DCN under similar circumstances would strengthen the argument that substantial contributions to tinnitus development, and perhaps maintenance, are made by components of the lower brain stem, although this would not rule out the IC itself as an additional source of tinnitus-related activity.

Investigations of changes in neural behavior in the IC have been made using classic electrophysiological recordings in animal models and also through the use of the more recent imaging technologies of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) in human and animal subjects. The results of imaging studies of activity related to tinnitus are dealt with in some detail by Melcher (Chapter 8), and hence the present chapter focuses primarily on the results of neurophysiological experiments in animals.

For a number of reasons, the IC presents a rather convenient structure for studies of single-neuron electrical behavior and for making comparisons between normal animals and those subjected to treatments associated with tinnitus induction. The IC can be approached with minimally invasive surgery in numerous mammalian species, and it possesses a large central nucleus (CNIC) with a single, well defined tonotopic organization. Recording from substantial numbers of single neurons in individual animals is quite feasible in the IC of small mammals, allowing detailed investigations of the topography of changes in neuronal activity and their relationship to the features of perceived tinnitus as well as to the tonotopy of peripheral changes caused by tinnitus-inducing treatments.

It needs to be borne in mind, however, that certain aspects of IC physiology do pose complications for the conduct and interpretation of neurophysiological investigations. Despite the relatively simple tonotopic organization in the CNIC, this is not a uniform structure, with regional variations in neuronal morphology, dendritic architecture, and projection patterns from subcollicular structures (e.g., Morest and Oliver, 1984). The functional significance of these variations is not well understood (for review see Oliver, 2005). Further, there is a wide range of neuronal types based on responses to acoustic stimulation and there is no universally agreed system of classification of these response types (e.g., Davis et al., 1999; Ramachandran et al., 1999; Chase & Young, 2005), such as exists for neurons of the cochlear nucleus (Rhode & Smith, 1986; Young et al., 1988; Winter & Palmer, 1990). Comparisons between different single-neuron studies is therefore often difficult. Further, the IC is

a paired structure with bilateral inputs and commissural connections (Malmierca et al., 2005). Although the predominant excitatory input is generally regarded as emanating from the contralateral cochlear nucleus, the impact of ipsilateral inputs and the effects of changes in one IC on the other cannot be ignored, especially when interpreting the effects of unilateral cochlear trauma. In addition, other principal subdivisions of the IC, notably the external and dorsal cortices (ECIC and DCIC) form part of a noncore ascending auditory pathway, whose neurons differ in their auditory responses compared to the CNIC, including possessing multimodal characteristics (mainly somatosensory as well as auditory responses; Syka et al., 2000). The DCIC in particular is also the target of a substantial corticofugal projection (Andersen et al., 1980; Winer et al., 1998). Many of these more complicated aspects of IC physiology may have a significant bearing on tinnitus generation, and they are mentioned again where appropriate in the remainder of this chapter.

Biochemical and molecular biological investigations have also been carried out in the IC, focusing on changes that might explain abnormal neural electrical behavior associated with tinnitus. Details of such investigations are contained elsewhere in Knipper et al., Chapter 3) and the treatment of such issues in the present chapter (Section 6.5) is therefore not extensive.

2 Changes in Neural Activity

A variety of different animal models have been employed in studies of the IC. These range from systemic administration of drugs known to cause tinnitus (e.g., salicylate and quinine) to selective cochlear damage induced by loud sounds, ototoxic drugs, or direct mechanical trauma. In general, it can be stated that all such methods result in changes in the level of ongoing, spontaneous neural activity in the IC, although the issue of whether there are subtle differences in the nature of these changes depending on the mechanisms of tinnitus induction is not resolved. In addition to this spontaneous neural hyperactivity, there are also changes produced in sound-evoked responses (e.g., Sun et al., 2009), but these presumably relate to the behavioral phenomenon of hyperacusis rather than tinnitus, and therefore are not discussed here.

With regard to changes in spontaneous firing behavior of neurons in the IC, a common feature of most studies seems to be that the average changes in neural activity across the entire sampled population are significant but rather modest. As discussed later, this reflects the fact that changes are not uniform across all neurons in the affected regions of the IC. In fact, alterations in parameters such as spontaneous firing rates and patterns of firing can, in individual neurons, be quite dramatic.

2.1 Salicylate Models

Jastreboff and Sasaki (1986) first described changes in neural activity in the IC of guinea pig caused by systemic administration of salicylate, a drug long associated with tinnitus. The basic change they described in this early study was an increase in

the magnitude of spontaneous action potential firing, so-called "hyperactivity" evident some hours after drug administration. They suggested that such elevated firing in the absence of sound might constitute a neural substrate for the phantom auditory percept of tinnitus. These authors also reported a potentially important alteration in the pattern of firing in some IC neurons, notably an increase in the regularity of the spontaneous discharge patterns. Importantly, Jastreboff and Sasaki (1986) showed that similar changes were not seen in nonauditory brain regions, supporting the notion that the salicylate-induced changes were not a nonspecific systemic effect on the entire nervous system. In subsequent studies in rats, this group showed that animals that received salicylate showed behavioral evidence of tinnitus (Jastreboff et al., 1988).

Such early studies on the effects of salicylate have been confirmed by several independent studies, most recently by PET imaging in rats showing significant elevation of metabolic activity in CNIC of rat after salicylate administration (Paul et al., 2009). The one dissenting voice regarding IC correlates of salicylate effects is a study by Ma et al. (2006) in mice. These authors reported that salicylate caused decreases in spontaneous firing rates of mainly low-frequency IC neurons. The reason for this disparity is unclear, but may be related to species, dose, and time course of action. It is worth noting also that Ma et al. did not provide behavioral evidence of tinnitus in their study.

In a further study in rats, Chen and Jastreboff (1995) reported that IC neurons not only showed elevated spontaneous firing rates after salicylate administration, but also exhibited unusual protracted bursting patterns of firing. Chen and Jastreboff also reported that these neural changes were eliminated by dietary calcium supplementation, a treatment they had previously shown prevented salicylate-induced tinnitus (Jastreboff et al., 1992). In this study, 80% of neurons were recorded in the ECIC and only 20% in the CNIC, and it remains unclear whether the burst firing and the ameliorating effects of calcium supplementation were confined to the ECIC.

2.2 Cochlear Trauma Models

Both unilateral and bilateral cochlear traumas have been shown to induce changes in neural firing behaviors in the IC. Trauma has been produced in animal models by a variety of means: ototoxic drugs, acoustic trauma, and direct mechanical injury to the organ of Corti. In the case of ototoxic drugs and acoustic trauma, behavioral evidence of tinnitus has also been obtained. The reported changes in the IC include hyperactivity in the form of mean spontaneous firing rate increases, increased synchrony between neurons, and high rate bursting firing patterns (Bauer et al., 2008; Dong et al., 2009; Mulders & Robertson, 2009).

The most thorough investigation of abnormal firing patterns such as bursting in the IC have been performed by Bauer et al. (2008). Intriguingly, these authors reported that the tinnitus percept in their animals appeared to be at approximately 1 kHz regardless of the type of treatment and the pattern of hair cell damage in the cochlea. Further, in animals with evidence of tinnitus, neurons in the IC contralateral to the

damaged cochlea showed within-burst rates of 1000 spikes/s. A notable result in the Bauer et al. study is that in one group of animals treated with an ototoxic drug that caused inner hair cell damage in the treated cochlea, there was behavioral evidence of tinnitus and abnormal bursting behavior, apparently more often in IC "shell" neurons (likely corresponding to the ECIC), but there was no significant increase in mean spontaneous firing rates. These authors therefore suggest that the bursting pattern of behavior in a subpopulation of CNIC neurons, rather than an increase in average discharge rate, is more likely to be the underlying mechanisms of tinnitus. Although not explicitly stated, one implication is that the regular periodicity of abnormal burst firing in IC neurons may relate directly to the spectrum of the tinnitus percept (1 kHz in these animals), presumably through the activation of a periodicity-based rather than a topographic, or place code, for pitch.

Despite the aforementioned results, it cannot be logically ruled out that hyperactivity, as well as burst firing patterns, may generate tinnitus. Indeed, it is possible that burst firing and hyperactivity may represent separate tinnitus mechanisms. An indirect study using magnesium-enhanced MRI as a measure of overall neural activity (Brozoski et al., 2007) showed enhanced signal in the IC of noise-exposed rats with behavioral evidence of tinnitus. The increased neural activity seen in these animals in the absence of sound was similar to that observed during presentation of acoustic stimuli. Administration of the γ-aminobutyric acid (GABA) agonist vigabatrin caused a concomitant reduction in tinnitus severity and IC hyperactivity, further strengthening the argument for hyperactivity being important in tinnitus generation.

A significant area of confusion and lack of agreement in the aforementioned studies is the relative involvement of the CNIC and the noncore regions of the IC such as the ECIC and DCIC in the hyperactivity and altered discharge patterns. This is of some significance in the context of the somatic modulation of tinnitus described by many human tinnitus sufferers. Unlike the CNIC, the ECIC is a multimodal subdivision of the IC and is therefore a prime candidate for somatosensory influences on neural behaviors related to tinnitus.

Most animal studies of the effects of unilateral cochlear lesions have measured activity only in the contralateral IC. Only two studies exist in which the effects of a unilateral cochlear trauma on spontaneous firing rates and other neural properties in the IC both ipsilateral and contralateral to the trauma were studied. Both studies report abnormal firing patterns and/or elevated spontaneous firing rates in both colliculi (Bauer et al., 2008; Dong et al., 2010a). This result shows that intact drive from one normal cochlea is insufficient to maintain normal levels and patterns of neural excitability in the IC in the face of the altered input from the ipsilateral, damaged cochlea. The implications of this result for lateralized tinnitus percepts are unclear at this stage.

2.2.1 Map Changes in the IC After Cochlear Lesions?

It is well known that the tonotopic map in the AC exhibits reorganization after restricted cochlear lesions (Robertson & Irvine, 1989; Rajan et al., 1993). The reor-

ganization consists of the appearance of neurons with normal thresholds and characteristic frequencies (CFs) corresponding to the immediately adjacent normal threshold regions in the cortical zone representing the lesioned frequencies. It has been suggested that this expanded representation of some frequencies may give rise to phantom auditory percepts (tinnitus), in a manner perhaps analogous to the phantom limb sensations associated with reorganization of the somatotopic map after peripheral nerve deafferentation (Montoya et al., 1998; Eggermont, 2006).

With regard to the IC, however, the weight of evidence is that such large-scale map reorganization does not occur in this subcortical structure (Irvine et al., 2003; Izquierdo et al., 2008). Cochlear lesions do result in changes in the tuning curves of IC neurons in the lesioned region but these changes do not exhibit the key feature of map plasticity seen in the AC. Changes consist of loss of sharp tuning tip and sometimes hypersensitivity of non-CF portions of the neurons' tuning curves. Some of these changes no doubt reflect the immediate changes in peripheral afferent tuning associated with loss of outer hair cell function in the cochlea (Patuzzi & Robertson, 1988), while others may reflect changes (either immediate or progressive) in the levels of intrinsic surround inhibition in the IC (Wang et al., 2002). However, none of these changes is directly analogous to the map reorganization that is seen in the AC, because neurons in the lesioned regions of the IC do not exhibit normal thresholds to frequencies outside the lesioned frequency region in the cochlea.

2.3 Types of IC Neurons Affected

Bauer et al. (2008) have cogently argued that the rather modest effects of tinnitus on general auditory function and the seemingly contradictory difficulty that is commonly encountered in achieving complete masking of tinnitus are together consistent with a neural model in which tinnitus is the result of rather dramatic changes in activity confined to a small, specific subpopulation of neurons. Single-neuron recordings in the DCN support this general notion. Several studies indicate that elevated spontaneous firing rates in DCN after cochlear damage are found only in certain well identified cells types (Brozoski et al., 2002; Shore et al., 2008; Finlayson & Kaltenbach, 2009).

Similarly, in the IC, it is a general finding that not all neurons in affected CF regions exhibit abnormal spontaneous firing rates or discharge patterns. However, unlike the situation in DCN, the precise identity of the cell types involved in the IC is not yet clear. After acoustic trauma in chinchilla, Bauer et al. (2008) noted a subgroup of IC neurons with a triad of abnormal discharge features that showed the strongest statistical association with behavioral tinnitus. Ma et al. (2006) found, in bilaterally noise-exposed mice, that hyperactivity was most prominent among CNIC neurons with broad excitatory bandwidths, although as previously mentioned, these same authors did not find similar changes after salicylate administration. Chen and Jastreboff (1995) reported that in animals receiving salicylate, neurons that were unresponsive to contralateral sound showed the most profound changes in their

spontaneous firing rates. The significance of this is unclear but these authors suggest these may have been ECIC neurons receiving predominantly somatosensory input.

In general, however, it is probably fair to say that this issue of precisely which neuronal subpopulations are most altered in their firing behaviors is yet to be systematically investigated in the IC. The multiple neuron classification systems; the fact that recordings are taken from different IC subdivisions in different studies; and the differences in treatments, recovery times, and species employed all make meaningful comparisons between different studies difficult.

3 Topography of Activity Changes in Central Nucleus of the IC

An important issue in tinnitus research, particularly in models in which tinnitus is associated with cochlear damage, is the topographic distribution of abnormal neuronal behavior in central auditory structures and its precise relationship, both to the perceived tinnitus spectrum and to the location of functional damage in the cochlea. Most behavioral evidence shows that the apparent spectral content of tonal tinnitus in humans is related to the frequency region of peripheral hearing loss, although there is some dispute as to whether it is related to the overall region of hearing loss or to the edge of the lesion (see, e.g., Norena et al., 2002; Moore et al., 2010). Therefore, it might be postulated that if hyperactivity in the IC is a genuine correlate of tonal tinnitus, its topographic distribution should closely match the pattern of peripheral hearing loss.

Detailed studies on this important question are surprisingly limited as far as the IC is concerned. A major limiting factor is the difficulty of obtaining sufficient neurons in narrow CF ranges so as to test the precise relationship between peripheral sensitivity change and the tonotopicity of the hyperactive regions in the IC. In addition, not all studies have made detailed measurements of peripheral thresholds in the same animals in which electrophysiological recordings had been made.

Bauer et al. (2008) found no evidence of clear topography of IC changes related to the extent of cochlear damage, or to the behaviorally measured tinnitus spectrum. However, inspection of their electrophysiological measures of threshold show rather broad hearing losses with ill-defined edges, and in some cases little residual hearing loss compared to controls. This may not provide an optimum situation for testing the overall hypothesis of a relationship of central changes to peripheral hearing loss.

Another technical difficulty that is encountered in such studies is the potential for shifts in neuron CF associated with loss of sensitivity in IC regions receiving input from lesioned cochlear regions (see Section 6.3.2.1). Care needs to be taken in assigning neuron CF when there are marked changes to tuning curve shape in the vicinity of the tip of the tuning curve. To circumvent this problem, Mulders and Robertson (2009) have used a correction method that assigns neuron CF in such cases on the basis of depth in the CNIC and an estimation of the CF-versus-depth map derived from unaffected regions in the same animals.

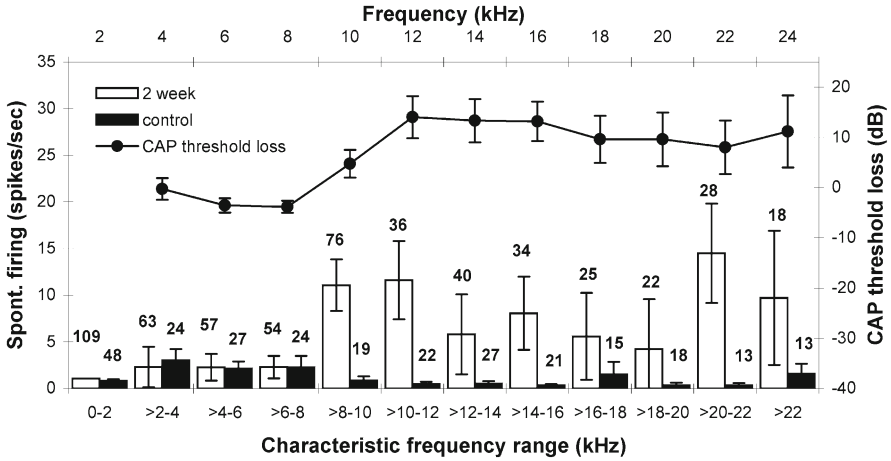

Fig. 6.1 Example of distribution of spontaneous hyperactivity of single neurons in CNIC in relation to peripheral sensitivity loss. Cochlear damage induced in guinea pig using acoustic trauma 2 weeks before single neuron recordings. Bars show mean spontaneous firing rates of CNIC neurons in each CF region. Numbers above each bar, number of single neurons. Solid line and circles show CAP threshold changes in cochlea. (Reproduced from Mulders & Robertson, 2009.)

The most recent studies have used measurements of the cochlear action potential threshold to assess peripheral damage and cochlear lesions with at least one well defined edge, combined with recordings from large numbers of CNIC neurons (Dong et al., 2009; Mulders & Robertson, 2009; Dong et al., 2010a) and the CF correction method described earlier. These studies suggest a rather close correlation between the tonotopic distribution of hyperactivity in the CNIC and the frequency range of peripheral threshold loss (Fig. 6.1). Mention can also be made here of the report by Chen and Jastreboff (1995) that for sharply tuned units in the IC, abnormal firing in the IC after salicylate was most marked for neurons with CFs in the 10–16 kHz region, apparently the same frequency region in which behavioral tinnitus can be demonstrated after similar treatment.

4 Site of Generation of Abnormal Neural Activity in the IC

An important issue with regard to abnormal neural behavior in the IC and its relationship to tinnitus is whether these changes are simply "feed forward" effects of altered activity in lower stages of the pathways such as the primary cochlear afferents, or the CN, or whether they are the result of intrinsic maladaptive plasticity in the IC itself. Biochemical and gene expression changes do occur in the IC concomitant with the development of hyperactivity and tinnitus, but these could be a consequence of altered activity that is driven by input from other regions.

There are conflicting findings on whether abnormal, elevated levels of spontaneous firing in primary cochlear afferents are the direct source of hyperactivity in higher centers. In a noise exposure hamster model, Zacharek et al. (2002) used multiunit surface recordings to measure hyperactivity in the DCN of hamsters exposed to acoustic trauma 4 weeks previously. They showed that hyperactivity persisted after cochlear ablation. This seems consistent with the fact that tinnitus in humans can persist after section of the VIIIth cranial nerve. It has also been reported that behavioral evidence of tinnitus persists after removal of the DCN (Brozoski & Bauer, 2005), and this has been interpreted as evidence that although hyperactivity and/or burst firing in DCN may accompany the development of tinnitus, the DCN is not necessary for its long-term maintenance, implying that the generators of persistent tinnitus must lie more rostrally than the primary afferents or the DCN.

On the other hand, recent studies in guinea pig have shown that at least within the first 4 weeks after a cochlear trauma, the spontaneous firing of cochlear afferents plays a major role in the maintenance of neural hyperactivity in the CNIC. In animals previously subjected to two types of cochlear trauma and in which hyperactivity is present in CNIC, cochlear ablation and other acute treatments that rapidly silenced cochlear primary afferent spontaneous firing (e.g., local cochlear cooling or intracochlear perfusion with L-type calcium channel blockers or α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate [AMPA] receptor blockers) caused an immediate reduction in the firing rates of hyperactive neurons in the IC (Mulders & Robertson, 2009). Further evidence for feed-forward influences from the cochlea comes from the effects of medial olivocochlear system (MOC) activation, which has also been shown to modulate IC hyperactivity (Mulders et al., 2010). Short-latency components of MOC suppression of hyperactivity in the IC were blocked by intracochlear perfusion of strychnine, establishing that the effects are mediated by MOC action in the periphery.

These more recent results showing an immediate effect of altered primary afferent drive on IC hyperactivity appear to contradict the generally held belief that the neural substrates of tinnitus, although they may be set in motion by peripheral damage, do not require peripheral input once they have become apparent. However, it is difficult to directly compare the numerous studies on this question because of the wide range of cochlear trauma methods, post-trauma survival times, and species used. For example, the experiments of Brozoski and Bauer (2005) showing persistent behavioral tinnitus after DCN removal were performed in rats approximately 6 months after cochlear trauma, whereas the experiments showing dependence of IC hyperactivity on cochlear afferent firing were carried out in anesthetized guinea pigs at periods up to only 4 weeks post trauma. On the other hand, although the experiments showing persistent DCN hyperactivity after cochlear ablation (Zacharek et al., 2002) were performed at a time after cochlear trauma similar to that used in the guinea pig IC experiments of Mulders and Robertson (2009), they were done in hamsters, using a different cochlear trauma regimen and multiunit rather than single-neuron recording.

It may be that dependence of central hyperactivity and tinnitus on peripheral drive may differ according to species and type of cochlear trauma. One possible way

of reconciling at least some of these disparate observations is the suggestion (Mulders & Robertson, 2009) that at relatively early stages of the development of hyperactivity, presumably within the first few weeks after a cochlear trauma, IC neurons become hyperexcitable but do not yet generate their own intrinsic spontaneous firing. At this stage IC neurons would generate abnormally high spontaneous firing rates when driven by the excitatory synaptic input from lower centers, ultimately driven by input from the cochlear primary afferents. With longer survival times however, the changes in excitability of IC neurons could progress to a point where they generate their own intrinsic firing and hence hyperactivity in the IC may become "centralized" and independent of input from lower stages of the pathway. If this sequence of events is correct, it might mean that there is a crucial early stage in tinnitus development at which reduction of cochlear firing could prevent the progression to a more severe, intractable form.

An additional factor that has not been considered, especially with regard to the impact of DCN ablation, is that there has been no systematic study of hyperactivity in the ventral subdivision of the cochlear nucleus (VCN), which provides substantial drive to the IC. Until it is known whether the VCN also exhibits hyperactivity, the effects of DCN ablation are difficult to interpret.

5 Biochemical Changes

The details of biochemical and molecular changes that accompany the development of tinnitus and abnormal neural activity in the IC as well as other locations in the auditory pathway are discussed by Knipper et al. (Chapter 3). One of the difficulties in evaluating the true relationship between tinnitus and biochemical and molecular changes in the IC is the enormous diversity of animal models. Some employ ototoxic drugs, others cochlear ablation, and still others employ more selective mechanisms of cochlear damage such as loud sound or direct mechanical lesions to circumscribed regions of the cochlea. In the case of acoustic trauma, both broadband and narrowband noise and pure tones have been used, as well as a wide range of intensities and durations of exposure. The methods used to study biochemical alterations have also varied, including measurements of mRNA expression levels of various genes of interest, immunocytochemistry of the level of transmitter synthesizing enzymes, uptake systems, and receptors. In very few instances has a systematic study been made of the extended time course of biochemical changes in the IC, or of the development of hyperactivity and tinnitus associated with the changes seen at different time points.

One example may serve to illustrate the complexity of effects seen, and the need for further, more detailed studies. In a guinea pig model of restricted cochlear damage using acoustic and direct mechanical cochlear trauma, mRNA levels of key excitatory and inhibitory genes were measured in the same animals in which neural hyperactivity was demonstrated in the contralateral CNIC 2 weeks and 4 weeks after the cochlear lesions were made (Dong et al., 2010a). There was no major dif-

ference in the mean level of hyperactivity between these two time points or between the two methods of inducing hyperactivity. However, there were complex variations in the pattern of gene expression changes. In the case of acoustic trauma, there was downregulation of $GABA_A$ and glycine receptor mRNA levels in the contralateral IC 2 weeks after the trauma, but at 4 weeks, only $GABA_A$ levels were still depressed relative to normal. In the ipsilateral IC, on the other hand, in the same animals, only glycine receptor mRNA expression was depressed at 2 weeks after cochlear trauma, whereas after 4 weeks, there was actually a significant increase above normal levels in the expression of mRNA for the glycine receptor and now, an increased expression of mRNA for the *N*-methyl-D-aspartate (NMDA) receptor pore-forming subunit. At both time points, there was persistent downregulation of mRNA for a variant of a two-pore K^+ channel (KCNK15) but only in the contralateral IC. In the case of direct mechanical trauma, in addition to various changes in the genes mentioned earlier, there was also a depression in the mRNA levels for glutamic acid decarboxylase (GAD), the synthesizing enzyme for GABA. Hence, although it is commonly stated that the cause of hyperactivity in the central nervous system is an alteration in the balance between excitation and inhibition, the precise molecular players in this imbalance in the IC vary according to location, time after the peripheral insult, and the nature of the peripheral insult that triggers the hyperactivity. Such results have important implications for the development of pharmacological therapies designed to correct the "imbalance."

Few of these studies have investigated the detailed topographic distribution of molecular changes in the IC, but in a recent report using restricted cochlear lesions (Dong et al., 2010b), evidence has been found for reduced $GABA_A$ receptor expression in the same tonotopic region of the CNIC in which hyperactivity was demonstrated and that also corresponded to the region of cochlear damage. No significant changes in receptor expression were found in the ECIC or DCIC. This result further strengthens the link between reduced inhibition in the CNIC and the development of hyperactivity and perhaps tinnitus. Interestingly, in this study, less significant reductions of $GABA_A$ receptor levels were seen in the CNIC ipsilateral to the damaged cochlea, suggesting that the bilateral hyperactivity reported in the ipsilateral CNIC after unilateral cochlear damage may be more a consequence of commissural influences rather than being endogenously generated in the ipsilateral CNIC.

6 Summary

A variety of changes in neural activity in the IC have been documented after tinnitus-inducing treatments. The strategic role of the IC in the transmission and processing of ascending auditory information means that such changes are potentially important for understanding tinnitus. However, the body of results to date suffers from a range of limitations and hence it is still unknown at this stage how, and to what extent, such changes in the IC contribute to the neural code for tinnitus perception.

Many questions remain concerning neuronal changes in the IC, their mechanism and origin, and their relationship to tinnitus. The ideal test of the relevance of IC hyperactivity and abnormal firing patterns for tinnitus would be to ablate the CNIC and test for the persistence or otherwise of behavioral tinnitus. Such an experiment would, however, be fraught with interpretational problems. In the case of cochlear nucleus ablations, some of the more widely used tests for the behavioral evaluation of tinnitus rely on the presence of the normal auditory input from the intact unablated side. However, the complex binaural projections to the CNIC mean that the effect of unilateral IC ablation could adversely affect such behavioral tests of tinnitus. The finding that hyperactivity may be bilateral in the CNIC after unilateral cochlear trauma poses an additional complication. If ablation of the CNIC contralateral to the damaged cochlea did not result in loss of tinnitus, this could be due to persistent hyperactivity in the unablated colliculus. A key issue that remains to be resolved in the IC, as elsewhere, is whether it is an increase in mean rate (spontaneous hyperactivity) or other aspects of neural activity (burst firing and interneuronal synchronization) that are the real correlates of tinnitus perception.

The nature and relative significance of changes in CNIC and in the other extralemniscal subdivisions of the IC (the DCIC and ECIC) also needs more systematic study, both in relation to hyperactivity and to abnormal patterns of discharge such as synchrony and burst firing. This issue is an important one in view of the multimodal sensory inputs to the ECIC and the phenomenon of somatosensory modulation of tinnitus. Studies of the specific cell types that change their activity in the IC are still in their infancy and there needs to be a systematic investigation of neuronal response types, coupled perhaps with intracellular tracing techniques to identify the cells involved and their projections to other brain regions involved in generating the tinnitus percept.

There are still insufficient data on the detailed topography of changes in neuronal activity along the CF axis of the tonotopic map in the CNIC, and how this distribution of electrophysiological changes relates to the spectral features of tinnitus in the same animal models and to the pattern of peripheral damage in cochlear trauma models. Ideally future studies should also investigate these multiple parameters for a wide range of post trauma times, to gain better understanding of their interrelationships. Similarly, there is inadequate information on the time course of electrophysiological and molecular changes in the IC and the progression of behavioral tinnitus and electrophysiological changes in the same animal models. Such studies may reveal different tinnitus mechanisms depending on the time since the precipitating event, and this may have profound implications for methods of treatment.

Also unresolved is the issue of whether the changes in the IC are endogenous reactions of the IC neurons and circuits to the treatment, or whether they are a passive reflection of alterations in activity elsewhere in the pathways. Although changes in afferent input from the sense organ itself have long been recognized as an important trigger for the subsequent development of central electrophysiological changes and tinnitus, recent findings reviewed in this chapter have reopened the question of the involvement of the primary afferent neural discharge in the maintenance of central hyperactivity in the IC. As has already been mentioned, the involvement of

descending as well as ascending projections to the IC needs to be taken into account when addressing these questions.

A final point to be made is that the whole question of the neural locus of tinnitus and the origins of abnormal firing patterns is confounded by the fact that there are reciprocal connections between most, or possibly all, of the structures involved. The IC receives major centrifugal input from the AC, and the IC in turn sends descending projections to a number of lower brain stem auditory centers. Finally, the lower brain stem, via the olivocochlear system, sends descending projections to the peripheral sense organ, which in turn supplies input to the lower brain stem. Hence in theory, hyperactivity and abnormal firing patterns at any point in these complex reciprocal pathways have the capacity to set up interdependent patterns of activity in a number of auditory centers. Rather than focusing on DCN, or IC or AC, it may be more appropriate to ask what neural "systems" are involved in the development and persistence of abnormal firing and tinnitus.

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Chapter 7
Cortex: Way Station or Locus of the Tinnitus Percept?

Jos J. Eggermont

1 Introduction

One extreme position for the cortical participation in the tinnitus percept is that the cortex just responds to the changing neural activity from subcortical areas in a way similar to its processing of auditory information originating in the outside world. The other extreme position is that the cortex not only initiates the tinnitus percept but also changes the activity in subcortical structures via corticofugal pathways. It is more likely that an interaction exists between changes at subcortical levels, including the auditory periphery and the thalamocortical system combined with the limbic system, that function to modulate the subcortical activity. One has to realize that even in the input layers of auditory cortex, at most 10% of this input is the result of afferent activity from the thalamus, whereas the remainder originates from other cortical layers or other cortical areas. Because there are about 13 cortical areas in primates, including humans and cats (Winer & Lee, 2007), ample opportunity exists for the cortex to continually process its own activity.

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1.1 Role of Auditory Cortex in Sound Perception

When exploring the potential role of auditory cortex in sound perception, investigators in general followed two routes: lesioning the auditory cortex or reversibly inactivating it. Lesion studies have a long history (Meyer & Woolsey, 1952; Butler et al., 1957; Goldberg & Neff, 1961) and basically showed that bilateral lesions of all auditory cortical areas were needed to abolish frequency discrimination ability. The animals were typically able to relearn this but only for discrimination of tones that lasted longer than 1 minute. More recent studies (Heffner, 1978; Ohl et al., 1999; Bowen et al., 2003) emphasized that cortical ablation invariably produced temporal processing deficits, particularly high frequency-modulation (FM) or amplitude-modulation (AM) rates and gap detection. These discrimination deficits did not recover after the ablation, in contrast to simple tone detection tasks.

Mice, 1 month after bilateral auditory cortex ablations, were statistically indistinguishable from controls on all suprathreshold measures of the acoustic startle response (ASR). Averaged auditory brain stem responses (ABRs) indicated no effects of these lesions on auditory sensitivity. If auditory cortex plays a modulatory role with regard to the ASR, it is apparently nonessential and/or readily compensated for after ablation (Hunter & Willott, 1993). This is important in interpreting gap-startle procedures to identify tinnitus (Heffner and Heffner, Chapter 2), that is, they may not reflect cortical changes in neural activity.

Lomber and Malhotra (2008) localized temporal deficits to inactivation by cooling of AI and anterior auditory field (AAF) in cats, but not to posterior auditory field (PAF), which was involved in sound localization. Inactivating auditory cortex of rats by local application of the γ-aminobutyric acid (GABA) agonist muscimol immediately resulted in a profound inability to detect tones; this recovered over a few hours but the ability for tone discrimination took more time (Talwar et al., 2001). Thus auditory cortex is critically involved in normal hearing. In primates, where the flow of information is more hierarchical than in cats and rats (where there is parallel input to nearly all auditory cortical areas from the thalamus), it is likely that the patency of AI is crucial for perception to occur. Strictly speaking, conscious sound perception will involve more than auditory cortex (see Langguth et al., Chapter 11 for a more extensive argument).

2 Coding of Sound in Auditory Cortex

Because tinnitus is often characterized by its pitch and loudness (Moore, Chapter 9), it is useful to review briefly some aspects of the coding of loudness and pitch in auditory cortex. It is increasingly clear that pitch requires a place code as temporal coding breaks down at lower and lower frequency/repetition-rate levels going from the auditory periphery to more central locations (Joris et al., 2004). Loudness coding may depend on intensity-tuned cortical neurons, and may be controlled by both excitation

and inhibition mechanisms that may be differentially affected by tinnitus-inducing agents. Tinnitus loudness appears to correlate with the amount of hearing loss (Savastano, 2008; Mazurek et al., 2010), likely as a result of loudness recruitment.

2.1 Coding of Loudness in Auditory Cortex

Loudness increases with stimulus intensity and may correlate with an increase of the spatial extent of the blood-oxygen level–dependent (BOLD) signal (Melcher, Chapter 8) in the superior temporal gyrus (STG). Hart et al. (2003) found larger activation in lateral Heschl's gyrus (HG) and the planum temporale for AM and FM of single tones and harmonic complexes compared to the unmodulated tones. In a functional magnetic resonance imaging (fMRI) study Langers et al. (2007), comparing normal hearing and hearing impaired subjects, showed that the observed differences in brain activation were directly related to differences in the experienced loudness of the stimuli. Because of loudness recruitment, increases in stimulus intensity will lead to disproportionately large increases in loudness for the impaired subjects. Therefore the cortical activation level reflects stimulus loudness more closely than stimulus intensity. Indeed, in spite of the severely disturbed sound perception in the impaired subjects, the increase in cortical activation was not significantly different between the two subject groups if expressed as a function of loudness.

Studies using magnetoencephalography (MEG) have also suggested that brain activity increases abnormally steeply with stimulus intensity in individuals with loudness recruitment (Morita et al., 2003). Animal studies show that loudness coding is shaped by associative learning (Polley et al., 2006) and that in particular intensity-tuned neurons are responsible for this effect (see Section 7.5 for more details about the underlying mechanisms).

2.2 Coding of Pitch in Auditory Cortex

Tinnitus usually has a high-frequency pitch (Penner, 1980). Pitch is related to the temporal regularity or periodicity of a sound (Cariani & Delgutte, 1996). Tonotopicity provides an explicit representation of carrier frequency in primary cortical areas. Phase-locked responses to pure tones have also been described in AI of the guinea pig (Wallace et al., 2000), and show that some cells may use a temporal code for representing frequencies of 60–300 Hz rather than the rate or place mechanisms used over most of AI. The phase-locked units gave the strongest response in cortical layers III and IV but phase-locked units were also recorded in layers II, V, and VI. These units form a column representing cells with characteristic frequencies of 80–1300 Hz (Wallace et al., 2010). These units may be candidates of coding for both low pitch and roughness of sound.

MEG experiments in humans have suggested that in AI a pitch map coexists with the tonotopic map. Pitch map topographies may be both parallel (Pantev et al., 1989) and orthogonal (Langner et al., 1997) to the tonotopic map of AI. These data with relatively poor spatial resolution do not rule out that pitch is processed in parallel with frequency but in separate brain regions, such that frequency is represented topographically in primary areas and pitch is represented in nonprimary areas. Human imaging studies have revealed a cortical pitch processing region anterolateral to primary auditory cortex (Patterson et al., 2002; Penagos et al., 2004). Bendor and Wang (2005) showed the existence of neurons in auditory cortex of marmoset monkeys (*Callithrix jacchus*) that responded to both pure tones and missing fundamental harmonic complex sounds with the same fundamental frequency, providing a neural correlate for pitch. These pitch-selective neurons were located in a restricted low-frequency cortical region near the anterolateral border of primary auditory cortex, consistent with the location of a pitch-selective area identified in the imaging studies in humans. Using optical recording of intrinsic signals, Langner et al. (2009) demonstrated that a periodicity map might also exist in AI of the cat. While low-level pure tone stimulation confirmed the well known frequency gradient along the rostrocaudal axis of AI, stimulation with harmonic sounds revealed segregated bands of activation, indicating spatially localized preferences to specific periodicities along a dorsoventral axis, nearly orthogonal to the tonotopic gradient. Their results suggest that the fundamental importance of pitch, as evident in human perception, may also be reflected in the layout of cortical maps.

The pitch of tinnitus may reflect its purported phantom character, that is, resulting from a central substitution of missing afferent activity due to partial hearing loss. Here, the so-called pitch spectrum reflects the frequency range and amount of the hearing loss (Noreña et al., 2002). It would be difficult for the tinnitus spectrum model to explain purely tonal tinnitus. Periodicity in the firings reaching the inferior colliculus may be converted into a place code in that structure (Langner & Schreiner, 1988; Schreiner & Langner, 1988). It has been suggested that high-frequency periodic firing in bursts may be the reason that sometimes behavioral experiments in animals suggest tinnitus with a pitch 1 kHz or less (Bauer et al., 2008). This type of firing pattern, however, would not be able to explain tonal tinnitus with pitches above 1 kHz. Steeply sloping hearing loss potentially could generate pitch effects at the edge frequency of the audiogram, just as steeply filtered noise has an edge frequency pitch (Dai, 2010). The pitch of somatic tinnitus is also reported to be typically of high frequency (Levine, 1999), suggesting afferent connections from dorsal column nuclei innervating high-frequency regions of the dorsal cochlear nucleus (DCN).

3 Neural Correlates of Tinnitus in Human Auditory Cortex

fMRI and positron emission tomography (PET; see Melcher, Chapter 8) both indirectly provide a measure of the number of neurons that are active and the degree to which they are. PET has been used effectively in people with gaze-induced tinnitus

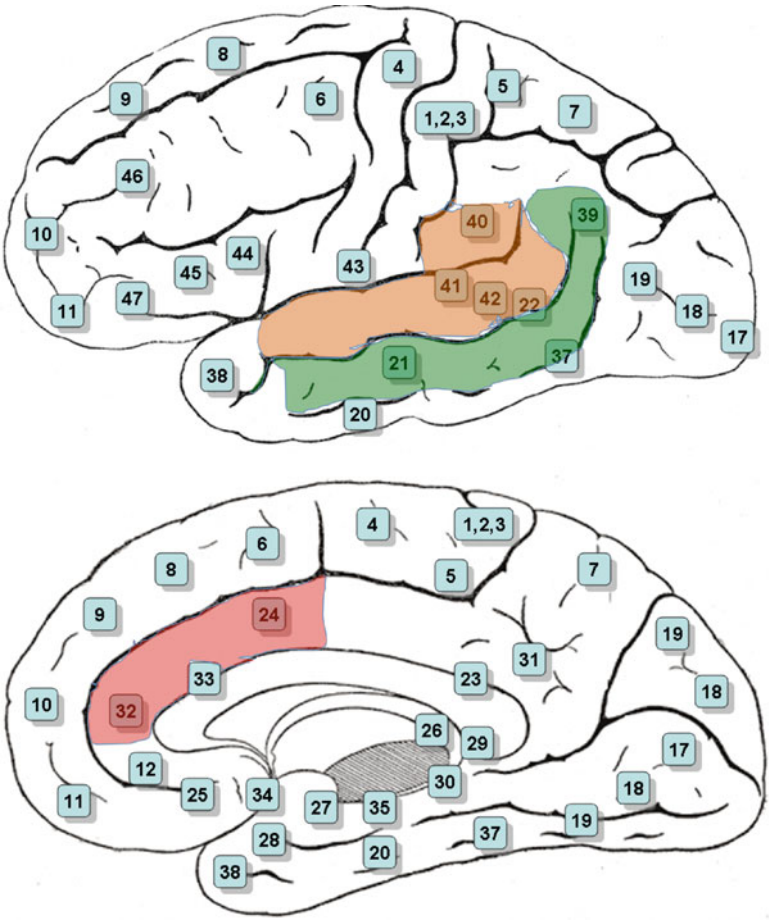

Fig. 7.1 Brodman areas involved in various aspects of tinnitus. The orange/green areas combined represent the auditory cortex and the sites where the strength of gamma-band activity correlates with tinnitus loudness (Van der Loo et al., 2009). The green part, representing the human equivalent of the parabelt region of auditory cortex, represents the sites where activity is blocked by intravenous lidocaine and correlates with the suppression of tinnitus (Plewnia et al., 2007). The red color represents the anterior cingulate cortex where the strength of the alpha and beta band activity correlates with tinnitus distress (Vanneste et al., 2010)

(Giraud et al., 1999; Lockwood et al., 2001) whereby each subject can be his or her own control. These studies found increased activation during the perception of tinnitus in auditory association cortex but not in primary auditory cortex. Lidocaine can effectively suppress tinnitus in more than half of the patients, thereby also allowing within-subject comparisons. Plewnia et al. (2007) showed in a PET study that the lidocaine-suppressed tinnitus signal was mostly generated in the parabelt areas (BA 21, 31, 37, and 39) of auditory cortex (Fig. 7.1).

In addition, electroencephalography (EEG) recording by pasting multiple electrodes on the scalp or by surrounding the head with magnetic field sensors (MEG) can detect differences in the strength of brain rhythms in people with tinnitus compared to those without. Weisz and colleagues (2005a, 2007) showed that in tinnitus patients the strength of oscillations was increased in the delta frequency range (2–4 Hz), decreased in the alpha range (8–14 Hz), and increased again in the gamma frequency range (especially 50–60 Hz). As gamma band activity is typically associated with conscious sensation, this is an important correlate of tinnitus.

Van der Loo et al. (2009) performed dipole-source analysis of resting-state EEG gamma-band oscillations in the contralateral auditory cortex of unilateral-tinnitus patients, and showed a strong positive correlation with Visual Analogue Scale loudness scores. Thus, phantom auditory percepts might have similar sound level–dependent activation of the contralateral auditory cortex as observed in the normal auditory system. Typically unilaterally presented sound produces stimulus-evoked activation in both contralateral and ipsilateral auditory cortex, both in normal hearing (Ponton et al., 2000) and in unilateral deafness (Khosla et al., 2003). The finding of contralateral activation of auditory cortex in unilateral tinnitus patients thus suggests a source central from the auditory midbrain, that is, above the level where bilateral activation is found.

Vanneste et al. (2010) subsequently focused on the cortical and subcortical source differences in resting-state EEG between tinnitus patients with different grades of distress. They again used continuous EEG recordings and low-resolution tomography (LORETA), showing more alpha activity in tinnitus patients who experienced serious distress particularly in emotion-related areas such as the anterior cingulate cortex, the insula, the parahippocampal area, and the amygdala. A comparison between the tinnitus group with distress and a large normative database showed that LORETA activity in the alpha and beta bands was higher for distressed tinnitus patients in anterior cingulate cortex (BA24 and BA32; Fig. 7.1). Decreased delta and theta activity accompanied the increased alpha and beta activity in the anterior cingulate. Unpleasant pain also activates the anterior cingulate and prefrontal cortices, amygdala, and insula, suggesting that distress may be functionally related to alpha and beta activity in the anterior cingulate cortex.

These studies indicate that tinnitus loudness correlates with the current-source density of gamma band activity in the contralateral auditory cortex (van der Loo et al., 2009), whereas tinnitus-induced distress is related to increased activity in the alpha and beta activity in the amygdala–anterior cingulate cortex–insula–parahippocampal area (Vanneste et al., 2010). These findings still need to be reconciled with the reduction of alpha band power over temporal sources in the EEG of tinnitus patients (Weisz et al., 2005a) as well as the decreased coherence of alpha activity over large areas of the brain including the anterior cingulate cortex and increased coherence in gamma band activity in the same network (Schlee et al., 2009).

Using the same recording techniques, one can also measure auditory evoked potentials (AEPs) or auditory evoked magnetic fields (AEFs). What determines both the strength of brain rhythms and the amplitude of AEPs (AEFs) is the amount of synchronization of the neuronal activity. Here the findings are more at variance; both decreases in AEP amplitude (Attias et al., 1993; Jacobson & McCaslin, 2003)

and increases (Hoke, et al., 1989; Weisz et al., 2005b) have been reported in tinnitus subjects. It is interesting that the increased AEFs were found for frequencies in the normal part of the audiogram (about one octave below the edge frequency), suggesting that the inhibition provided by neurons in the hearing loss region was substantially reduced, leading to both increased evoked activity (potentially a correlate of hyperacusis) and potentially also increased spontaneous synchrony in the EEG (Weisz et al., 2005b).

The auditory steady-state magnetic field (ASSR) was recorded in tinnitus subjects and controls, with both having similarly high-frequency hearing loss (Diesch et al., 2010). Three carrier frequencies were used to match the "audiometric edge," or the frequency above which hearing loss increases more rapidly, a frequency $1^1/_2$ octaves above the audiometric edge, and a frequency $1^1/_2$ octaves below the audiometric edge, respectively. Stimuli with the same carrier frequency but different modulation frequency (39.1 vs. 41.1 Hz), thereby allowing separate extraction, were simultaneously presented to the two ears. Compared with the single presentation mode, in multiple-mode the ASSR amplitude was reduced in controls, but increased in tinnitus subjects. Thus, although in controls multiple response components seem to inhibit one another, in tinnitus subjects facilitation seems to predominate, reflecting a downregulation of inhibition in the auditory cortex of the tinnitus subjects (see Section 5).

High-resolution fMRI and AEP/AEF measurements can detect potential changes in the tonotopic map in the cortex (Formisano et al., 2003; Talavage et al., 2004, Humphries et al., 2010). So far high-resolution fMRI has not been applied to tinnitus subjects. Deriving a tonotopic map with AEPs/AEFs, especially using the N100 component, is impossible, as the spatial resolution is insufficient and the various components tend to be generated by several areas (Lütkenhöner et al., 2003a). Somewhat better results are expected based on the ASSRs (Lütkenhöner et al., 2003b; Wienbruch et al., 2006). Despite these technical problems, AEP/AEF measurements have detected clear tonotopic map changes in both primary and secondary cortical areas in tinnitus subjects (Mühlnickel et al., 1998; Weisz et al., 2005b; Wienbruch et al., 2006).

To summarize, this overview of neural findings in humans (more details in Melcher, Chapter 8) suggests at least three potential neural correlates of tinnitus: increased spontaneous firing rates (SFRs), increased neural synchrony, and changes in the cortical tonotopic maps.

4 Cortical Findings After Noise Trauma and Salicylate Application in Animals

4.1 Acute Effects of Salicylate and Quinine in Auditory Cortex

Although drug-induced tinnitus represents only a small percentage of human tinnitus cases (Henry et al., 2005), the number of animal studies that applied salicylate to induce it is disproportionally high (from 212 animal-research articles on tinnitus listed in PubMed, and published between 1965 and 2010, 122 used noise trauma

and 90 used salicylate to induce tinnitus). The ease of application by injection and predictable result also allow the study of the same neurons before, during, and after the injection. The same applies to quinine, but this has been used only sporadically. Both drugs induce likely direct central effects in the auditory system (Kenmochi & Eggermont, 1997), in addition to causing a temporary hearing loss. Both drugs in relatively low dose do not affect, or cause a decrease in, the SFR of auditory nerve fibers (Stypulkowski, 1990; Mulheran, 1999). The few cases where very high systemic doses of salicylate were used have to be considered with care, especially in cats that gradually developed a fever after injection of high-dose salicylate or perilymph perfusion was used to produce very high systemic dose levels (Ruel et al., 2008; Nouvian et al., Chapter 4). In humans salicylate doses greater than 150 mg/kg cause toxicity; if the same applies to animals care must be taken in interpreting results obtained for high doses. Chronic salicylate application may increase spontaneous activity in the auditory nerve (Cazals et al., 1998) but also causes subsequent spiral ganglion cell loss (Chen et al., 2010).

Ochi and Eggermont (1996) administered a dose of 200 mg/kg in cats that resulted in a peripheral hearing loss of about 20 dB but did not change the overall SFR in AI neurons that were recorded before during and up to 6 hours after the injection. However, when the AI neurons were split in a group of neurons with initial SFR 1 spikes/s or less and SFR greater than 1 spikes/s it was noted that the low-SFR group showed a significant increase in SFR, whereas the high-SFR group showed a significant decrease. In contrast, there was a clear overall effect in secondary cortex (Eggermont & Kenmochi, 1998). Zhang et al. (2011) recorded neural spike activities from chronically implanted electrodes in AI of awake cats, and investigated stimulus-evoked and spontaneous firing rate changes after systemic injection of 200 mg/kg salicylate. They found that sound-evoked spike activities were significantly increased from 1 hour after salicylate administration, and the increase of neural responses lasted longer than 3 days, with a peak at 12 hours. This significant enhancement of neural responses was observed over the entire tested frequency range (0.1–16 kHz), with a relative peak in the band of 3.2–9.6 kHz. Salicylate administration, however, decreased the mean spontaneous rate in AI units, and the decrease of spontaneous rate was larger in the units with a high initial spontaneous rate, partially confirming the findings of Ochi and Eggermont (1996) in anesthetized cats.

Salicylate induced in guinea pigs a systematic and reversible increase in amplitude of cortical local field potentials evoked by tone bursts over a wide range of frequencies and intensities. The effects of noise trauma (2 hours to a one-third octave band of noise with a center frequency of 8 kHz, at 115 dB sound pressure level [SPL]) induced in the same guinea pigs about a week after the salicylate, though much more variable than those of salicylate, resulted in both increases and decreases in the amplitude of cortical responses. These alterations of cortical response amplitudes likely reflect salicylate-induced gain changes in the auditory system (Noreña et al., 2010).

Quinine at a dose of 50 mg/kg had no effect in cats, but at 100 mg/kg it produced increased neural synchrony in AI without overall changes in SFR (Ochi &

Eggermont, 1997). Also in this case the low-SFR group showed a significant increase in firing rates and the high-SFR group showed no change. Again, just as for salicylate, there were clear SFR increases after quinine application in secondary auditory cortex (Eggermont & Kenmochi, 1998). The effect of both drugs was to increase SFR for high–characteristic frequency (CF) sites and a tendency to decrease them for low CF sites. No indications of changes in burst firing were found after either salicylate or quinine. The increase in SFR in AII, combined with increases in firing rate for the external nucleus of the inferior colliculus (Chen & Jastreboff, 1995; Manabe et al., 1997), suggests involvement of the extralemniscal pathway.

Two behavioral measures confirmed the presence of tinnitus induced by salicylate in rats (see Heffner and Heffner, Chapter 2; Yang et al., 2007). Sun et al. (2009) chronically monitored the local field potentials (LFPs) and SFRs from multiunit clusters in the auditory cortex of awake rats before and after treatment with 150 mg/kg of salicylate. The amplitude of the LFP elicited with 60 dB SPL tone bursts increased significantly 2 hours after salicylate treatment, particularly at 16–20 kHz, or frequencies associated with the tinnitus pitch. LFP amplitudes had largely recovered 1–2 days post-salicylate when behavioral results showed that tinnitus was absent. The mean SFR recorded from a nine–multiunit cluster pre- and post-salicylate decreased from 22 spikes/s before treatment to 14 spikes/s 2 h post-salicylate and recovered 1 day post-treatment, in line with results in cats (Zhang et al., 2011). This suggests that salicylate-induced tinnitus is associated with sound evoked hyperactivity in auditory cortex and reduced SFRs. Despite these reduced SFRs in auditory cortex, the same dose produced besides the behavioral indices of tinnitus, a significant increase in metabolic activity in rat auditory cortex and inferior colliculus as measured using microPET by the same group (Paul et al., 2009). It is therefore not evident whether the behavioral measures reflect tinnitus, or potentially hyperacusis.

4.2 2-DG and c-fos Expression After Salicylate Application

Mongolian gerbils (*Callithrix jacchus*) that received salicylate a few hours after salicylate administration showed c-*fos* expression in auditory brain stem nuclei that was as low as after saline treatment. *C-fos* is used as an indirect marker of neuronal activity because it is often expressed when neurons fire action potentials. If c-*fos* mRNA is upregulated in a neuron, this indicates recent activity. Pronounced differences between the salicylate and control groups were found, however, in areas susceptible to stress of salicylate-treated animals More extensive data were presented in Walhäusser-Franke et al. (2003) for both salicylate and impulse noise and also included structures above the brain stem. Salicylate injections as well as noise trauma always initiated c-*fos* expression in auditory cortex and sometimes in dorsal medial geniculate body (for salicylate), in the inferior colliculus (IC) (for noise and low dose of salicylate), or in DCN (noise).

4.3 Acute Effects of Noise Exposure in Auditory Cortex

With the recording electrodes in place, Eggermont and colleagues exposed the cat to loud sound (e.g., 5 kHz, 120 dB SPL) for 1 hour, and then recorded the activity from the same recording sites again and as a function of time after the trauma (Kimura & Eggermont, 1999; Noreña et al., 2003). The results showed, as expected, an initial loss of sensitivity, with the highest increase in threshold around 8 kHz (about one half an octave above 5 kHz); these thresholds improved over the following 6 hours of recording from the same sites. On average, 40-dB hearing loss remained 6 hour after the exposure. It was interesting that neurons with a pretrauma CFs around 10 kHz had a CF close to 5 kHz after the trauma, a frequency that they did not respond to before the trauma. This effect was immediate and must be attributed to the loss of activity in the 10-kHz region, activity that normally would inhibit thalamic inputs to the 5-kHz area. This disinhibition unmasks previously silent excitatory inputs and shifts the tuning curve dramatically to lower CFs. This is likely a precursor to subsequent changes in the tonotopic map that take place only after several weeks (Eggermont, 2006). Immediately after the trauma (Noreña & Eggermont, 2003), there was a slight decrease in SFR, regardless of the CF of the neuron. It took approximately 2 hours before the SFR had increased (on average twofold) in neurons with CFs below the trauma tone frequency and those with CFs more than one octave above the trauma tone frequency. Surprisingly, the one-octave-wide region above the trauma tone frequency did not show a change in SFR compared to pretrauma conditions. One could interpret the increases at lower and higher CFs again to a loss of inhibition from the one-octave-wide CF region above the trauma tone frequency. On average the before trauma SFR was 3.5 spikes/s, 15 minutes after the trauma 3.7 spikes/s, and ≥2 hours after the trauma 5.1 spikes/s. Only the latter SFR was significantly different from the before trauma SFR. It should be noted that the increase in SFR was stronger for low-SFR units than for high-SFR units, as previously found also for salicylate and quinine (see earlier). The fact that the SFR change was not instantaneous suggests that other factors than hearing loss play a role. In stark contrast, the neural synchrony was significantly increased immediately after the trauma. Because tinnitus tends to develop immediately after a noise trauma (but may disappear again later), this suggests that the neural correlate, at least for transient tinnitus, is not increased SFR but increased neural synchrony.

4.4 Chronic Effects of Noise Exposure in Auditory Cortex

The 1-hour exposure at 120 dB SPL presented in the previous section would hardly result in a permanent hearing loss when measured at 3 weeks postexposure. Exposures of 2–4 hours at 115–120 dB SPL were used in three follow-up studies (Komiya and Eggermont, 2000; Seki & Eggermont, 2003; Noreña & Eggermont, 2005).

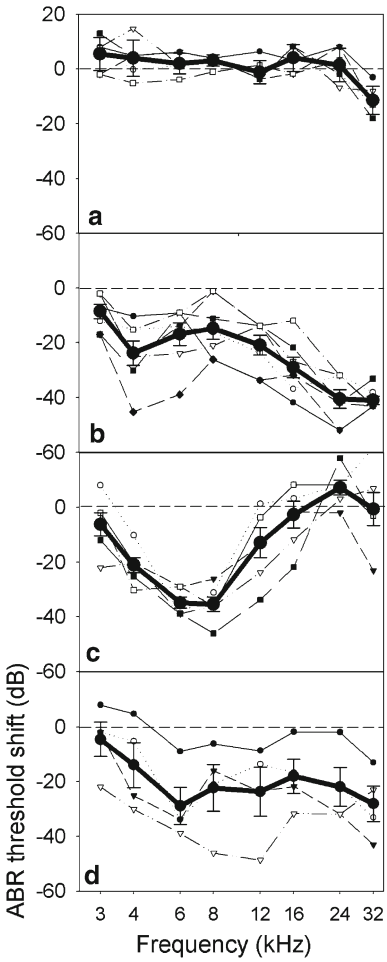

Fig. 7.2 Audiograms for control cats (**a**), noise-exposed cats with recovery in quiet (**b**, group 1), noise exposed cats with recovery in a high-frequency EAE (**c**, group 2), and noise-exposed cats with recovery in a low-frequency EAE. (After data from Noreña & Eggermont [2006], with permission.)

Recordings were performed 7–16 weeks after the exposure and recovery in a quiet room. Nonexposed littermates and other normal hearing cats were used as age-matched controls. Tonotopic maps in the primary auditory cortex were reorganized in such a way that the area normally tuned to frequencies of 10–40 kHz was now entirely tuned to 10 kHz. SFRs were significantly higher in reorganized areas (2.3 spikes/s) than in normal areas (1.4 spikes/s) and control cats (1.3 spikes/s). For the frequency range in which reorganization was found, the *R*-values in reorganized cortex were significantly higher than those in control cats. This suggested a potential correlation between cortical reorganization, increased SFR, and interneuronal synchrony that might be related to tinnitus found in high-frequency hearing loss induced by acoustic trauma.

Average audiograms for individual control and exposed animals after recovery in a quiet room (Norena & Eggermont, 2005) are shown in Figure 7.2 a and b.

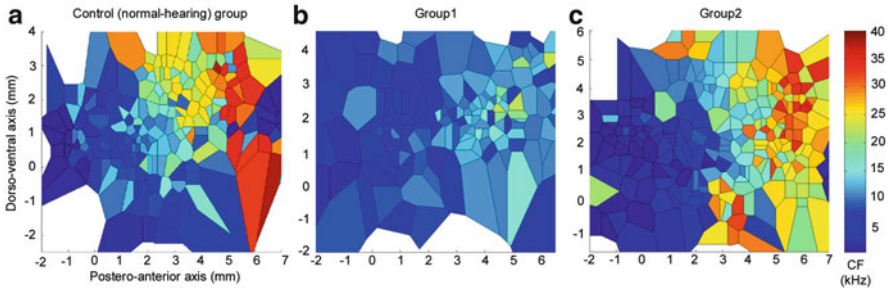

Fig. 7.3 Compound CF maps in AI in control cats (**A**), group 1 cats (**B**), and group 2 cats (**C**). The center of each polygon corresponds to the coordinates of a recording site in auditory cortex along the anteroposterior axis (abscises) and the ventrodorsal axis (ordinates). The tip of the posterior ecto-Sylvian sulcus was taken as the (0, 0) coordinate. The CF is represented by color as indicated by the color bar. (From Noreña & Eggermont [2005], with permission.)

One notices a two-part hearing loss: a 10–45-dB (mean 25) dip around 4 kHz and a sloping loss for higher frequencies. The activity of cortical neurons was recorded and compared to that of the control group presented previously. Again, the tonotopic maps were changed dramatically (see Fig. 7.3 a and b) such that there were hardly any cortical sites that were sensitive to frequencies above 10–15 kHz. Second, the SFR was significantly increased in those neurons that likely had preexposure CFs in the hearing loss range (as judged by their recording site and the newly acquired CF). Third, neural synchrony was increased in all neuron pairs that involved a neuron in the reorganized CF area (Noreña & Eggermont, 2006). Thus, the findings after drug-induced tinnitus and noise-induced tinnitus comprise different changes in the central nervous system (CNS), likely because of the central effects induced by salicylate in addition to its peripheral actions.

5 The Neural Imbalance Hypothesis Underlying Tinnitus

Several studies have found molecular changes in the effectiveness of the excitatory and inhibitory transmitter systems at the brain stem, midbrain, and cortical levels after noise trauma (Abbott et al., 1999; Milbrandt et al., 2000; Wang et al., 2005). The findings are that the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor system (that processes glutamate) is initially downregulated (brain stem), that the γ-aminobutyric (GABA) receptor system (inhibitory) is initially also downregulated (midbrain), but that the other glutamate processing receptor system (*N*-methyl-D-aspartate [NMDA]) is initially upregulated (cortex). However, within a few weeks to a month, all these changes have reverted back to (nearly) preexposure values. Thus, immediately after the noise trauma, there is an imbalance between the excitatory and inhibitory receptor systems, particularly between the NMDA and the GABAergic systems. This imbalance may underlie the increased SFRs and the unmasking of new excitatory inputs that were observed immediately after the trauma.

Continued imbalance for a few weeks may also initiate the reorganization of the tonotopic maps. Reorganization of maps and increased neural synchrony appear to be intricately linked (Bao et al., 2003; Eggermont, 2007).

Neurons in primary auditory cortex are tuned to the specific level and frequency of sounds. Inhibition appears to have a functional role in the formation of cortical receptive fields because pharmacological blockade of inhibition broadens tuning curves. The excitatory and inhibitory receptive fields cover almost exactly the same intensity-frequency areas, in contrast to the predictions of classic lateral inhibition models. Thus, although inhibition is typically as strong as excitation, it appears not necessary to establish tuning, even in the receptive field surround. This all happens at the input of the cortical neuron. However, the tuning of spikes, reflecting the output of the neuron, is much narrower than that for either excitatory or inhibitory currents (Tan et al., 2004). Further, inhibition and excitation occur in a precise and stereotyped temporal sequence that truncates the spiking response to within a few (1–4) milliseconds after stimulus onset (Wehr and Zador, 2003; Zhang et al., 2003).

In vivo whole-cell recordings in rat auditory cortex revealed that intensity-tuned neurons, mostly clustered in a posterior zone, receive imbalanced tone-evoked excitatory and inhibitory synaptic inputs (Tan et al., 2007). Excitatory inputs exhibit nonmonotonic intensity tuning, whereas for tone intensity the temporally delayed inhibitory inputs increase monotonically in strength. In addition, this delay reduces with the increase of intensity, resulting in an enhanced suppression of excitation at high intensities and a significant sharpening of intensity tuning. In contrast, non–intensity-tuned neurons have covarying excitatory and inhibitory inputs, and the relative time interval between them is stable with intensity increments, resulting in monotonic response-level function. Thus, cortical intensity tuning is determined primarily by excitation and shaped by cortical inhibition through a dynamic control of excitatory and inhibitory timing (Wu et al., 2006).

Acute acoustic trauma disrupts the balance of excitation and inhibition in auditory cortex (Kotak et al., 2005) by selectively increasing and reducing the strength of inhibition at different positions within the receptive field. Inhibition was abolished for frequencies far below the trauma-tone frequency but was markedly enhanced near the edges of the region of elevated peripheral threshold. These changes in inhibition led to an expansion of receptive fields but not by a simple unmasking process (Scholl and Wehr, 2008). Rather, membrane potential responses were delayed and prolonged throughout the receptive field by distinct interactions between synaptic excitation and inhibition. Far below the trauma-tone frequency, decreased inhibition combined with prolonged excitation led to increased responses. Near the edges of the region of elevated peripheral threshold, increased inhibition appeared to delay rather than to abolish responses driven by prolonged excitation. Thus, acoustic trauma simultaneously causes a selective increase and decrease of synaptic inhibition in distinct regions of the receptive field. Consequently, the synaptic mechanisms underlying receptive field changes after acoustic trauma include unmasking by selective loss of inhibition but also include a selective gain of inhibition elsewhere in the receptive field. A profound loss of inhibition occurred for low tone frequencies at which no peripheral threshold shift was observed, potentially a neural correlate of hyperacusis and potentially of tinnitus (Scholl and Wehr, 2008).

6 Preventing or Reversing Cortical Tonotopic Map Changes

6.1 Effects of an Enriched Acoustic Environment After Noise Trauma

Noreña and Eggermont (2005) reasoned that the imbalance of excitation along the tonotopic array of auditory nerve fibers (less for the hearing loss frequencies) would set up an imbalance between excitation and inhibition in the central auditory system, as stronger excitation typically causes disproportionally stronger inhibition. By providing the animals with extra stimulation in the hearing loss range (equivalent to providing a well fitted hearing aid), one would even out the excitation across the auditory nerve fiber array. Thus the next group of noise-exposed cats was placed in a room with an 80-dB SPL (A-weighted) multifrequency dynamic sound environment in the frequency range of 4–20 kHz (covering the expected hearing loss range taking into account the upward spread of activity above 20 kHz).

The post-trauma (5 kHz, 4 hours at 120 dB SPL) sound condition was called an enriched or enhanced acoustic environment (EAE). The cats were in this sound field for 24 hours/day, 7 days/week, and for at least 3 weeks (the time expected for full cortical reorganization after noise trauma). The first surprise came when we measured their peripheral hearing thresholds using the auditory brain stem response. The previously pronounced hearing loss in the high frequencies encountered in the animals recovering in quiet after the trauma was now completely absent (Fig. 7.2c); the remaining noise dip remained and was stronger than for the 2-hour–exposed cats. Noreña and Eggermont (2005) interpreted this as the result of a reconnection of the neurites to the inner hair cells, guided by the continued output of glutamate by those still intact inner hair cells. Raising noise-trauma cats in a low-frequency EAE did not change the audiogram significantly compared to quiet postexposure (Fig. 7.2d).

The tonotopic map appeared normal in the EAE cats (Fig. 3c), and even detailed analysis could not detect any difference from that in the control cats (Noreña & Eggermont, 2005). No significant changes in the SFR in this group of EAE cats and no increases in neural synchrony were observed. This suggested that all potential neural correlates of tinnitus were completely normal and thus that tinnitus likely would be absent in cats that received the EAE treatment. Needless to say, applying a low-frequency EAE (covering the normal range of the audiogram) had no effect on the increased SFR and neural synchrony and had only a minor effect (largely based on one animal) on restoring the tonotopic map (Noreña & Eggermont, 2006). This low-frequency EAE obviously did not balance the excitation and inhibition deficit produced by the hearing loss. It is important to realize that this EAE was applied immediately after the trauma. Given that the imbalance between excitation and inhibition likely exists for only up to a month (if the translation from rats to cats to humans applies) after the trauma, this suggests a relatively short window of opportunity for sound treatment (e.g., a morning-after sound) that could prevent tinnitus.

6.2 *Effects of Vagus Nerve Stimulation Paired with Tones*

Engineer et al. (2011) induced noise trauma by exposing rats to 1 hour of 115-dB SPL, octave-band noise centered at 16 kHz. This resulted in about 15–20 dB permanent hearing loss at 11 weeks post trauma between 4 and 32 kHz. Eleven weeks after noise exposure, there were clear indications of tonotopic map reorganization. The average SFR was significantly increased by 23%. Note that this is far less than the 100% increase found in cat auditory cortex by Noreña and Eggermont (2003) and Seki and Eggermont (2003). The degree of synchronization during silence between multiunit activities recorded at nearby sites was significantly increased as well. Thus, the standard triad of cortical changes after noise trauma was observed.

Eighteen out of 28 noise-exposed rats used in this study were significantly impaired in their ability to detect a gap, evidenced by an increased gap-startle response (Heffner and Heffner, Chapter 2), in narrowband noise centered on 8 or 10 kHz, but showed no impairment when the gap occurred in narrowband noise centered on 2 or 4 kHz or in broadband noise. This was considered an indication for the presence of tinnitus in this subset of rats. Tonotopic map reorganization and tuning curve broadening, but not increased SFR or synchronization, correlated significantly with the degree of gap-startle impairment in untreated noise-exposed rats. In addition, hearing loss and potential hyperacusis (as assessed from steeper rate level functions) did not correlate with gap-startle response impairment.

Four weeks after noise exposure, vagus nerve stimulation (VNS) was repeatedly paired with multiple pure tones 300 times per day for 18 days in seven noise-exposed rats with impaired gap detection for mid-frequency sounds. The vagus nerve arises from the medulla and carries both afferent and efferent fibers. The afferent vagal fibers connect to the nucleus of the solitary tract, which in turn projects connections to other locations in the CNS. Proposed mechanisms of VNS include alteration of norepinephrine release by projections of solitary tract to the locus coeruleus, elevated levels of inhibitory GABA related to vagal stimulation, and inhibition of aberrant cortical activity by reticular system activation. VNS is used in humans as a treatment for certain types of intractable epilepsy and treatment-resistant depression. Pairing VNS with tones is assumed to have the same effect as the well known combinations of tone pairing with basal forebrain stimulation (Kilgard & Merzenich, 1998) and ventral tegmentum stimulation (Bao et al., 2001). Because gap impairment occurred for octave bands centered at 8 and 10 kHz, the frequency of each randomly interleaved tone was chosen outside the frequency range in which gap-startle response impairment occurred. After 10 days of pairing VNS with multiple tones the behavioral effect of noise exposure was reversed, which suggests that the rats' presumed tinnitus was no longer present. In addition, most of the A1 properties that were affected by noise exposure returned to pre-trauma levels. For example, the proportion of A1 neurons with characteristic frequencies between 12 and 23 kHz was indistinguishable from that in naive controls after VNS/multiple tone treatment. VNS/multiple tone pairing also reversed the increase in cortical synchronization observed in noise-exposed rats to control levels, but surprisingly further increased

the cortical SFR observed in noise-exposed rats. Engineer et al (2011) concluded that noise-induced increases in cortical SFR and local synchronization did not significantly correlate with behavioral correlates of tinnitus (as reflected by the gap-startle response) in individual rats. This provides another serious discrepancy between the assumptions underlying the gap-startle response test as an indicator for tinnitus, namely the filling in of the gap by the spontaneous activity underlying tinnitus (compare Section 4.1). However, the model may still be saved if the increased SFR occurs in the presumed gap-startle pathway. It is widely assumed that the gap activates the ascending auditory pathway in the IC and thereafter the colliculus superior, which in turn affects the startle pathway by activating an inhibitory cholinergic pathway from the pedunculopontine tegmental nucleus to the caudal pontine reticular nucleus (Koch, 1999). Thus increased SFR in the pathway leading up to the IC may be sufficient to affect the startle response.

7 What Does the Auditory Cortex Do?

7.1 Cortex Contains a Representation of the Outside World

It is time to return to the question what the role of auditory cortex is in the tinnitus percept. First of all, auditory cortex or more generally the thalamocortical system is likely necessary for perceiving tinnitus; without it there is usually not a conscious auditory percept, and likely not the annoyance aspect. Second, the thalamocortical system does more than just relaying information from the midbrain to cortical association areas. A case in point is that more than 99% of neural inputs to a cortical neuron are from other cortical cells; even in the input layers of auditory cortex at most 10% of the inputs are of thalamic origin (Abeles, 1991). It is thus likely that auditory cortex works mostly on its own output. Further, the output of auditory cortex to the thalamus potentially far outweighs the input the thalamus receives from the auditory midbrain, at least if it parallels the visual system (Van Horn et al., 2000), suggesting that the cortex in general exhibits a control function on subcortical structures. This points to a cortex that is more a representational system than a bottom-up information processing system. The cortex has a worldview that can be changed only when the input from the outside world (i.e., from the thalamus) violates its expectations, as an old and trusted learning rule expresses (Rescorla & Wagner, 1972). This sensitivity to change is also reflected in the large number of so-called event-related potentials that are generated by such violations of expectation. One has only to think about the preattentive mismatch negativity (MMN) and the task-dependent P300 as odd-ball or deviant-stimulus signaling event-related potential components. Further, for language-related potentials there are the additional semantic-violation (N400) and syntactic-violation (P600) signaling components (Friederici, 2002).

Tinnitus, as reflected in its potential relation to changes in the cortical tonotopic maps, may be a result of maladaptive auditory plasticity. In this respect, it is useful

to briefly summarize what properties remain plastic in the adult auditory system. Starting with cortical auditory receptive fields, one notices that these are pliable by learning (Fritz et al., 2003; Polley et al., 2006) and therefore dependent on behavioral responses of the animal. Long-term passive exposure, that is, not requiring responses from the animal, with low-level sound also can cause widespread changes (Pienkowski and Eggermont, 2009). Peripheral hearing loss induced by noise trauma or mechanical damage to the cochlear hair cells changes the tonotopic maps in auditory cortex (Rajan et al., 1993) and auditory thalamus (Kamke et al., 2003), but not in the auditory midbrain (Irvine et al., 2003) or cochlear nucleus (Rajan & Irvine, 1998). Noreña and Eggermont (2005, 2006) have shown the intricate connection between tonotopic map changes, increased SFR, and increased neural synchrony. This clearly points to an important role for thalamus and cortex in the generation of tinnitus through maladaptive plasticity, whereas other mechanisms may be responsible for the changes in SFR observed in the DCN and auditory midbrain (Noreña, 2011).

An aspect of the aforementioned "learning by violation" rule may be that the cortex tries to adjust the output of subcortical structures by its corticofugal feedback activity (Yan & Suga, 1998; Suga et al., 2000). In this way, increased activity at a particular cortical site can, for instance, change the representation of frequency in the auditory midbrain, and even affects the activity of hair cells in the cochlea.

7.2 Cortical Influences on Subcortical Structures

Yan and Suga (1998) found in the big brown bat that electrical stimulation of a column in primary auditory cortex paired with a tone of frequency equal to the best frequency (BF) of the cortical column, enhances the extent of the corresponding frequency representation in the IC. Moreover, the plastic changes were asymmetric; IC neurons with best frequencies higher than that of the stimulated cortical site showed downward shifts in their best frequencies, toward that of the stimulated neurons, whereas neurons tuned to lower frequencies were relatively unaffected. Surprisingly, 30 minutes of stimulation with tone bursts presented at 50 dB SPL without concurrent electrical stimulation also induced a shift in the frequency tuning in the IC. The changes were smaller than but similar to those observed after combined tone and electrical stimulation of the corresponding BF site in the auditory cortex. Thus, behaviorally irrelevant tone bursts and/or direct cortical electrical stimulation can augment the midbrain representation of the stimulus tone frequency.

This effect was also demonstrated in mice (Yan & Ehret, 2001, 2002; Yan et al., 2005). Yan and colleagues observed that bipolar electrical stimulation of primary auditory cortex, one electrode at the surface, the other one in layer VI, so spanning the depth of a cortical column, did not affect best frequencies in IC when the BFs of stimulated cortical neurons and recorded collicular neurons were similar. However, BFs in IC shifted toward the BF of the cortical stimulation site when cortical and collicular frequencies were different. In addition to frequency-specific shifts in collicular BFs, cortical stimulation elevated minimum thresholds in IC and reduced both

dynamic ranges and response magnitudes if cortical and collicular BFs were different. If BFs in AI and IC were similar but minimum thresholds were different, collicular minimum thresholds shifted toward the thresholds of the stimulated cortical sites.

He et al. (2002) found similar modulatory effects descending from the auditory cortex to the thalamus in guinea pigs. Corticofugal modulation on thalamic neurons was again obtained by electrical activation of auditory cortex. Neuronal activity was recorded along the frontal and sagittal planes of the auditory thalamus, focusing on the ventral division (MGv) of the medial geniculate body (MGB). The corticofugal effect on the MGv of the guinea pig resulted in strong facilitation and very little inhibition. The MGv neurons showed the greatest facilitations to stimulation of cortical sites with the closest correspondence in BF. The comparative results of the corticofugal modulatory effects on the MGv of the guinea pig and the cat, together with anatomical findings, hint that the strong facilitatory effect is generated through the strong direct corticothalamic connection to thalamic principal cells and that the weak inhibitory effect might be mainly generated via the interneurons of the MGv (He, 1997).

In exploring the corticofugal effects on levels below the midbrain, Luo et al. (2008) found that cortical activation increased the response magnitudes and shortened response latencies of CN neurons with BFs matched to the cortical stimulation site, whereas decreased response magnitudes and lengthened response latencies of unmatched CN neurons. In addition, cortical activation shifted the frequency tunings of unmatched CN neurons toward those of the activated cortical neurons. This suggests that cortical activation selectively enhances the neural processing of particular auditory information and attenuates others at the first processing level in the central auditory system based on sound frequencies encoded in the auditory cortex. The auditory cortex apparently implements a long-range feedback mechanism to select or filter incoming signals from the ear.

The role of corticofugal activity does not end in the CN, as Xiao and Suga (2002) found that electric stimulation of cortical neurons in the awake bat even modulates cochlear hair cell activity as expressed in the cochlear microphonic. This happens again in a highly specific way determined by the difference BF between cortical neurons and hair cells.

Yan and Suga (1998) suggested that the corticofugal system is involved in the long-term improvement and adjustment of subcortical auditory information processing, largely because the corticofugal effects slowly disappeared over 2–3 hours after the cessation of the 30-minute cortical electrical stimulation (Fig. 7.4). The development of the corticofugal effect is rapid and asymptotes after about 30–60 minutes of stimulation (Ma & Suga, 2001).

Corticofugal feedback may be an important factor in the manifestation of tinnitus (Jastreboff, 1990; Eggermont, 2008). Magnetic dipole-source imaging suggests that tinnitus is accompanied by a reorganization of the auditory cortical tonotopy (Muhlnickel et al., 1998; Wienbruch et al., 2006). The pattern of reorganization correlates with the subjective tinnitus strength and with the shift in the representation of tinnitus frequencies in the auditory cortex. Corticofugal feedback, induced by the

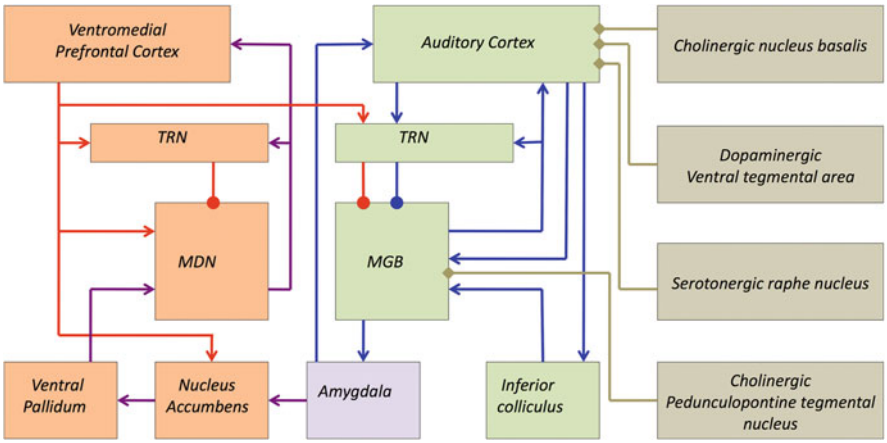

Fig. 7.4 The auditory cortex is involved is several feedback loops. The most direct is based on corticofugal activity (light green boxes and blue connections). Here afferent activity arriving from the IC reaches the cortex via the MGB, which provides excitatory feedback to the MGB and the IC (as well as to lower brain stem nuclei) and to the TRN, which inhibits the MGB. The auditory system is under several modulatory influences from cholinergic, dopaminergic, and serotonergic nuclei, affecting mainly the MGB and cortex (brown boxes and connections). Auditory cortex is also involved with the limbic system via the amygdala (purple box), which receives input from the MGB and from secondary auditory cortex (not shown). The amygdala connects to the NAc and via the ventral pallidum affects the MDN and ventromedial prefrontal cortex (vmPFC, purple connections). The vmPFC provides feedback (red connections) to the NAc as well as the MGB via the inhibitory action of the TRN. The loop is closed via the effect of the MGB on the amygdala. This has been proposed to function as a gate that may block tinnitus. MDN, medial dorsal nucleus of the thalamus; MGB, medial geniculate body; NAc, nucleus accumbens; TRN, thalamic reticular nucleus. Arrows indicate excitatory effects; filled circles indicate inhibitory effects

tinnitus to which a person directs her or his attention, could enhance the processing of tinnitus-related frequencies and suppress the processing of surround frequencies in the brain stem and auditory midbrain. Therefore, this frequency-specific amplification by corticofugal feedback in subcortical areas might contribute to stabilizing the tinnitus percept, leading to the chronic form of tinnitus. Feedback loops tend to stabilize systems. In the long run, peripheral and central activity may enhance each other, and the result is that there is no particular site in the central auditory system that can be held solely responsible for tinnitus. Opening the loop by blocking connections, for example, by using drugs such as lidocaine (Baguley et al., 2005; Langguth et al., Chapter 11), or by desynchronizing the activity of the nested loops, for example, by stimulation through a cochlear implant (Quaranta et al., 2004), by direct electrical (De Ridder et al., 2006; Langguth et al., Chapter 11) or transcranial magnetic stimulation (Plewnia et al., 2003) of the cortex, or even by deep brain stimulation (Cheung and Larson, 2010) are potential ways to alleviate tinnitus.

8 Cortex: Way Station or Locus of the Tinnitus Percept?

Gating studies suggest modulation of auditory signals in the limbic areas of the brain that incorporate feedback loops either to the thalamus (MGB–amygdala–nucleus accumbens [NAc]–thalamic reticular nucleus [TRN]–MGB) or to the cortex (MGB–amygdala–basal forebrain–cortex) as illustrated in Figure 7.4. This indicates that the thalamocortical system is crucial for the perception of tinnitus, but may be tuned out (in normal hearing subjects) by the NAc, which is deficient at least in some tinnitus patients (Rauschecker et al., 2010) or by stimulating the caudate, which may function insufficiently in tinnitus (Cheung and Larson, 2010).

Still, incorporating the view that the auditory system is governed by a set of nested loops in addition to those previously, the thalamocortical complex may play the dominant role. Ignition points for tinnitus may differ according to etiology but the percept is cortically based and modulated in coordination with limbic and other subcallosal systems.

Summarizing, 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 not a single locus for igniting tinnitus in the auditory system either.

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Chapter 8
Human Brain Imaging of Tinnitus

Jennifer R. Melcher

1 Introduction

This chapter describes the study of tinnitus in humans by means of neuroimaging to measure brain function and structure. Here, "neuroimaging" is defined to mean any of a variety of noninvasive techniques, from scalp recordings of electrical activity, to images permitting quantification of the gray and white matter of the cerebral cortex, to neurally coupled changes in blood flow. This chapter focuses specifically on the use of neuroimaging to understand chronic, subjective tinnitus, that is, tinnitus that is lasting and cannot be explained by either an external sound source, or a source within the body (Eggermont and Zeng, Chapter 1). Although defined as the perception of sound lacking a physical sound source, the clinical condition of tinnitus is more than the percept. The tinnitus patient often presents with depression, anxiety, difficulties concentrating, and/or difficulties sleeping. These nonperceptual aspects of the condition are what make tinnitus a clinical problem for approximately 5–10% of the population (Coles, 1984; Shargorodsky et al., 2010).

There are two main reasons for applying neuroimaging methods to humans with tinnitus. One is to identify objective markers for tinnitus that can be used to assess the efficacy of candidate tinnitus treatments. The other is to investigate the neurophysiological processes underlying tinnitus directly in the species of clinical interest. Although there are powerful animal models for tinnitus (Turner, 2007; Heffner & Heffner, Chapter 2), they are not a replacement for direct measurements in humans, in part because it is not clear that animals manifesting behavioral evidence of the

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tinnitus percept also experience nonauditory aspects of the tinnitus condition, such as anxiety or sleeping problems (Zheng et al., 2011a,b).

Over the past two decades, the pace of neuroimaging work on tinnitus has rapidly increased. There are several reasons for this: the development of functional magnetic resonance imaging (fMRI) during the early 1990s, major advances in computational power and instrumentation that have taken place across neuroimaging modalities, and a surge of interest in tinnitus in the last 5–10 years. However, despite the growing body of work and many intriguing results, neuroimaging work on tinnitus has not matured to the point that there is a corpus of investigations systematically following one from another to build a clear, well-developed understanding of the neural processes underlying tinnitus. Therefore, this chapter does not attempt to present a synthesized view of tinnitus from the perspective of neuroimaging. Rather, it focuses on providing background needed to understand the previous neuroimaging literature on tinnitus and to begin designing new investigations to move the field forward.

The following sections first briefly describe perceptual and psychological aspects of tinnitus (Section 8.2). Section 8.3 provides a brief overview of the neuroimaging techniques dealt with in this chapter: neuroelectric recording, neuromagnetic recording, positron emission tomography (PET), structural magnetic resonance imaging (sMRI), and fMRI. This is followed in Section 8.4 by a review of representative neuroimaging investigations of tinnitus. Throughout this latter section suggestions for future work are provided.

2 Overview of the Condition of Tinnitus

The clinical problem of tinnitus has multiple facets, described in the following sections (8.2.1–8.2.6).

2.1 Tinnitus and Hearing Threshold

Tinnitus commonly occurs with hearing loss (Shargorodsky et al., 2010). Although it can also occur in people with clinically normal hearing thresholds, there are data to suggest that such cases may show threshold loss at frequencies above the standard clinical range (i.e., above 8 kHz) or peripheral damage that is not reflected in threshold loss (Roberts et al., 2008; Kujawa & Liberman, 2009).

2.2 Perceptual Aspects of Tinnitus

Standard characterizations of the tinnitus percept include assessment of the quality of the percept, the pitch or spectrum, the loudness, and the minimum level of sound needed to mask the tinnitus percept (minimum masking level; Stouffer & Tyler,

1990; Roberts et al., 2008; Moore, Chapter 9). The quality of the percept can be ringing, hissing, or cricket-like, among other things. The percept can be localized to one or both ears or within the head. Its localization can range from punctate to diffuse. Like sound, the tinnitus percept can be acoustically masked. However, unlike monaural sound, unilateral tinnitus can sometimes be masked by sound to the contralateral ear (Feldmann, 1984). Also, unlike sound, the tinnitus percept may remain suppressed for seconds after the masker is turned off, a phenomenon known as residual inhibition (Feldmann, 1984).

2.3 Hyperacusis

A symptom that often accompanies tinnitus is hyperacusis, or reduced tolerance of normal environmental sounds on the basis of loudness (Baguley, 2003; Tyler et al., 2003). Importantly, "hyperacusis" does not imply a better-than-normal threshold sensitivity to sound, nor is it the same as loudness recruitment, the abnormally rapid growth in perceived loudness with increasing sound intensity that occurs with hearing loss. Even people with clinically normal auditory thresholds can have hyperacusis, just as they can have tinnitus.

2.4 Nonauditory Manipulations That Can Modulate the Tinnitus Percept

The tinnitus percept can be altered in loudness or pitch, for instance by maneuvers of the head and neck, a phenomenon thought to be mediated by somatosensory projections to the central auditory system (Levine, 2004; Dehmel et al., Chapter 5). The phenomenon of somatic modulation is fairly common. For instance, in one tinnitus clinic, 60% of patients had tinnitus that could be modulated by somatic means (Levine, 2004).

Tinnitus can also be modulated by other means. Tinnitus modulation with changes in eye position can follow resection of a vestibular schwannoma (Coad et al., 2001). Lidocaine administered intravenously is widely known for its suppressive effects on tinnitus (Melding et al., 1978). In some it can increase tinnitus loudness rather than reduce it (Reyes et al., 2002).

2.5 Affective and Other Nonperceptual Aspects of the Tinnitus Condition

Tinnitus patients can suffer from depression and anxiety. They often report sleep disturbances such as having difficulty falling asleep or being awoken from sleep (Hébert et al., 2011). Diminishments in cognitive performance have also been reported (Andersson & McKenna, 2006; Stevens et al., 2007).

2.6 Diversity of Tinnitus Characteristics

The facets of tinnitus just described occur in various combinations across patients. The resulting diversity of tinnitus profiles likely corresponds to underlying physiological diversity, which poses a challenge to any physiological investigation of tinnitus, neuroimaging studies included. Even in the most careful comparison between tinnitus subjects and non-tinnitus controls, there is the danger that variables of unrecognized importance will introduce sufficient heterogeneity in the tinnitus group to obscure tinnitus-related effects.

3 Neuroimaging Techniques Applied to Tinnitus

Major neuroimaging techniques available for the study of tinnitus are as follows.

3.1 Neuroelectric Recordings

When a pair of electrodes is positioned on the surface of the head, an electric potential, or voltage, can be recorded as a function of time. When care is taken to avoid signal contamination from muscle or heart activity, this voltage reflects ongoing activity of neuronal populations of the brain. A measurement of this time-varying voltage is the electroencephalogram (EEG). With stimulation and/or a task, an event-related potential (ERP) can be measured that reflects neural stimulus- or task-related activity (Hillyard et al., 1993; Melcher, 2009). This activity is generally too low in amplitude to be detected over the background EEG on a single trial. However, it can be extracted from the background by averaging the voltage signal of multiple trials. When this is done for a brief sound stimulus, such as a click, the resulting measurement is a series of voltage fluctuations reflecting activity of the auditory nerve and brain stem in the first 10 ms after the stimulus. This is followed by fluctuations reflecting thalamic and cortical activity. The fluctuations reflect neuronal activity that is synchronized to the stimulus and across a large enough number of neurons to give a measurable response. EEG or ERP recordings from an array of electrodes distributed over the scalp are commonly used to spatially localize the neuronal sources of the surface-recorded voltages.

3.2 Neuromagnetic Recordings

In addition to producing electric potentials, active neurons in the brain also produce magnetic fields that can be recorded from sensors outside the head (Hari, 1990; Nagarajan et al., 2012). These fields are quite small (approximately 100,000 times

smaller in amplitude than Earth's magnetic field), so their measurement requires a special low-noise sensor called a superconducting quantum interference device (SQUID). Present-day devices for neuromagnetic recordings often comprise more than a hundred such sensors mounted in a supercooled Dewar that fits over the head. Thus, recordings of the magnetic fields produced by the brain can be made simultaneously from hundreds of locations distributed over the scalp. A magnetoencephalogram (MEG), the magnetic analog of the EEG, is a measurement of time-varying magnetic fields produced spontaneously by the brain. In the same manner that ERP measurements are made, event-related magnetic recordings can be measured in response to a stimulus and/or coinciding with the performance of a task. However, neuromagnetic and neuroelectric recordings do not show identical brain activity (Cohen & Cuffin, 1987). For instance, neuromagnetic recordings are insensitive to activity deep within the brain.

3.3 PET

PET provides spatial mappings of brain activity by detecting the product (positrons) of the decay of radioactive tracers (Johnsrude et al., 2002). Two forms of PET imaging have been applied to tinnitus. In one, baseline levels of glucose metabolism are mapped following injection of flurodeoxyglucose ([^{18}F]DG). In the other, changes in blood flow are mapped after inhalation or injection of radiolabeled oxygen. For the latter, measurements are compared between two or more conditions to yield mappings sensitive to local blood flow, which is closely coupled to local neural activity levels. PET does not have the high temporal resolution of neuroelectric and neuromagnetic recordings, but provides superior spatial localization of activity. It also has the capability of mapping receptor distribution in the brain (e.g., dopamine, serotonin), in addition to mapping activity. PET hasn't been used for receptor mapping in tinnitus subjects, but pilot investigations have used single-photon emission computed tomography (SPECT), a related technique, for receptor imaging in tinnitus (Daftary et al., 2004).

3.4 sMRI and fMRI

MRI uses a combination of static and time-varying magnetic fields and radiofrequency excitation of protons in the body to generate images (Huettel et al., 2004). Using commonly available MRI scanners with static magnetic field strengths of 1.5 Tesla or greater, images of the brain can be obtained with millimeter or submillimeter spatial resolution. With sMRI, aspects of brain structure such as gray and white matter of the cerebrum can be readily distinguished, enabling examination of the thickness and volume of cortical gray matter regions (Fischl & Dale, 2000; Desikan et al., 2006), the volume of subcortical structures (Fischl et al. 2002), or spatial

mappings of the degree of spatial coincidence of gray or white matter across brains (Ashburner & Friston, 2000; Good et al., 2001). The grayscale images to the left in Figure 8.1 are examples of sMRI images contrasting gray and white matter.

Diffusion tensor imaging (DTI) is a form of sMRI that images the propensity of protons to follow the trajectory of fiber tracts rather than contrasting tissue types (Bandettini, 2009). It allows quantitative measures of the fiber directionality at a particular location (e.g., fractional anisotropy) to be spatially mapped. It also allows the trajectory of white matter tracts to be followed when intersections between the tract of interest and other white matter tracts is not too tortuous.

Data on brain *function* can be obtained using fMRI (Talavage et al., 2012). With fMRI, slices through the brain are imaged repeatedly using imaging parameters optimized to show changes in image signal resulting from changes in neural activity. The most widely used form of fMRI is blood oxygenation level–dependent (BOLD), in which changes in population neural activity result in colocalized changes in blood oxygenation via a chain of hemodynamic processes (Bandettini, 2009). The change in oxygenation results in a change in image signal intensity, which is detected as fMRI activation. Because changes in neural activity are detected indirectly with fMRI via slow, hemodynamic processes, the temporal resolution of fMRI (seconds) is far less than that of neuroelectric or neuromagnetic recordings. Figure 8.1 shows an example of sound-evoked activation measured with BOLD fMRI.

A major issue for fMRI is the substantial acoustic noise produced during the imaging process (Ravicz et al., 2000). Use of imaging methods, such as clustered volume acquisition (CVA), to mitigate the effects of imaging-generated acoustic noise on brain activation is crucial for fMRI studies of tinnitus (Melcher et al., 2009). With CVA, the effects of the noise are reduced by rapidly imaging multiple slices through the brain in brief (<1 s) clusters spaced by intervals of 8 or more seconds (Edmister et al., 1999; Hall et al., 1999; Talavage et al., 2012).

MR spectroscopy, another form of MRI that has been applied to tinnitus, involves measuring the spectrum of the signal produced by protons excited in the imaging process (Cacace & Silver, 2007). Different peaks in the signal spectrum are produced by protons within different metabolites. Measurement of the peaks allows quantification of metabolites such as glutamate, an excitatory neurotransmitter.

Fig. 8.1 (continued) The p-value result of the statistical comparison (using a Student's t test) is coded on a blue ($p = 0.001$) to yellow ($p = 2 \times 10^{-9}$) scale. Both the activation maps (in-plane resolution of 3.1×3.1 mm) and the anatomical images (1.5×1.5 mm) have been interpolated for these displays. The images are shown in radiological convention, so the subject's right appears on the left side of the figure. HGpm, posteromedial Heschl's gyrus, which is overlapped by PAC; PT, planum temporale, which includes nonprimary, lateral belt areas of auditory cortex (Kaas & Hackett, 2000); AMA, anteromedial area, which corresponds to the portion of the planum polare immediately medial to PAC and includes nonprimary, medial belt areas. Sound stimulus: broadband noise. Single subject data. (Reprinted from Sigalovsky, I. S., & Melcher, J. R. [2006]. *Hearing Research*, 215, p. 70, with permission from Elsevier.)

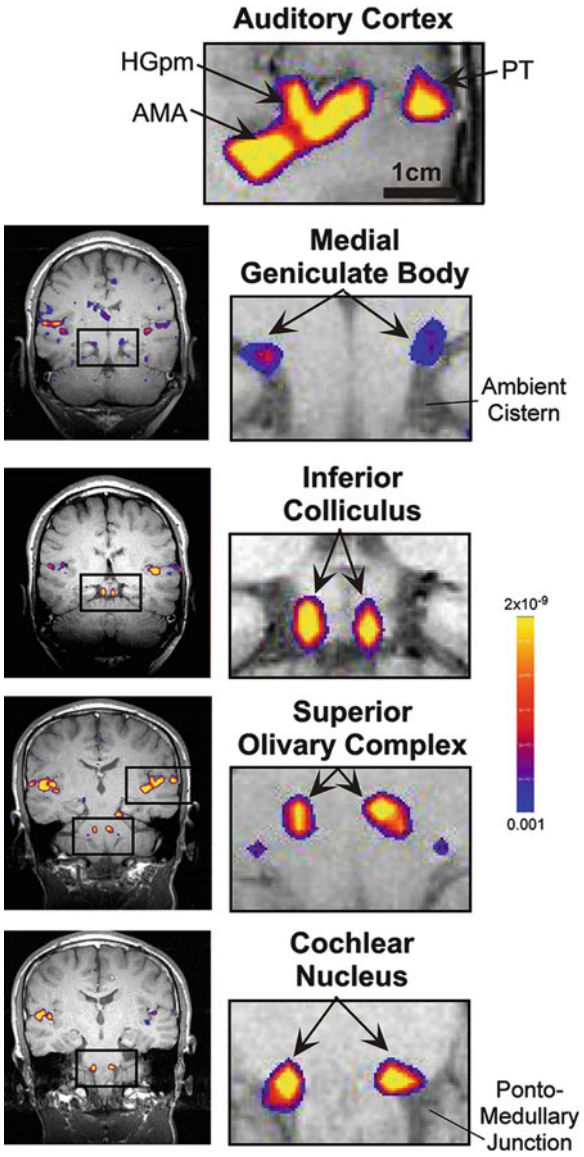

Fig. 8.1 fMRI activation to binaural sound in centers throughout the auditory pathway. (Left) Images of four slices oriented perpendicular to the Sylvian fissure (which can be seen in Fig. 8.2B). (Right) Enlargements of the regions enclosed by rectangles at left. In each panel, activation, shown in color, is superimposed on a grayscale sMRI image optimized to contrast gray and white matter. Activation was measured using a standard fMRI block paradigm, in which a sound was turned on for 10's of seconds and off for 10's of seconds repeatedly. Images of selected slices were obtained approximately every 8 s while the sound was cycled on and off. The signal level in images obtained during "on" periods was compared statistically to that of images obtained during "off" periods

An initial tinnitus study using this technique found that transcranial magnetic stimulation (Langguth et al., Chapter 11), a proposed treatment for tinnitus, produced reductions in both tinnitus loudness and levels of glutamate in the stimulated auditory cortex (Cacace et al., 2011).

4 Neuroimaging Studies of Tinnitus in Humans

The experimental design of physiological studies of people with tinnitus can be divided into five main categories: (1) studies testing for abnormally elevated spontaneous activity; (2) studies based on the premise that any change in the tinnitus percept must correspond to a change in brain activity, and therefore designed to alter tinnitus perception and look for corresponding changes in brain activity; (3) investigations examining sound-evoked responses in people with tinnitus with the idea that differences compared to people without tinnitus might be seen since tinnitus is an "auditory" percept; (4) studies examining the spectrum of spontaneous brain activity; and finally, (5) investigations of brain structure.

4.1 Testing for Elevated Spontaneous Activity

There are two motivations for measuring spontaneous activity levels in people with tinnitus. First are hypotheses that tinnitus reflects abnormally elevated spontaneous activity in the auditory pathway (Eggermont, Chapter 7). Second are reports of such elevations in animals manifesting behavioral evidence of tinnitus (Brozoski et al., 2002; Kaltenbach et al., 2004). The state of the literature on this topic follows in Sections 8.4.1.1 and 8.4.1.2).

4.1.1 Baseline Activity Measurements Using PET

In a first examination of baseline neural activity levels in humans with tinnitus, Arnold et al. (1996) used [^{18}F]DG PET to measure cortical activity in the absence of explicit sensory stimulation in tinnitus patients and non-tinnitus controls. The authors compared the relative amount of activity in left and right auditory cortex (rather than examining absolute levels) presumably to normalize for inter-individual differences in the overall activity level of auditory cortex. The main study result was significantly more asymmetric activity in tinnitus patients, with the left auditory cortex showing greater activity than the right in almost all subjects. There was no relationship between the laterality of the tinnitus percept and the direction of the asymmetry. A similar asymmetry in tinnitus patients compared to non-tinnitus controls was subsequently reported (Wang et al., 2001).

The asymmetry of activity seen in the PET data of tinnitus subjects is intriguing, but not necessarily related to tinnitus given the prevalence of hearing loss among the

tinnitus subjects, but not the control subjects, in the studies just described. It is also unclear whether the asymmetry reflects abnormally elevated spontaneous activity in auditory cortex. There is a small amount of data bearing on this point that comes from Langguth et al. (2006), which, in addition to tabulating an asymmetry index for auditory cortical activity for each tinnitus patient, also reported a potentially better measure of hyperactivity: activity in the more active auditory cortex normalized to the activity in the remainder of the imaged brain slice. This latter measure showed near-zero correlation with the asymmetry index, suggesting that an asymmetry of auditory cortical activity may not imply cortical hyperactivity. However, it also showed no correlation with tinnitus severity. It was not examined whether there might be correlations with other behavioral characteristics of the tinnitus such as tinnitus loudness or minimum masking level. Whether or not there is tinnitus-related hyperactivity measurable with [^{18}F]DG PET remains an open question.

4.1.2 Neuromagnetic Measurement of Baseline Activity

Although it was not the primary purpose of their study, Diesch et al. (2010b) determined baseline activity levels in auditory cortex by means of neuromagnetic recordings in tinnitus and non-tinnitus subjects with high-frequency hearing loss. The primary focus of the study was examination of a particular evoked response, the auditory steady-state response (ASSR; discussed further in Section 8.4.3.2). Evidence indicates that the ASSR is produced by neuronal activity in primary auditory cortex (PAC; Gutschalk et al., 1999). An estimate of baseline activity was obtained by (1) modeling the sources of the ASSR, (2) inferring source amplitude versus time from neuromagnetic recordings over the surface of the head, and (3) subtracting the portion of the source signals time locked to the sound stimulus. The resulting residual activity—activity *not* time locked to the stimulus—was an estimate of baseline activity at the ASSR source locations. This baseline activity was found to be significantly greater in tinnitus subjects, even after accounting for effects of potentially confounding factors such as subject age or degree of high-frequency hearing loss. Given the site of ASSR generation (PAC), the results provide support for theories of tinnitus involving diminished neural inhibition and/or facilitation in PAC (Eggermont & Roberts, 2004; Eggermont, Chapter 7).

4.2 Brain Activity Changes Elicited by Manipulations That Alter the Tinnitus Percept

4.2.1 Overview

Some of the earliest PET and fMRI studies of tinnitus were designed to take advantage of the fact that the tinnitus percept can be changed by maneuvers of the head and neck (Lockwood et al., 1998; Lanting et al., 2010), by eye movement or sustained lateral gaze (Giraud et al., 1999; Lockwood et al., 2001), and by intravenous

delivery of lidocaine (Mirz et al., 1999; Reyes et al., 2002). A premise of these experiments was that a change in tinnitus should correspond to a change in neural activity, which will manifest as activation in PET or fMRI. Thus, the experiments involved modulating peoples' tinnitus by various means and comparing brain images acquired in different tinnitus states (during louder vs. softer tinnitus, for example) in order to detect changes in activity. Such "modulate and image" experiments are technically challenging because PET and fMRI involve comparing images acquired at successive times; images must be in close spatial registration for activation to be detected. Therefore, subject movement must be carefully controlled during tinnitus modulation. With fMRI, changes in the volume of air spaces within the head or in the location of air/tissue interfaces are another potential source of artifact. In the following section, "modulate and image" studies of one type are described in more detail to illustrate the approach. The study results are then analyzed and synthesized so as to suggest next logical steps in this line of experimentation.

4.2.2 Somatic Modulation of the Tinnitus Percept

Two studies have examined sites of brain activation produced during somatic maneuvers, specifically oral–facial maneuvers (OFMs), that modulated the tinnitus percept. One used PET to examine people whose tinnitus increased or decreased in loudness with jaw clenching (Lockwood et al., 1998). Images were acquired during conditions of sustained jaw clenching and rest in both tinnitus subjects and non-tinnitus controls. Images acquired in the two conditions were compared to identify activation induced by the clenching OFM. The second study used fMRI and a somewhat different OFM: jaw protrusion, which had the effect of increasing tinnitus loudness in most of the studied subjects (Lanting et al., 2010). Images were acquired in a CVA paradigm in which image acquisition followed a 4.5-s period of sustained protrusion, or a period of rest. With this approach, the jaw (and therefore the air/tissue interfaces in the mouth) was in the same position for each image acquisition, thus reducing the potential for artifacts as mentioned in Section 8.4.2.1. Activation induced by the protrusion OFM was identified by comparing images acquired just after protrusion to those obtained just after rest.

The results reported by Lockwood et al. (1998) and Lanting et al. (2010) showed similarities:

1. Tinnitus subjects, and also non-tinnitus control subjects, showed OFM-induced activation in auditory cortex, which presumably reflected the influence of somatosensory inputs on the central auditory system (Shore et al., 2007; Dehmel et al., Chapter 5). In Lockwood et al. (1998), the OFM-induced activation of auditory cortex was seen in the two subjects (of the four studied) who, like the majority of the subjects in the study of Lanting et al., reported an increase in tinnitus loudness during the OFM. Note that Lockwood et al. (1998) did not explicitly report OFM-induced cortical activation in non-tinnitus subjects. However, they reported that subtracting the effect of OFMs in control subjects from the significant

OFM-induced activation in a subset of tinnitus subjects yielded no net difference in auditory cortex. The implication is that the controls, like the tinnitus subjects, displayed OFM-induced activation in auditory cortical areas.

2. Subcortical centers showed differences in OFM-induced activation between tinnitus and control subjects. In the study of Lanting et al. (2010), the cochlear nucleus and inferior colliculus showed differences, with activation in tinnitus subjects being greater. In the study of Lockwood et al. (1998), the two tinnitus subjects mentioned in (1) showed differences in activation compared to controls in a region near the medial geniculate body (MGB).

The results raise the possibility of OFM-induced activity related to tinnitus, but with the following caveat: the tinnitus subjects in both studies had poorer thresholds than the controls with whom they were compared. The difference in threshold is relevant in view of animal data suggesting that somatosensory influences on the auditory system increase after damage to the auditory periphery (Shore et al., 2008). It is possible that the differences in OFM-induced activation between tinnitus and non-tinnitus control subjects resulted from differences in the state of the auditory periphery, not tinnitus. Future studies could examine this possibility by comparing OFM-induced activation between tinnitus and non-tinnitus subjects closely matched in hearing threshold.

A final point concerns the two tinnitus subjects studied by Lockwood et al. (1998), who reported a *decrease* in tinnitus loudness with OFM. These subjects showed no OFM-induced activation within the classic auditory pathway, in contrast to the other two tinnitus subjects who reported an increase in tinnitus loudness during OFM in the same study. The data suggest that subjects reporting opposing effects of an OFM on tinnitus loudness do not necessarily show opposing effects in brain activity. Thus, the relationship between tinnitus loudness and auditory activity levels, if any, remains a matter worthy of examination in future experiments.

4.3 Studies Using Sound Stimulation

Sound-evoked activity of the auditory pathway in people with tinnitus has been examined primarily using neuromagnetic recordings (Sections 8.4.3.1, 8.4.3.2) and fMRI (Section 8.4.3.3).

4.3.1 Long-Latency Neuromagnetic Responses

Hoke et al. (1989) proposed one of the first neurophysiological markers for tinnitus. They described robust differences between tinnitus subjects and non-tinnitus controls in long-latency, sound-evoked responses from auditory cortex. The responses, recorded neuromagnetically, are analogs of the well known neuroelectric responses, N100 and P200, which occur at latencies of approximately 100 and 200 ms, respectively (Fig. 8.2). N100 and P200 are generated by multiple cortical sources, but in

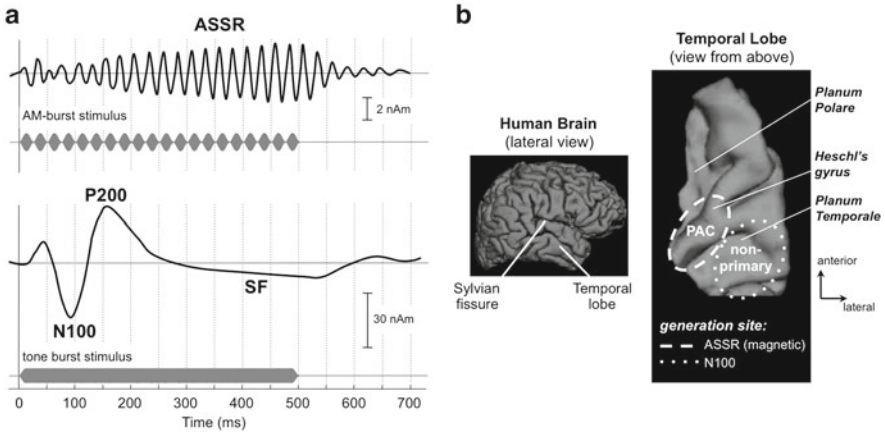

Fig. 8.2 Neuromagnetic responses to sound (**A**) and sites of generation on the superior temporal lobe (**B**). (**A**) The black traces were derived from recordings made from an array of coils over the surface of the head. The recordings were modeled by a dipole source on the superior temporal lobe. The black traces show the time-varying dipole amplitude for an AM-burst stimulus after band-pass filtering (24–65 Hz) to extract the ASSR (top) and for a tone burst stimulus, which produces an N100 and P200 (bottom). (**B**) Generation sites of the ASSR (PAC) and N100 (nonprimary areas of the planum temporale) are shown on a reconstruction of the superior temporal lobe. SF: sustained field. (Portions of **A** use elements of Figs. 4 and 5 in Ross et al. (2002), *Hearing Research*, 165, p. 76, with permission from Elsevier.)

large part by nonprimary auditory cortex (Lütkenhöner & Steinsträter, 1998; Ross & Tremblay, 2009). The specific finding was a reduction in the amplitude ratio, P200/N100, in tinnitus subjects compared to non-tinnitus controls, mainly because P200 was absent or greatly attenuated. A reason for attributing the result to tinnitus instead of hearing loss (which may not have been matched between subject groups) came from a case study documenting an increase in the P200/N100 amplitude ratio over time in one person whose tinnitus progressively resolved (Pantev et al., 1989).

However, since the initial reports of Hoke et al. (1989) and Pantev et al. (1989), the story regarding N100 and P200 in tinnitus has become increasingly murky. On the one hand, attempts to replicate the original results have failed (Colding-Jørgensen, 1992; Jacobson & McCaslin, 2003). On the other hand, there have been reports that: (1) The cortical site generating N100 was displaced in tinnitus subjects relative to controls when the frequency of the evoking stimulus corresponded to the pitch of the tinnitus (Mühlnickel et al., 1998). (2) N100 showed reductions coinciding with reductions in tinnitus loudness over the course of sound therapy (Okamoto et al., 2010). (3) There is greater phase stability of N100 across stimulus presentations in more versus less distressed tinnitus subjects (Strauss et al., 2008). In short, the questions of whether the neuronal activity underlying N100 and P200 is related to tinnitus, and if so how, are still being addressed.

4.3.2 ASSR Recorded Neuromagnetically

Another focus area of tinnitus neuroimaging research examined auditory cortical function by means of neuromagnetic recordings of the ASSR (Fig. 8.2). Evidence indicates that the ASSR, when recorded neuromagnetically, mainly reflects neuronal activity on posteromedial Heschl's gyrus where PAC resides (Gutschalk et al., 1999; Clarke & Morosan, 2012). The ASSR stimulus comprises an amplitude-modulated carrier tone lasting multiple modulation cycles. In response to the onset of such a stimulus, there are middle- and long-latency response components as seen for click and tone burst stimuli. However, there is also a superimposed, near-sinusoidal response at the stimulus modulation frequency that lasts throughout the stimulus. This response, extracted via narrow-band filtering centered at the modulation frequency, is the ASSR (e.g., see Fig. 2 of Diesch et al., 2004). In a first ASSR investigation of tinnitus, Diesch et al. (2004) showed a correlation between subject ratings of tinnitus intrusiveness and ASSR response amplitude. The correlation occurred for ASSR stimuli with a carrier tone frequency corresponding to the tinnitus pitch and not for other carrier frequencies, suggesting a link between ASSR and tinnitus. Subsequently, Wienbruch et al. (2006) reported elevated ASSR amplitudes and a different spatial organization of the ASSR generators in tinnitus subjects compared to non-tinnitus controls. Both of these initial studies have caveats: lack of non-tinnitus controls in Diesch et al. (2004) and substantial threshold differences between tinnitus and non-tinnitus subjects in Wienbruch et al. (2006). However, since these initial studies, the ASSR of tinnitus subjects has been compared to closely matched non-tinnitus control subjects, and any residual differences between groups, in threshold or age for instance, factored out in post hoc analyses. The results provide additional evidence for a relationship between the neural activity underlying the ASSR and tinnitus (Diesch et al., 2010a,b), including confirmation of the correlation between tinnitus intrusiveness and ASSR amplitude found by Diesch et al. (2004).

Beyond establishing correlations between tinnitus and a neuroimaging measure, the recent studies of Diesch et al. (2010a,b) also investigated cortical mechanisms of tinnitus. For instance, Diesch et al. (2010a) compared the response to a conventional ASSR stimulus to that of multiple, simultaneously presented ASSR stimuli, each with a different carrier tone frequency and slightly different modulation rate. Modulating the carrier tones at different rates made it possible to separate the ASSRs produced by each of the simultaneously presented stimuli in analysis. In non-tinnitus controls, ASSR amplitude for a given carrier frequency was suppressed in the condition of multiple stimuli compared to the conventional condition of a single stimulus—a result consistent with lateral inhibition in the neurons generating the ASSR. In contrast, tinnitus subjects showed little suppression or even enhancement (depending on carrier frequency) in the multiple stimulus condition—a result suggestive of reduced lateral inhibition in the tinnitus subjects and generally supportive of theories and data suggesting reduced cortical inhibition in tinnitus (Roberts & Eggermont, 2004; Eggermont, Chapter 7).

4.3.3 fMRI Activation to Sound

In another body of tinnitus studies, fMRI was used to examine sound-evoked responses in the auditory pathway. The first of these studies reported an asymmetry of activation in response to binaural sound in the inferior colliculi (IC) of subjects with lateralized tinnitus and symmetric hearing thresholds, which differed significantly from the symmetric activation found in non-tinnitus controls (Melcher et al., 2000). Subsequently, a similar asymmetry was reported again, also in subjects with lateralized tinnitus, but this time in the MGB and auditory cortex in addition to the IC (Smits et al., 2007). However, two more reports, one focused on the IC and the other focused on both IC and auditory cortex, did not find systematic activation asymmetries related to tinnitus laterality and instead noted an overall elevation in sound-evoked activation in tinnitus subjects (Lanting et al., 2008; Melcher et al., 2009). The report by Melcher et al. (2009) compared especially closely matched tinnitus and non-tinnitus subject groups, re-imaged several subjects from the original Melcher et al. study from 2000, and examined the effects of background acoustic noise during fMRI on stimulus-evoked activation. Several conclusions were reached: (1) Tinnitus subjects, on average, showed elevated activation in response to sound in the IC compared to controls matched in a variety of ways: threshold, age, anxiety, and depression. (2) The presence of background acoustic noise can eliminate this effect by suppressing activation evoked by sound stimulation in the IC, particularly in tinnitus subjects whose elevated responses to sound approach the upper limit of response magnitude. (3) The asymmetry reported by Melcher et al. (2000) was probably not the important differentiator of tinnitus and non-tinnitus subjects in that earlier work, but rather the activation magnitude differences underlying the asymmetry. With respect to the activation asymmetries reported by Smits et al. (2007), Melcher et al. (2009) offer an explanation: The lateralized tinnitus subjects in the study may have had greater hearing loss in the tinnitus ear, as is common (Nuttall et al., 2004), and the asymmetry resulted from threshold asymmetry, not tinnitus. This possibility cannot be ruled out given the limited data on subject thresholds in the Smits et al. (2007) report. Thus, taken together, the available fMRI data are consistent with elevations in sound-evoked activity of the IC in subjects with tinnitus.

Building on the findings just summarized, Gu et al. (2010) used fMRI to test whether the elevations in sound-evoked activation seen in the IC of tinnitus subjects might be related to hyperacusis, which was not taken into consideration in the previous studies, rather than tinnitus per se. Gu et al. (2010) also studied more rostral auditory centers, in addition to the IC. Importantly, closely matched subject groups were compared, defined by whether tinnitus or hyperacusis was present or not. The main findings are as follows: (1) Elevations in sound-evoked activation of the IC were related to hyperacusis, not tinnitus. (2) PAC and nonprimary auditory cortical areas also showed elevated activation related to hyperacusis. (3) PAC showed elevated activation related to tinnitus, as well as hyperacusis. A relationship between elevated responses to sound and hyperacusis is fairly intuitive; sound perceived to be louder than normal also produces abnormally high amounts of activity. A relationship between tinnitus and elevated sound-evoked activation, as occurred in PAC,

is less so. Gu et al. (2010) speculated that tinnitus-related elevations in cortical activation might result from undue attention drawn to the auditory domain by the presence of tinnitus. This as-yet untested hypothesis follows in part from data showing that selective attention to the auditory domain can result in increases in sound-evoked auditory cortical activity (Degerman et al., 2006; Paltoglou et al., 2009).

4.4 Spectra of Spontaneous Activity

The past 10 years has seen growing interest in the spectral properties of spontaneous or "resting" brain activity, an interest that has extended to the tinnitus field. Some of the first experiments examining the spectral content of brain activity in tinnitus used neuromagnetic recordings and examined the spectrum of activity averaged across sensors. Comparisons between tinnitus and non-tinnitus subjects showed greater delta band (1–4 Hz) power in tinnitus subjects but greater alpha band (8–12 Hz) power in controls (Weisz et al., 2005, 2007). Subsequent studies have employed neuroelectric as well as neuromagnetic recordings, spatially mapped the power in different frequency bands, and correlated power in different frequency bands and brain areas with various tinnitus characteristics (van der Loo et al., 2009; Moazami-Goudarzi et al., 2010; Vanneste et al., 2010). Many of the results are intriguing. Collectively, they touch on numerous aspects of tinnitus. However, there remain important unresolved questions, including the extent to which the results reflect tinnitus as opposed to other uncontrolled variables.

4.5 Structural Neuroimaging

The speed and relative ease with which sMRI data can be obtained, combined with the ready availability of software for automatically analyzing brain structure, have led to a large number of studies searching for structural differences between patient populations and control subjects. In tinnitus, several studies have compared structural scans from subjects with tinnitus to others without tinnitus. Results from these studies are summarized in the following three Sections (8.4.5.1–8.4.5.3) and in Figure 8.3.

4.5.1 Voxel-Based Morphometry Studies

Most of the previous sMRI work on tinnitus has used voxel-based morphometry (VBM) to compare, in essence, the relative occurrence of gray matter (or white matter) at a given location between tinnitus and non-tinnitus subject cohorts. The most striking VBM result is that of Mühlau et al. (2006). The major reported difference between groups was in the gray matter of medial prefrontal cortex immediately ventral to the rostral extent of the corpus callosum, although a less significant

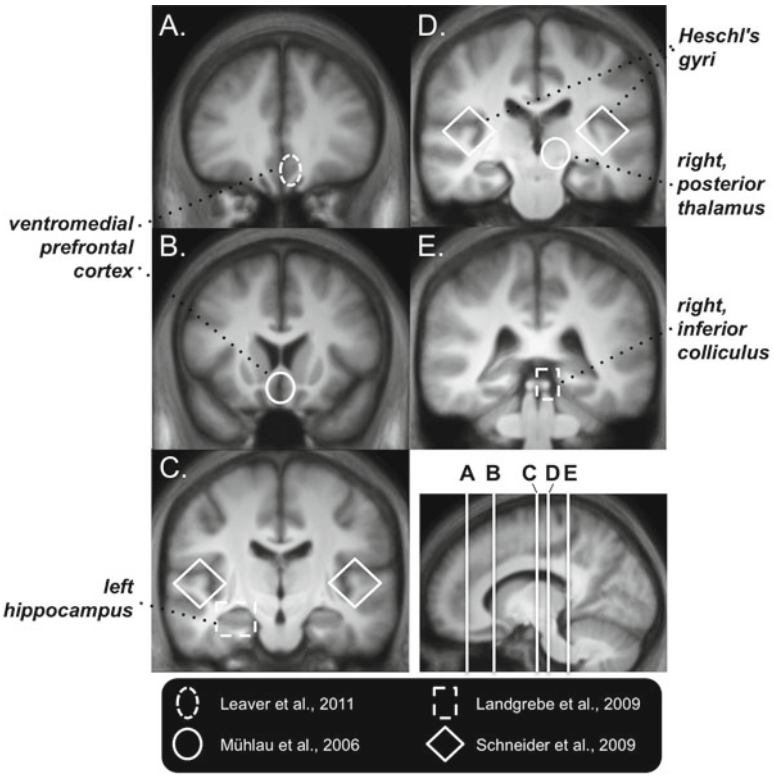

Fig. 8.3 Summary of results from sMRI studies of tinnitus. The locations of reported structural differences between tinnitus and non-tinnitus subjects are indicated on coronal images (**A**–**E**). The images are an average of sMRI data from 27 subjects. The anterior–posterior positions of the coronal images are indicated on the sagittal image at bottom right

difference in right, posterior thalamus, near the MGB, was also found. The authors were able to make a compelling case that the structural differences between groups were related to tinnitus because the tinnitus and non-tinnitus, control groups were closely matched in respects known to be related to brain morphology including age, sex, and hearing threshold (clinically normal; Good et al., 2001; Sowell et al., 2007; Husain et al., 2011). More recently, Leaver et al. (2011), again using VBM, reported structural differences between tinnitus and non-tinnitus subjects in ventromedial prefrontal cortex. While their study did not have the same close matching between subject groups as the study of Mühlau et al. (2006), detailed post hoc analyses were conducted to take into account the intergroup differences in age and hearing loss.

In contrast to the two reports of tinnitus-related structural differences in ventromedial prefrontal cortex, there are also reports showing no tinnitus-related effects in this area. One study, almost identical in design to that of Mühlau et al. (2006), found differences between closely matched tinnitus and non-tinnitus subject groups, but in the left hippocampus and right inferior colliculus (Landgrebe et al., 2009). The other study

examined tinnitus and non-tinnitus subjects with hearing loss, as well as non-tinnitus subjects with clinically normal hearing (Husain et al., 2011). Although the results demonstrated clear effects of hearing loss, any effects of tinnitus were not definitive. Specifically, comparison of the tinnitus and non-tinnitus subjects with hearing loss indicated structural differences between groups on the superior temporal gyrus, which contains nonprimary auditory cortical areas, and in the superior and medial frontal gyri. However, these effects were not confirmed in a comparison between the tinnitus group and the second non-tinnitus group, which had normal hearing.

At a very broad level, the VBM results show some consistencies: effects in brain areas considered part of the limbic system or closely related to it (ventromedial prefrontal cortex: Mühlau et al., 2006; Leaver et al., 2011; hippocampus: Landgrebe et al., 2009) and effects in auditory centers (MGB: Mühlau et al., 2006; inferior colliculus: Landgrebe et al., 2009; possibly superior temporal gyrus: Husain et al., 2011). However, the specific limbic and auditory areas implicated by each study are different such that there is almost no corroboration across studies. The reasons for the disparities across VBM studies of tinnitus are unclear. One possibility is that some of the results are spurious. However, another is that all of the findings are correct, and that experimental differences may account for the inconsistency of results, perhaps even experimental differences as subtle as the source of study subjects. For instance, Mühlau et al. (2006) recruited subjects from an otolaryngology clinic whereas Landgrebe et al. (2009) recruited from a tinnitus clinic based in a psychiatry department. If people with different, as-yet unappreciated types of tinnitus are attracted to different types of clinics, it could result in study samples with different underlying bases for their tinnitus.

4.5.2 Structural Examination of Heschl's Gyrus

Different from the studies just described, the sMRI study of tinnitus conducted by Schneider et al. (2009) did not use VBM or look broadly throughout the brain for structural differences between tinnitus and non-tinnitus subjects. Rather, it focused on a region that is generally overlapped by PAC: posteromedial Heschl's gyrus (Clarke & Morosan, 2012). In hemispheres with two Heschl's gyri, the more anterior one was analyzed since it is the more likely location of PAC (Rademacher et al., 2001). Specifically, the authors quantified the volume of gray matter on Heschl's gyrus in individual subjects with tinnitus and without. Subjects were further categorized as "musicians" and "non-musicians" in light of a previous report of increased gray matter volume on Heschl's gyrus in musicians (Schneider et al., 2002). Taking effects of hearing loss, age, sex, and handedness into account, the authors confirmed the previous finding of increased gray matter volume in musicians while also demonstrating a diminishment of gray matter volume related to tinnitus. In other words, musicianship and tinnitus had opposing relationships to gray matter volume. One implication of the Schneider et al. (2009) study is that musicianship may be an important variable to control in sMRI studies of tinnitus, and of auditory cortex more generally.

4.5.3 DTI

The white matter tracts of tinnitus subjects have been examined in a few studies using DTI (Lee et al., 2007; Crippa et al., 2010; Husain et al., 2011). However, only one compared tinnitus subjects to non-tinnitus subjects of similar age and hearing threshold (Husain et al., 2011), both of which are known to influence DTI measures of white matter morphology (Barrick et al., 2010). Although Husain et al. (2011) found white matter differences related to hearing loss, they found none that could be definitively related to tinnitus.

5 Summary and Discussion

The use of neuroimaging to understand tinnitus might best be described as a work in progress. As described in the present chapter, there are many powerful neuroimaging methods available to examine the neurophysiological and neuroanatomical bases of tinnitus directly in humans. Most of these methods have been applied to tinnitus in at least a preliminary way. The next challenge is to use neuroimaging to develop a corpus of rigorous findings that build on one another to form a comprehensive picture of brain structure and function in human tinnitus. In building such a picture, reliable, objective indicators of tinnitus will emerge, as well as a clarified understanding of the tinnitus condition.

To make efficient progress toward understanding, and ultimately treating tinnitus, it is imperative that future neuroimaging studies include careful experimental controls so effects of tinnitus can be distinguished from those of other variables. Controlling for hearing threshold has been emphasized in the present chapter. However, depending on the experiment being performed, there are other important variables, including age, sex, and depression, with demonstrated relationships to neuroimaging measures of brain function and/or structure (e.g., Sowell et al., 2007; Sheline et al., 2009). Not controlling for such variables is tantamount to assuming their relationship to brain function and structure is negligible compared to that of tinnitus, which may not be the case. Efficient progress will also benefit from careful, agnostic interpretation of the experimental results.

While still evolving, the neuroimaging literature taken as a whole generally indicates that the tinnitus brain differs from the non-tinnitus brain in ways that are not always predicted by differences in the auditory periphery. In other words, tinnitus is not just a problem of the ear, but also a problem of the brain per se. Moving forward, some of the major challenges for neuroimaging will be singling out those aspects of brain structure and function most directly related to tinnitus and understanding how these identified players conspire to develop and perpetuate the tinnitus condition.

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Abbreviations

ASSR	auditory steady-state response
BOLD	blood oxygenation level–dependent
CVA	clustered volume acquisition
DTI	diffusion tensor imaging
EEG	electroencephalogram
ERP	event-related potential
IC	inferior colliculi
MEG	agnetoencephalogram
MRI	magnetic resonance imaging
OFM	oral–facial maneuvers
PAC	primary auditory cortex
PET	positron emission tomography
SPECT	single-photon emission computed tomography
SQUID	superconducting quantum interference device
VBM	voxel-based morphometry

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Chapter 9
The Psychophysics of Tinnitus

Brian C.J. Moore

1 Introduction

Tinnitus is the perception of sound in the absence of an external sound source. The percept can take many forms, including sounding like a single or multiple tones, hissing, buzzing, crickets, or roaring. This chapter is concerned with the perceptual properties of tinnitus as revealed using psychophysical experiments. These perceptual properties may be relevant to diagnosing the cause of tinnitus and for selection of relevant treatment options. The implications of the results for the mechanism and site of generation of the tinnitus are also considered.

2 The Subjective Quality and Pitch of Tinnitus

2.1 Pitch Matching and Its Associated Problems

Many researchers have attempted to explore the subjective quality of tinnitus by asking people with tinnitus to adjust a sound so that it matches their tinnitus in some way. Perhaps the simplest, but rather rare, case is when the tinnitus is described as sounding like a single pure tone. In that case, the person with tinnitus can be asked

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to adjust a sine wave in frequency until it matches the pitch of his or her tinnitus and in level until it matches the loudness of the tinnitus (see Section 9.3.2 for details of loudness matching). Such an approach may be less appropriate in the more common situation in which the tinnitus does not sound like a pure tone. Nevertheless, people with tinnitus often report that it has one or more pitches, and in such cases they can be asked to make a match to the most prominent pitch. This is often found to be difficult to do. Reed (1960) reported that only about 25% of participants with tinnitus were able to achieve a satisfactory match with a pure tone. Also, although participants may make consistent matches within a short period of time (within a given test session), the matches may vary considerably across sessions (Penner, 1983). The consistency within a session may be partly a consequence of participants remembering their previous match and attempting to behave in a consistent way; it may not reflect a stable percept or a percept corresponding to a narrowband sound.

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. People with tinnitus often report that it is localized toward one ear. Some researchers have advocated presenting the matching tone to the ear contralateral to the side where the tinnitus is perceived, to avoid the matching sound masking the tinnitus and to reduce confusion of the tinnitus with the matching sound (Vernon et al., 1980). Conversely, some researchers have advocated presenting the matching tone to the ear where the tinnitus is perceived to avoid problems with binaural diplacusis, the perception of a difference in pitch at the two ears when a tone of fixed frequency is presented (Tyler & Conrad-Armes, 1983b). This issue is still not resolved.

A second problem is selection of the level of the matching sound. It has been reported that people with tinnitus sometimes confuse loudness and pitch, especially when they have no musical training (Vernon & Fenwick, 1984). Hence, it has been suggested that it is necessary to adjust the level of the matching tone to achieve a loudness match to the tinnitus, before a pitch match is made (Fowler, 1940; Vernon & Fenwick, 1984). However, as discussed in Section 9.3, loudness matches are difficult, and prone to bias effects, when the adjustable matching sound differs in pitch from the sound to which it is being matched. There is thus a circular problem: Valid pitch matches to tinnitus require a prior loudness match to the tinnitus, and valid loudness matches require a prior pitch match.

A third problem arises when the matching sound itself does not have a clear pitch. This can occur, for example, when the frequency of the matching sound leads to maximum basilar-membrane vibration in a dead region, which is a region of the cochlea with few or no functioning inner hair cells and/or neurons (Moore & Glasberg, 1997; Moore, 2001). Tones whose frequencies produce peak vibration in a dead region are often reported as sounding noise-like rather than tone-like (Huss & Moore, 2005b), and their pitch is often indistinct (Huss & Moore, 2005a). Henry and Meikle (2000) noted "we have encountered patients for whom all frequencies above a certain value (e.g., 3000 Hz) sound similar" (p. 146). All of these problems need to be borne in mind in interpreting the results described in the text that follows.

2.2 Relation of Pitch Matches to the Audiogram

When tinnitus is matched with a single pure tone, the hearing loss at the frequency corresponding to the tinnitus pitch tends to be greater than at adjacent (usually lower) frequencies (Fowler, 1940; Graham & Newby, 1962; Pan et al., 2009). Usually, the tinnitus is matched to a relatively high frequency, above 3000 Hz.

Some theories of tinnitus lead to the prediction that in cases of tonal tinnitus the tinnitus pitch should be related to the "edge frequency" of the audiogram, corresponding to the boundary between a region of normal or near-normal hearing and a region with greater hearing loss, although clearly this cannot be applicable to people with normal hearing who have tinnitus. When a region of the cochlea is damaged, the cortical area that is normally tuned to frequencies maximally exciting that region can become tuned to adjacent frequencies (Robertson & Irvine, 1989). This reorganization leads to a cortical over-representation of the adjacent frequencies, and that might be associated with tinnitus corresponding to the edge frequency (Eggermont, 2006); see also Eggermont, Chapter 7. Another theory leading to the same prediction is based on the idea that there is mutual inhibition between adjacent tonotopically organized regions at several levels of the auditory pathway, including the cochlear nucleus and inferior colliculus (Carterette, 1969). When there is a hearing loss in a certain frequency region, that may result in a loss of inhibition from neurons tuned to that region; this release from inhibition may in turn lead to increased neural activity in an adjacent region tuned to frequencies where there is less hearing loss, giving rise to tinnitus corresponding to the edge frequency.

Several early researchers reported results consistent with the idea that the pitch of tinnitus corresponds either to the edge frequency of the audiogram, as defined previously, or to the frequency where the loss is maximal (Josephson, 1931; Mortimer et al., 1940; Fowler, 1942). However, subsequent research has revealed a less clear picture. For reviews of research up to 2000, see Henry and Meikle (2000) and Tyler (2000). Henry and Meikle (2000) concluded that "pitch matches for tinnitus can occur practically anywhere in frequency regions where there is hearing loss" (p. 142). König et al. (2006) reported that, for people with noise-induced hearing loss (mainly with hearing loss at high frequencies), there was a "clear association between the tinnitus pitch and the edge of the audiogram, with tinnitus pitch being on average 1.48 ± 0.12 octaves above the audiogram edge frequency" (p. 59). However, the correlation, r, between the tinnitus pitch and the edge frequency was low ($r = 0.3$), although it was statistically significant at $p = 0.04$.

Pan et al. (2009) studied the relationship between the characteristics of the audiogram and tinnitus pitch for 195 people with a large variety of audiogram configurations and origins of hearing loss. The mean edge frequency of the audiogram (for the 97 cases in which an edge frequency could be determined) was 2237 Hz, while the mean tinnitus pitch match was markedly higher at 4968 Hz. Seventy-five of the 195 pitch matches fell at 8000 Hz or above. The mean match was higher for participants reporting tone-like tinnitus than for participants reporting noise-like tinnitus. No relationship was found between the tinnitus pitch and the edge frequency. There was also no

relationship between the tinnitus pitch and the frequency at which the hearing loss was maximal. Although the matches for some participants fell close to the edge frequency of the hearing loss, the authors were unable to find any characteristic that distinguished those participants from the others.

Moore et al. (2010) examined the relationship between tinnitus pitch and the edge frequency of the hearing loss using 11 participants selected to have mild-to-moderate sloping hearing loss (greater loss at high frequencies than at low frequencies) and tonal tinnitus. Before being tested in the main experiment, subjects were given specific training to help them to avoid octave errors in their pitch matches. Pitch matches made after this training were generally lower in frequency than matches made before such training, often by one or two octaves. A clear relationship was found between the values of the edge frequency of the hearing loss and the mean pitch matches after training; the correlation was 0.94. Generally, the pitch matches were close in value to the values of the edge frequency of the hearing loss.

Moore et al. (2010) suggested that the reason that they found a clear relationship between the values of the edge frequency of the hearing loss and the mean pitch matches while other researchers mostly have not found a clear relationship was the training that they gave to reduce octave errors. This is consistent with an early report of Graham and Newby (1962) showing that training to reduce octave errors reduced the variability of pitch matches to tinnitus, although Penner (1983) argued that "the variability in matches to the tinnitus is not due to octave confusion" (p. 266). Clearly, replication of the experiment of Moore et al. with a larger number of participants would be desirable.

As noted earlier, when pitch matches to tinnitus are made across several sessions, the matches are often found to vary markedly from one session to the next (Penner, 1983; Tyler & Conrad-Armes, 1983b; Burns, 1984). The variability may reflect genuine variability in the underlying percept, or it may reflect the fact that the tinnitus percept does not usually resemble the percept of a pure tone; rather it sounds much more complex, perhaps having multiple pitches or sometimes not having a clear pitch at all. Participants may match one of the component pitches in one session, and a different component pitch in another session.

2.3 Characterization of the Tinnitus "Spectrum"

Noreña et al. (2002) attempted to characterize the percept of the tinnitus in more detail by measuring what they called the "tinnitus spectrum," using 10 participants who described their tinnitus as tonal. After measurement of audiometric thresholds over a wide frequency range (up to 14 kHz for some participants), participants were presented with a tone whose frequency was pseudo-randomly selected from the range used for audiometry. Each participant was asked to adjust the level of the tone until it matched the loudness of his or her tinnitus and then to indicate whether the tone matched the pitch of one of the components of the tinnitus. If so, the participant was asked to rate its contribution to his or her tinnitus, on a scale from 0 to 10. This was repeated for a series of pseudo-randomly selected tone frequencies.

The results showed that frequencies judged to form part of the tinnitus spectrum covered a wide range, although the frequencies contributing most generally fell within the range where a hearing loss was present. There was a trend for the contribution to tinnitus to increase for frequencies where the hearing loss was greatest. Despite the participants reporting tonal tinnitus, there was often a relatively flat frequency region where the rated contribution was high. For example, one participant gave a rating of about 8 for all frequencies from 2000 to 9000 Hz, and another gave ratings of 8–9 for all frequencies from 6000 to 12000 Hz. Only one participant had a tinnitus spectrum with a distinct major peak. The peak fell toward the lower edge of a dip in the audiogram extending from about 4500 to 7500 Hz. Similar tinnitus spectra have been reported by Roberts et al. (2006, 2008). It can be concluded that, even for people reporting tonal tinnitus, the percept is usually more complex than that evoked by a pure tone.

2.4 Matching Tinnitus with Complex Sounds

Several researchers have explored the complex perceptual character of tinnitus using a matching sound consisting of multiple sinusoidal components, each of which can be varied in level and frequency (Hazell, 1981; Penner, 1993). It has been found that many sinusoidal components may be required to give a reasonable match. While the rated similarity of the matching sound and the tinnitus generally increased with an increase in the number of components in the matching sound, participants seemed never to be satisfied with the match; the synthesized sound was never rated as identical to the tinnitus.

It may be the case that the percept of tinnitus cannot be matched by any synthesized sound. In other words, a person with tinnitus may have a perceptual experience that could not occur with an acoustic stimulus. This may happen because it is impossible to match both the spectral and temporal attributes of the tinnitus and the synthesized sound. Although some people report fluctuating tinnitus, it is more common for tinnitus to be reported as relatively steady. However, synthetic matching sounds containing multiple sinusoidal components give rise to complex patterns of beats; these correspond to amplitude fluctuations produced by the interaction of the sinusoidal components on the basilar membrane. For example, two components with frequencies of 5000 and 5050 Hz will interact to give beats at a 50-Hz rate. This gives rise to a sensation of "roughness" (Terhardt, 1974), an aspect of sensation that may not form part of the tinnitus percept.

2.5 Relationship of Pitch Matches to Etiology

Several researchers have investigated whether the pitch of tinnitus is related to the etiology of the hearing loss. Nodar and Graham (1965) obtained pitch matches to tinnitus for participants with tinnitus associated with Ménière's disease, conductive hearing loss, or sensorineural loss other than Ménière's disease. They found that the

group with sensorineural loss usually made matches to relatively high frequencies (range 545–7500 Hz, median = 3900 Hz), while the other two groups usually made matches to low frequencies: for the Ménière's group all matches were below 1000 Hz with a median of 320 Hz; for the conductive group the range was 90–1450 Hz, with a median of 490 Hz. Douek and Reid (1968) also reported that participants with Ménière's disease made matches to low frequencies. Indeed they reported that matches were usually in the range 125–250 Hz, which is lower than reported by Nodar and Graham (1965).

2.6 Pitch of Tinnitus Caused by Exposure to Intense Sound

It has been known for many years that exposure to intense sounds often leads to tinnitus. An early systematic investigation of this was presented by Davis et al. (1950). They exposed male participants with normal or near-normal hearing (including three of the authors of the paper) to pure tones with frequencies of 500, 1000, 2000, and 4000 Hz and to a noise resembling airplane noise. Exposure levels ranged from 110 to 130 dB sound pressure level (SPL), and exposure durations ranged from 1 to 64 minutes. The sounds were delivered via a loudspeaker, and one ear was plugged to reduce the exposure in that ear. They found that tinnitus was common after exposures that led to a temporary threshold shift (TTS, an elevation in absolute threshold; it should be noted that, for some of the participants, including first author Hallowell Davis, the exposure led to permanent hearing loss). As has been found in many studies, the maximum TTS produced by the pure-tone exposures typically occurred for a test frequency about 0.5 octave above the exposure frequency. The tinnitus after exposure to a pure tone was more likely to have a clear and constant pitch than tinnitus after exposure to noise. Pitch-matching experiments, using an adjustable tone presented to the ear that was plugged during exposure, indicated that the pitch of the tinnitus corresponded to the upper edge of the frequency region over which TTS occurred.

Loeb and Smith (1967) exposed participants with normal hearing (for frequencies up to 4000 Hz) to: (1) pure tones with frequencies of 300, 500, 1000, and 2000 Hz; (2) broadband white noise; (3) one-octave wide noise bands centered at 900, 1800, and 3600 Hz. The exposure duration was 5 minutes and the stimulus was presented via a loudspeaker with one ear plugged. Initially an exposure level of 90 dB SPL was used, but the level was progressively increased until a TTS of 40 dB occurred or until the exposure level was 120 dB SPL. If tinnitus was experienced after exposure, the participant was asked to match its pitch by adjusting the frequency of a tone presented to the previously plugged ear, via an earphone. About 75% of the participants reported hearing tinnitus when the exposure level was about 114 dB SPL or higher. For most, a tonal percept was recorded, although a few reported a buzz or a noise-like percept. There was a general tendency for both the frequency of maximum TTS and the frequency of the matching tone to increase with increasing center frequency of the exposure stimulus, although considerable individual variability occurred.

Atherley et al. (1968) exposed participants with normal or near-normal hearing to 1/3-octave wide bands of noise centered at 2, 3, 4, or 6 kHz, using a level of 110 dB SPL and an exposure duration of 5 minutes. The sounds were delivered to one ear via an earphone. Eighty-nine percent of participants experienced tinnitus after exposure. Tinnitus in the exposed ear occurred most often for the exposure center frequency of 3 kHz. After exposure, participants were asked to match the frequency and level of a tone presented to the nonexposed ear, so that it matched the pitch and loudness of the tinnitus heard in the exposed ear. The matching frequency was always slightly below the frequency at which the TTS was maximal.

Cahani et al. (1983) obtained pitch matches to tinnitus for 56 participants who had been exposed to noise in the past. The participants were divided into two groups: one, group P, showed a sensorineural hearing loss typical of acoustic trauma; the other, group N, had hearing within normal limits. The matching frequencies for group P fell mostly at high frequencies, whereas the matches for group N fell at low and medium frequencies. The authors concluded that different processes were involved in the generation of tinnitus for the two groups.

It is possible that the tinnitus for group N was related to the abnormal spiking activity in the inferior colliculus (IC) reported by Bauer et al. (2008). They assessed behavioral evidence of tinnitus and spontaneous neural activity in the IC after inducing unilateral cochlear trauma in chinchillas. The trauma was produced in three ways, designed to produce different patterns of cochlear damage: acoustic exposure (AEx), which produced sparse low-frequency inner hair cell (IHC) and outer hair cell (OHC) loss; round window cisplatin (CisEx), which produced marked OHC loss mixed with some IHC loss; and round window carboplatin (CarbEx), which produced marked IHC loss without OHC loss. Compared with controls, all experimental groups displayed psychophysical evidence of tinnitus with features resembling a 1-kHz tone. Contralateral IC spontaneous activity was elevated for the AEx and CisEx groups, which showed increased spiking and increased cross-fiber synchrony. There was a subpopulation of neurons that were more prevalent in animals with tinnitus and showed high bursting, low variance of interspike intervals, and within-burst peak spiking of approximately 1000/s. This abnormal activity may be a correlate of tinnitus (Eggermont, 1990).

In summary, tinnitus occurs often after exposure to intense sounds, especially when the sounds produce TTS. The pitch of the tinnitus often seems to correspond approximately to the upper edge of the frequency range over which maximum TTS occurs. However, the pitch of the tinnitus sometimes corresponds to a frequency at which absolute thresholds are normal or near normal.

2.7 Conclusions on the Pitch of Tinnitus

In summary, the percept of tinnitus is usually complex in quality. Although tinnitus can sometimes be matched by adjusting the frequency of a pure tone, the matches are often unreliable across sessions. The matching frequencies tend to fall in regions

where the hearing loss is greatest. The matching frequencies are also usually high. Training to reduce octave confusions may result in lower pitches, and may increase the reliability of the pitch matches, although more research is needed to determine whether this is the case. In cases where the tinnitus is described as tonal, and for people with sloping audiograms, the frequency that matches the tinnitus may correspond to an edge in the audiogram, where the hearing loss increases relatively abruptly. Again, however, more research is needed to confirm this finding. For temporary tinnitus produced by exposure to intense sounds, the frequency that matches the tinnitus may correspond to the upper edge of the region over which maximum TTS occurs. The frequency corresponding to the tinnitus pitch may be useful for diagnostic purposes. For example, tinnitus matched with a low frequency may be indicative of Ménière's disease.

3 The Loudness of Tinnitus

3.1 Definition of Loudness and Loudness Level

Loudness refers to the subjective magnitude of a sound. It is defined as "that attribute of auditory sensation in terms of which sounds can be ordered on a scale extending from quiet to loud" (ANSI, 1994, p. 35). The most commonly used unit of loudness is the sone. One sone is defined as the loudness of a 1000-Hz tone with a level of 40 dB SPL, presented binaurally from a frontal direction in free field (without any reflections from surfaces in a room), as judged by listeners with normal hearing. For a person with normal hearing, loudness roughly doubles with each 10-dB increase in sound level, for sounds with levels above about 40 dB SPL. Thus, a 1000-Hz tone with a level of 50 dB SPL is usually judged as about twice as loud as a tone with a level of 40 dB SPL and has a loudness of 2 sones.

Sometimes, an alternative measure is used, called the loudness level. For a given sound, X, its loudness level is defined as the level (in dB SPL) of a diotic 1000-Hz tone that is equal in loudness to X. The unit of loudness level is the phon. For a diotic 1000-Hz tone, its loudness level is equal to its physical level in dB SPL. It should be noted that the loudness level of a sound in phons is NOT directly proportional to its loudness, although the two are monotonically related.

3.2 Tinnitus Loudness Matching and the Choice of Units

The loudness of tinnitus has most often been estimated by asking the individual to adjust an external sound so as to match the loudness of the tinnitus. Usually, the individual first selects a sound that is similar to their tinnitus (Penner, 1983; Meikle et al., 2008), as described in Section 9.2. For example, if the tinnitus is tonal, the listener might adjust the frequency of a pure tone until it matches the pitch of their

tinnitus. This is done because it is easier to match the loudness of sounds that are similar in pitch and/or quality than it is to match the loudness of sounds that are very dissimilar in pitch or quality, and the results are less subject to bias effects (Marks, 1994; Gabriel et al., 1997). Once the external tone has been adjusted in frequency to match the pitch of the tinnitus, it is adjusted in level so as to match the loudness of the tinnitus. Often, the matching sound is presented to the ear opposite to that for which the tinnitus is reported to be louder, so as to avoid the matching sound masking the tinnitus, or reducing its loudness.

The magnitude of the matching sound can be specified in several ways. One straightforward way is to specify the level in dB SPL. However, more commonly, the level has been expressed in dB sensation level (SL), which is the level relative to the absolute threshold of the individual for the matching sound. Consider an example where the matching sound is a 5000-Hz tone and the absolute threshold of the individual at 5000 Hz is 50 dB SPL. If the matching tone were adjusted to a level of 60 dB SPL to match the tinnitus, then that would correspond to a matching level of 10 dB SL. The level of the matching sound is also sometimes specified in dB hearing level (HL, sometimes called hearing threshold level [HTL]). This is the level of the sound relative to the average absolute threshold for the same sound for young listeners with normal hearing. This measure is often used when the sounds are generated and delivered using an audiometer because such devices are calibrated in dB HL.

3.3 Data on Loudness Matching and the Role of Loudness Recruitment

A common finding is that tinnitus is matched in loudness by a sound with a low SL. Fowler (1941) reported that most matches were at 5 or 10 dB SL. Reed (1960) reported that 41% of matches corresponded to a level of 5 dB SL or less, 69% to a level of 10 dB SL or less, and 87% to a level of 20 dB SL or less. Graham and Newby (1962) found that the majority of people with troublesome tinnitus matched to a level of 5 dB SL or less. Vernon (1976) reported no matches higher than 20 dB SL. For a review of other studies showing similar results, see Tyler and Conrad-Armes (1983a). Recently, automated methods for computerised assessment of tinnitus loudness have been described (Henry et al., 2006): unsurprisingly, these produced similar results. However, when participants are asked to make loudness matches to their tinnitus over a series of days, they sometimes give matches at SLs up to 30–45 dB SL (Penner, 1983).

The finding that tinnitus was usually matched in loudness with tones at low SLs initially led to the idea that tinnitus is perceived as soft, despite causing marked distress for some people (Fowler, 1942). Vernon (1976) considered three possible explanations for this apparent paradox: first, the method for estimating the loudness of tinnitus may not be valid; second, distress may not be related to loudness; third, the loudness of the tinnitus may actually be quite high even when the matching sound has a low SL, because of the existence of loudness recruitment at the frequency of the

matching sound. Loudness recruitment is a phenomenon usually associated with cochlear hearing loss (Fowler, 1936; Steinberg & Gardner, 1937; Moore, 2007). For a frequency where a person has a hearing loss, the loudness of a tone or other sound increases more rapidly than normal once the sound level is more than 4–6 dB above the absolute threshold, and at high levels the loudness is similar to what would be experienced by a person with normal hearing (Miskolczy-Fodor, 1960; Moore, 2004). Thus, if the listener has a hearing loss at the frequency of the tone used to obtain a tinnitus match, the loudness of the matching tone may be moderately high, even though its SL is low. This is discussed in more detail in Sections 9.3.4 and 9.3.6.

The explanation in terms of loudness recruitment was explored further by Goodwin and Johnson (1980). They tested nine adults with tonal tinnitus, all of whom had a "normal" audiometric threshold (20 dB HL or better) for at least one frequency. They compared loudness matches to the tinnitus using two methods: (1) The frequency of the matching tone was chosen to match the pitch of the tinnitus. This was called the matching frequency. For all listeners, the hearing loss was 25 dB or more at this frequency. The matching tone was presented to the ear opposite to the ear in which the tinnitus was loudest. Goodwin and Johnson (1980) called this the traditional method. (2) The frequency of the matching tone was chosen as the closest audiometric frequency to the matching frequency for which the absolute threshold was 20 dB HL or better. This was called the normal frequency. It was assumed that loudness recruitment would be small or absent at the normal frequency. In this case, the matching tone was presented to the same ear as the ear in which the tinnitus was loudest, as it was assumed that the matching tone would have a negligible effect in masking the tinnitus or reducing its loudness. Goodwin and Johnson (1980) called this the proposed method.

For every participant, the matching SLs were higher for the proposed method than for the traditional method. For the traditional method, the matches ranged from 1 to 20 dB SL, with a mean of 6.6 dB SL. For the proposed method, the matches ranged from 8 to 50 dB SL, with a mean of 33.4 dB SL. Goodwin and Johnson (1980) concluded that loudness recruitment did have a clear influence on the tinnitus matches, and that the proposed method gave more realistic estimates of the loudness of the tinnitus. Their results suggested that tinnitus is usually soft to medium in loudness. A similar study with similar findings was conducted by Tyler and Conrad-Armes (1983a).

3.4 Conversion of Tinnitus Loudness Matches to Loudness Estimates

Tyler and Conrad-Armes (1983a) used formulae based on abnormal loudness functions and uncomfortable loudness levels to calculate the effective loudness of their matching stimuli in sones. However, the values obtained depended strongly on the formula used; the mean calculated loudness of the tinnitus ranged from 6 sones

(a low to moderate loudness) to 76 sones (rather loud). For levels close to absolute threshold (i.e., at low SLs), the functions relating loudness in sones to sound level that they assumed are steeper than found experimentally (Miskolczy-Fodor, 1960; Moore & Glasberg, 1997; Moore, 2004). This may have led them to somewhat overestimate the loudness of the tinnitus in sones. This point is considered in more detail in Section 9.3.6.

Several other methods have been used to estimate the loudness of tinnitus. Hinchcliffe and Chambers (1983) and Jakes et al. (1986) proposed converting loudness matches to "personal loudness units" (PLU). One PLU was defined as the most comfortable level (MCL) of a 1000-Hz tone. As well as measuring the MCL, they measured the loudness level judged to be one half as loud as the MCL (i.e., 0.5 PLU) and the loudness level judged to be twice as loud as the MCL (i.e., 2 PLU). Tyler and Conrad-Armes (1983a) asked participants with tinnitus to rate the loudness of the tinnitus on a 6-point scale, where 1 corresponded to "very soft" and 6 corresponded to "very loud." Various other subjective scales have been used, including a visual analog scale, where participants mark a line to indicate where their tinnitus lies on a scale from "extremely quiet" to "extremely loud" (Jakes et al., 1986).

Jakes et al. (1986) compared results from several of these methods. They found only modest correlations between the results of the different methods; the correlations ranged from 0.22 to 0.77. When they compared the results of loudness matching with the results of the subjective rating of loudness, they generally found low correlations, the highest being 0.44. However, when they excluded the results for participants who were judged by the experimenter to have difficulty in making loudness matches, or who rated themselves as having difficulty with one or more of the subjective rating tasks, the correlations increased. The correlations were highest between the self-report measures and one of the measures based on the PLU transformation. There was also a reasonably high correlation (0.7) between the results of one of the subjective scales and the level of a 1000-Hz matching tone, when the level of the matching tone was expressed in dB SL. The correlation was lower (0.49) when the level of the matching tone was expressed in dB HL. However, this result is inconsistent with the finding of Tyler and Conrad-Armes (1983a) that the highest correlation between matched loudness and self-reported loudness occurred when the level of the matching sound was expressed in dB HL.

In a more recent study, Andersson (2003) assessed the loudness of tinnitus using a matching tone at the frequency whose pitch matched the tinnitus and at the frequency with the best audiometric threshold, as was done by Goodwin and Johnson (1980), Tyler and Conrad-Armes (1983a), and Risey et al. (1989). The matching levels were expressed both as SL and as HL. Participants also rated the severity of their tinnitus using a scale devised by Klockhoff and Lindblom (1967). The matching level in dB HL was significantly correlated with the rated severity of the tinnitus, both for the matching tone at the frequency whose pitch matched the tinnitus and for the matching tone at the frequency with the best audiometric threshold. In contrast, the matching level in dB SL was not significantly correlated with the rated severity of the tinnitus. Andersson also pointed out that several other studies

had failed to find a correlation between measures of the annoyance or severity of tinnitus and matching level in dB SL. He concluded that loudness matches to tinnitus expressed in dB SL provide "little clinically useful information."

Cope et al. (2011) obtained loudness matches to tinnitus using a matching tone whose frequency fell in a region where hearing was normal or near-normal. They tested two groups of subjects: one group had received surgery for vestibular schwannoma (VS, also called acoustic neuroma) that resulted in one deaf ear with tinnitus localized toward the deaf side; the other, comparison, group had tinnitus that arose from a variety of causes, excluding surgery for VS. For group VS, there was a correlation ($r=0.58$) between the loudness matches in dB HL and a measure of the subjective severity of the tinnitus. A correlation of $r=0.58$ with the subjective measure of tinnitus severity was also obtained when the loudness matches were converted to loudness level in phons (see Section 9.3.6). The correlations were significant based on a one-tailed test, which was justified on the basis that subjective severity should increase with increasing loudness. These data provide some evidence to support the idea that the subjective severity of tinnitus is related to its loudness for participants with tinnitus after surgery for VS. However, for the comparison group, no significant correlation was obtained between the loudness matches to the tinnitus and subjective severity of the tinnitus.

3.5 Constrained Loudness Scaling

Loudness scaling has been used to determine the relationship between the physical intensity of sounds and their perceived loudness in sones (Stevens, 1957); for brevity, this relationship is called the sone scale. There are many variations on methods of loudness scaling, but typically a sequence of sounds with different levels is presented in a random order and the participant is asked to give a number proportional to the perceived loudness of each sound (Hellman, 1976). In theory, loudness scaling could be used to estimate the loudness of tinnitus. However, a practical problem is that there can be considerable individual variability in the numbers assigned to a given sound, even among normally hearing participants.

In an attempt to overcome this problem, Ward and Baumann (2009) used a method called "constrained psychophysical scaling." They evaluated the method using 16 participants with tinnitus, 12 of whom described their tinnitus as hissing, and 4 of whom described it as tonelike. Participants had mild to moderate sloping hearing losses, mostly with near-normal hearing at 1000 Hz. Participants were trained to make loudness judgments of a 1000-Hz tone presented at levels ranging from 40 to 80 dB SPL. After each judgment, they were given feedback as to the "nominal" loudness of the tone on a standard sone scale. They were encouraged to adjust their loudness estimates so as to match the numbers on this scale. Following training, 14 of the 16 participants were able to do this reliably (the other 2 had a hearing loss at 1000 Hz sufficient to prevent them from hearing some of the stimuli).

After training, the participants were asked to give numbers according to the loudness of their tinnitus, or according to the loudness of 65- or 500-Hz tones presented at various levels. They also judged the loudness of pure tones at the frequencies that best matched their tinnitus. The results showed that the loudness scaling data for 65- or 500-Hz tones were similar to those for normal-hearing participants, suggesting that the training given at 1000 Hz allowed them to make reliable loudness judgments at other frequencies. For participants whose tinnitus was matched with a frequency well above 1000 Hz, the growth of loudness with increasing sound level at the tinnitus frequency was steeper than at 1000 Hz, consistent with the presence of loudness recruitment. The tinnitus loudness ranged from 0.68 to 8.9 sones, with a mean of about 3.7 sones. This is higher than typically estimated from studies using loudness matching.

3.6 Use of a Loudness Model to Interpret Tinnitus Loudness Matches

To understand why there is not a strong relationship between the loudness of tinnitus and loudness matches in either dB SL or dB HL, it is helpful to interpret the results in terms of a loudness model for impaired hearing proposed by Moore and Glasberg (2004). The model consists of a series of stages including: (1) a filter to account for the transformation from the sound field or headphone to eardrum sound pressure; (2) a filter to account for the transfer function from eardrum sound pressure to pressure in the cochlea; (3) calculation of an excitation pattern from the spectrum of the sound reaching the cochlea; (4) transformation of the excitation pattern to a specific loudness pattern; (5) calculation of the area under the specific loudness pattern, which gives the predicted loudness for the ear under consideration; and (6) summation of loudness across ears. For details see Moore et al. (1997) and Moore and Glasberg (2004).

To take into account the effects of cochlear hearing loss, it is assumed that the overall hearing loss at each audiometric frequency can be divided into two components, one related to loss of function of outer hair cells (HL_{OHC}) and one related to loss of function of inner hair cells and/or neurons (HL_{IHC}). It is assumed that, as HL_{OHC} increases, the excitation pattern gets broader (corresponding to a loss of frequency selectivity) and the function relating specific loudness to excitation level gets steeper (corresponding to a loss of compression on the basilar membrane). As HL_{IHC} increases, the effective excitation level is decreased. The model can also take into account the effects of dead regions in the cochlea, which are regions with few or no functioning IHCs and/or neurons (Moore & Glasberg, 1997; Moore, 2001). To predict loudness for a specific hearing-impaired individual, it is necessary to estimate the value of HL_{OHC} for each audiometric frequency; the value of HL_{IHC} is then derived by subtracting HL_{OHC} from the overall hearing loss at each frequency. The values of HL_{OHC} can be estimated using measures of frequency selectivity (Moore et al., 1999a,b; Lopez-Poveda et al., 2005), but this is time consuming.

Table 9.1 Predicted tinnitus matching levels for four hypothetical listeners, one with normal hearing and three with different degrees of hearing loss

Hearing loss at 4000 Hz	Absolute threshold, dB SPL	Level needed for loudness of 1 sone		
		dB SPL	dB SL	dB HL
0	10	56	46	46
40	50	72	22	62
47	57	76	19	66
55	65	81	16	71
67	77	89	12	79
77	87	97	10	87

It was assumed that the tinnitus had a constant loudness of 1 sone in each case, and that the matching tone was presented monaurally. The absolute threshold at 4000 Hz (column 2) is specified as the sound pressure level (SPL) at the eardrum.

In practice, it is simpler to use the default values of HL_{OHC}, which are meant to be representative of a typical listener with hearing loss. This model gives accurate predictions of the growth of loudness with increasing sound level for low SLs (Buus & Florentine, 2002; Moore, 2004).

Consider the predictions of the loudness model for six hypothetical listeners, one with completely normal hearing and five with different degrees of hearing loss. No dead regions were assumed in generating the predictions. The assumed degree of hearing loss at 4000 Hz is shown in column 1 of Table 9.1. Column 2 shows the absolute threshold in dB SPL, as measured at the eardrum (monaural listening was assumed). For purposes of illustration, it is assumed that each listener has tinnitus and that the loudness of the tinnitus is exactly 1 sone in each case. Imagine now that each listener has adjusted a 4000-Hz tone so that its loudness matches that of their tinnitus. The level required for this, according to the predictions of the loudness model, is shown in dB SPL in column 3 of the table. The corresponding level in dB SL is shown in column 4 of the table. The SL of the matching sound decreases as the hearing loss increases. This occurs because the amount of loudness recruitment (the steepness of loudness growth with increasing sound level) increases as the hearing loss increases (Miskolczy-Fodor, 1960). Finally, column 5 of the table shows the level of the matching tone expressed in dB HL. Now the matching level increases as the hearing loss increases. It is clear from these examples that, for a fixed loudness in sones, the level of the matching tone varies markedly with the degree of hearing loss, whether the level is expressed in dB SL or dB HL. Although it is not shown here, the predicted matching levels would also vary with the shape of the audiogram and with the assumed values of HL_{OHC}.

Figure 9.1 shows loudness in sones predicted by the loudness model as a function of sound level in dB HL for four hypothetical listeners, one with completely normal hearing (absolute threshold = 0 dB HL at all audiometric frequencies) and three with different amounts of "flat" hearing loss (20, 40, and 60 dB HL). The curves move to the right and become steeper with increasing hearing loss. This illustrates the difficulty in using the matching level in dB HL to estimate the loudness of tinnitus. For example, a level of 60 dB HL for a person with a 60-dB hearing loss would lead to a sound at threshold, which has a very low loudness of about 0.003 sones (Moore et al., 1997;

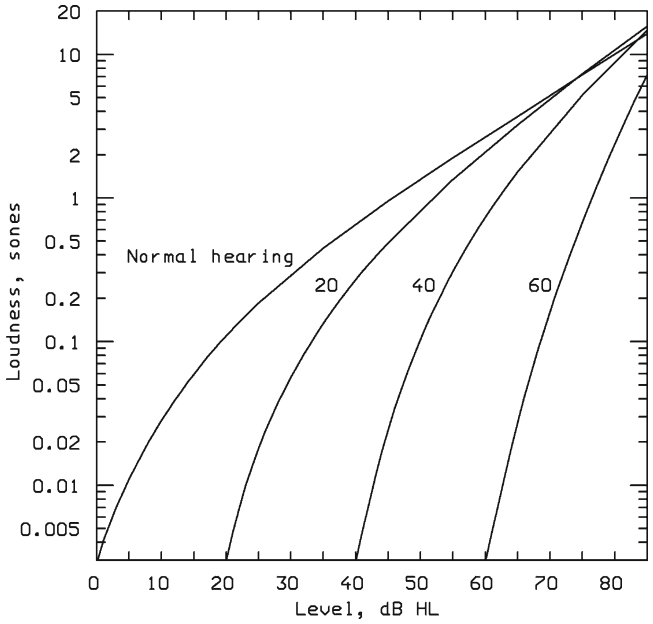

Fig. 9.1 Loudness in sones (log scale) predicted by the model of Moore and Glasberg (2004) as a function of sound level in dB HL for four hypothetical listeners, one with completely normal hearing (absolute threshold = 0 dB HL at all audiometric frequencies) and three with different degrees of "flat" hearing loss (20, 40, and 60 dB HL). All calculations are based on monaural listening. The author thanks Brian R. Glasberg for producing this figure

Moore & Glasberg, 2004). In contrast, a level of 60 dB HL for a person with normal hearing would evoke a relatively high loudness of about 2.65 sones.

Figure 9.2 shows predicted loudness in sones as a function of sound level in dB SL, for the same four hypothetical listeners. The curves coincide at 0 dB SL, corresponding to the fixed low loudness at absolute threshold (Moore et al., 1997; Moore & Glasberg, 2004). However, the curves diverge greatly for SLs above 0 dB. An SL of, say, 20 dB, leads to a loudness of 0.11 sones for a person with normal hearing, but a loudness of 2.13 sones for a person with a 60 dB hearing loss.

The conclusion from all of this is that loudness matches in either dB HL or dB SL are not related in a simple way to loudness in sones. To estimate loudness from such matches, it is necessary to use a loudness model, such as that described in the preceding text, and to take into account the hearing loss of the individual.

3.7 Tinnitus and Hyperacusis

Hyperacusis is characterized by abnormally sensitive hearing; normally tolerable sounds are perceived as annoying, distressing, and/or excessively loud. Hyperacusis is not associated with unusually low (good) thresholds for detecting sounds.

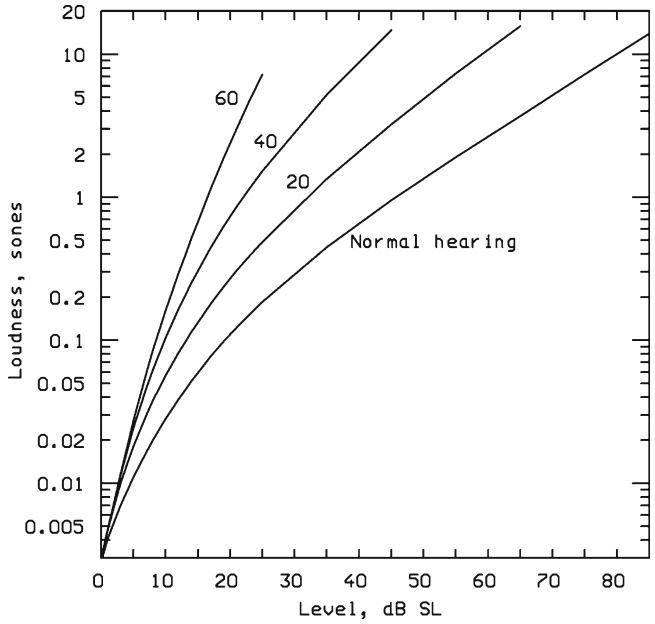

Fig. 9.2 As Figure 9.1, but with predicted loudness plotted as a function of sound level in dB SL

Rather, hyperacusis is manifested by aversive reactions to sounds that are clearly audible but would not lead to aversive reactions in most people. It has been reported that 40% of people seeking treatment for tinnitus have some degree of hyperacusis (Jastreboff & Jastreboff, 2000) and that 50% of children with hyperacusis have tinnitus (Coelho et al., 2007). It has been proposed that hyperacusis is a manifestation of increased gain in central auditory pathways and that tinnitus might sometimes be caused by this increased gain (Jastreboff & Hazell, 1993).

The German "Questionnaire on Hypersensitivity to Sound (GÜF)" (Nelting & Finlayson, 2004) has been used to assess the subjective distress related to hyperacusis. Bläsing et al. (2010) used this questionnaire with 91 patients being treated for tinnitus and hyperacusis, of whom about 74% had hearing loss. Bläsing et al. also assessed the overall severity of problems caused by tinnitus, using a German adaptation of the "Tinnitus Questionnaire (TQ)" (Hallam et al., 1988). They found a modest but highly significant correlation ($r=0.38$) between the overall GÜF score and the TQ score. This suggests that distress caused by tinnitus may be partly related to hyperacusis, at least for some patients.

The link between tinnitus and hyperacusis was explored by Gu et al. (2010). They tested participants with and without tinnitus, all with clinically normal absolute thresholds. Participants' degree of hyperacusis was assessed behaviorally and functional magnetic resonance imaging (fMRI) was used to measure sound-evoked activation of the central auditory system. Participants with hyperacusis showed higher activation in the auditory midbrain, thalamus, and primary auditory cortex than participants with normal tolerance. Primary auditory cortex, but not subcortical

centers, showed elevated activation specifically related to tinnitus. The authors hypothesized that the tinnitus-related elevations in cortical activation may reflect undue attention to auditory stimuli.

3.8 Conclusions on Tinnitus Loudness

In summary, loudness matches to tinnitus do not give a direct indication of the loudness of the tinnitus in sones, whether the matching level is expressed as dB SL or dB HL. The results of loudness matching can be used to predict the loudness in sones based on additional measurements to infer how loudness changes with sound level (Hinchcliffe & Chambers, 1983; Jakes et al., 1986), based on formulae relating loudness to level (Tyler & Conrad-Armes, 1983a), or based on a loudness model, as described in Section 9.3.6. When this is done, it becomes clear that tinnitus is not always very low in loudness. When there is hearing loss at the frequency of the matching sound, a matching level of only 10 dB SL can lead to a loudness of one sone, which would be described as soft but not very soft. Calculations using the loudness model, based on published audiograms and the levels of tones that matched the tinnitus in loudness, suggest that tinnitus typically has a loudness between 0.15 and 2 sones (Cope et al., 2011), but for a few individuals reaches values as high as 20 sones. Loudness estimates based on constrained loudness scaling (Ward & Baumann, 2009) suggest somewhat higher values, with a mean of about 3.7 sones.

For at least some people with tinnitus, the tinnitus may be perceived as soft but still cause significant distress, partly because of the coexistence of hyperacusis.

4 The Masking of Tinnitus

4.1 Individual Differences in Masking

It is well known that, for many people with tinnitus, the loudness of the tinnitus can be reduced by external sounds. If the external sound is sufficiently intense, the tinnitus may be rendered inaudible, that is, it may be masked (Andersson et al., 2005). Indeed, reduction of loudness or masking of tinnitus forms part of many methods for alleviating the effects of tinnitus (Jastreboff & Hazell, 1993; Henry et al., 2004; Aazh et al., 2008). However, the effect is variable between individuals. Some authors have reported that complete masking of tinnitus occurs in 90% or more of people with tinnitus (Vernon & Meikle, 1988; Mitchell, 1983). However, Slater et al. (1987) reported that 28% of 255 respondents to a questionnaire survey about tinnitus stated that external sound could result in tinnitus being more "noticeable." Further, after prolonged exposure to a sound that initially masked the tinnitus, the masking effect may decrease, so that the tinnitus becomes audible again; progressive increases in masker level are needed to keep the tinnitus masked (Penner et al., 1981). This effect is described in Section 9.4.3.

4.2 Frequency Selectivity and the Masking of Tinnitus

For an acoustic narrowband signal of fixed level, such as a sinewave or narrow band of noise, the level of a narrowband masker need to mask the signal is called a psychophysical tuning curve (PTC). For listeners with normal hearing, PTCs have the form roughly of a V, with a relatively sharp tip at the signal frequency (Chistovich, 1957; Kluk & Moore, 2004). If tinnitus resembles a narrowband signal and if it arises in the cochlea (Nouvian et al., Chapter 4), then one might expect a similar pattern of results when the tinnitus is used as a signal. In this chapter, the masker level required to mask the tinnitus, measured as a function of masker frequency, is referred to as a tinnitus tuning curve (TTC).

Fowler (1940, 1941) measured TTCs for eight participants. He found that participants fell into three groups. For one, the tinnitus could be masked by tones at low SLs, regardless of their frequency; for the second, high masker SPLs were required for all frequencies; and for the third the tinnitus could not be masked at all. These findings were replicated and extended by Feldmann (1971). He estimated TTCs for 200 people using both pure tones and narrow bands of noise as maskers. He expressed the masker levels in dB SL. He classified the TTCs into five types: (1) The tinnitus was masked by relatively low-level sounds, regardless of their frequency. (2) High-level sounds were required to mask the tinnitus, regardless of their frequency. (3) The tinnitus could not be masked by any sound (32% of cases). (4) The required masker level was high at low frequencies and decreased with increasing frequency, generally being low at a frequency corresponding to the pitch of the tinnitus. (5) The required masker level was low at low frequencies and increased with increasing frequency. This pattern was generally observed for patients with Ménière's syndrome, who often report a "roaring" type of tinnitus. Feldman also reported that some people experienced a temporary reduction or abolition of their tinnitus after the masker was turned off, an effect that later became known as "residual inhibition" (Vernon, 1977).

Similar results to those of Feldman have been reported by others (Mitchell, 1983; Penner, 1987). None of the types of TTCs found by Fowler or other researchers resembled PTCs. This might indicate that the tinnitus is not narrowband in nature; for most people, it may be more like a broadband complex sound (Noreña et al., 2002), as described earlier. However, the findings that tinnitus can sometimes be masked by low-level sounds of any frequency, or sometimes cannot be masked by sounds of any frequency, are consistent with the idea that tinnitus often does not arise in the cochlea (Dehmel et al., Chapter 5; Robertson and Mulders, Chapter 6, Eggermont, Chapter 7).

Tyler and Conrad-Armes (1984) pointed out that the interpretation of TTCs was complicated by the fact that many people with tinnitus have hearing loss, and cochlear hearing loss is associated with reduced frequency selectivity (Pick et al., 1977; Glasberg & Moore, 1986; Moore, 2007). This would lead to broader than normal tuning curves even for acoustic stimuli. To assess the importance of this, they compared TTCs and PTCs for eight people with tinnitus. The participants were

selected to have tinnitus that they described "as containing a single, narrow-band component," but some described their tinnitus as "hissing," which might be interpreted as sounding like a broadband noise. The signal frequency for measurement of the PTC was chosen to match the loudness and pitch of the tinnitus. To avoid the participants confusing their tinnitus with the acoustic tone used for measurement of the PTC, the acoustic tone was pulsed on and off.

Tyler and Conrad-Armes (1984) found several different patterns. For one participant, the PTC showed a distinct tip at the signal frequency while the TTC was flat and mostly at a higher level than the PTC. For another participant, the PTC showed a small tip at the signal frequency, while the TTC fell at lower levels and followed the shape of the absolute threshold curve, falling 5–10 dB above that curve. For most of the other participants, the PTCs fell above the TTCs over a wide frequency range; in other words, a higher masker level was required to mask the acoustic signal than to mask the tinnitus. However, neither the PTCs nor the TTCs showed clear tips at the signal frequency. For some of the participants, this probably happened because they had a dead region at the signal frequency. PTCs usually show tips that are shifted away from the signal frequency when the signal frequency falls in a dead region (Thornton & Abbas, 1980; Moore & Alcántara, 2001; Kluk & Moore, 2005).

Overall, the results are difficult to interpret because it is not clear whether the perceived tinnitus really corresponded to a narrowband signal, and because of the possibility of dead regions at the signal frequency. However, it does seem that for at least some of the participants the results support the idea that tinnitus involves relatively central mechanisms, even when peripheral hearing loss is the initial trigger (Dehmel et al., Chapter 5; Robertson and Mulders, Chapter 6, Eggermont, Chapter 7).

4.3 Temporal Effects in the Masking of Tinnitus

Penner et al. (1981) assessed the level of diotic broadband noise (presumably white noise) required to mask tinnitus for 20 participants reporting tonal tinnitus associated with sensorineural hearing loss caused by noise exposure. A method of adjustment was used (it is not clear whether the participant or the experimenter made the adjustment) and measurements continued over a 30-minute period. As a control condition, the level of broadband noise required to mask a 1000-Hz tone presented at 10 dB SL was also assessed. The level of the noise required to mask the tinnitus increased over the 30-minute period, by 20–45 dB, depending on the participant, with an average increase of 30 dB. Usually, the largest increase occurred during the first 10 minutes of exposure to the noise. In contrast, the noise level required to mask the external 1000-Hz tone remained almost constant over the 30-minute period. In a later study (Penner, 1988) participants were asked to adjust the level of continuous broadband noise, presented monaurally to the ear for which the tinnitus was perceived to be louder, so that the noise just masked their tinnitus over a 5-minute period. Again, the required noise level was found to increase. The mean increase was 16 dB over the 5-minute period, with a range of 6–26 dB.

Penner et al. (1981) offered an explanation for their results in terms of the adaptation that is known to occur in the auditory nerve (Kiang et al., 1965; Javel, 1996); the amount of neural activity decreases with prolonged exposure to a steady sound. They suggested that the neural response to the broadband noise would decline over time. The response to the external 1000-Hz tone would decline in a similar way and by the same factor, so that the effective signal-to-masker ratio would not change. This can account for why the amount of noise needed to mask the external tone did not change over time. However, the internal neural activity corresponding to the tinnitus does not decline over time, perhaps because it occurs at a more central level than the auditory nerve (Dehmel et al., Chapter 5; Robertson and Mulders, Chapter 6, Eggermont, Chapter 7). Hence, the noise level required to mask the tinnitus increases over time.

An alternative explanation of these results was tested by Penner (1988). She argued that the continuous noise might make the tinnitus increase in loudness over time, so that it was less easily masked. To test this idea, she selected participants who reported having tonal tinnitus that was heard mainly in one ear. Continuous noise was presented to that ear. During presentation of the noise, participants were asked to adjust the level of a pulsed tone presented in the opposite ear so that it matched the loudness of their tinnitus. The matching level hardly changed with time. Penner concluded that continuous presentation of noise to the ear at which the tinnitus was perceived did not have the effect of making the tinnitus louder.

A practical implication of the results of Penner et al. (1981) is that relatively high noise levels may be needed to mask tinnitus for a long time. For some of the participants tested by Penner et al., the noise level required to mask the tinnitus reached 90 dB SPL. Clearly, for such participants, it would not be practical to use broadband noise as a tinnitus masker (Noreña, Chapter 10), at least if the goal is to completely mask the tinnitus, since the required noise level would lead to unpleasant loudness, and the noise would mask most sounds that the participant might want to hear.

Most studies of tinnitus masking have involved the use of steady sounds as maskers. However, some commercial systems for tinnitus masking, such as those developed by Petroff Audio Technologies, involve sounds that are more dynamic, such as the sound of falling water, or sounds with changing formant frequencies. Such sounds may provide relief from tinnitus by distracting attention from the tinnitus rather than by making the tinnitus inaudible or reducing its loudness. Henry et al. (2004) compared the effectiveness of several static and dynamic sounds in providing relief from tinnitus, using 21 participants whose tinnitus was at least moderately annoying. Their results showed that the dynamic sounds were more effective than steady filtered noises in providing tinnitus relief. However, the steady and dynamic sounds differed in their overall spectral shape as well as in their dynamic properties, and the headphones used had a frequency response that rolled off at high frequencies. Henry et al. concluded that a larger scale study using better-controlled stimuli was needed to assess whether dynamic sounds really are more effective than steady sounds in providing relief from tinnitus.

More recently, Reavis et al. (2010) compared the effectiveness of steady sounds, such as tones and white noise, with that of frequency- or amplitude-modulated

tones, which are perceived as fluctuating, in alleviating tinnitus for adults with chronic tinnitus lasting longer than 6 months. More than 50% of the participants reported that the sounds produced a reduction in the loudness of their tinnitus, and this happened to a greater extent for the dynamic sounds than for the steady sounds. However, some participants experienced no reduction in loudness of their tinnitus. For those participants for whom the sounds were effective, the effect seemed to build up over time and it occurred even when the sounds were perceived as softer than their tinnitus. Reavis et al. referred to this as suppression of tinnitus rather than masking of tinnitus.

4.4 Effects of Noise on Tinnitus Loudness

As described earlier, Cope et al. (2011) tested two groups of participants, one with unilateral tinnitus after surgery for VS, and a comparison group with "conventional" tinnitus. In one experiment they assessed how the presence of background noise influenced the loudness of tinnitus. Participants were asked to match the loudness of their tinnitus as heard while background noise was being presented. For the comparison group, the noise was played continuously to one ear, and the adjustable matching tone was presented to the other ear. For the VS group, the noise was presented to the "good" ear and left on until the participant reported that the loudness of the tinnitus on the deaf side was stable, and that they had a good impression of its loudness. The noise was then turned off, and the participant was asked to adjust the level of the matching tone in the "good" ear to the *remembered* loudness of the tinnitus in the noise. The noise level was varied over a wide range.

For the comparison group, the level of the matching tone tended to decrease as the noise level was increased, indicating that the noise decreased the loudness of their tinnitus. However, the effect was small; on average, the matching level decreased by 2.1 dB for each 10-dB increase in noise level. For the VS group, the matching level *increased* as the level of the noise was increased, indicating that the noise presented to the "good" ear increased the loudness of the tinnitus heard on the deaf side.

Cope et al. (2011) suggested two explanations of the results for the VS participants. The first is that they reflect a plausible perceptual interpretation of the sensory evidence. For a "real" sound (as opposed to tinnitus) to be audible in the presence of a broadband background sound, the level of the target sound must be comparable to the level of the background at the output of at least one auditory filter (Moore et al., 1997). If tinnitus remains audible with increasing level of a background sound, as it did for the participants with VS, then the most plausible perceptual interpretation is that the source of the tinnitus is increasing in intensity with increasing background level, and this may give rise to the perception of increasing loudness of the tinnitus.

The second explanation is connected with the action of the efferent pathways in the auditory system, especially the medial olivocochlear (MOC) system. One role of the MOC system is to regulate the gain provided by the active mechanism in the

cochlea, by controlling the operation of the OHCs (Liberman & Guinan, 1998; Guinan, 2006). With increasing input sound level, signals from the MOC system cause a reduction of the gain of the active mechanism, effectively acting as a kind of automatic gain control, provided that the auditory system is functioning normally. The regulatory signals from the MOC system are taken into account in interpreting the information flowing from the auditory nerve to higher centers. For listeners with VS, MOC signals would still be sent from the brain stem, but they would not reach the cochlea, as the efferent system was severed at the VIIIth nerve level as part of the surgery. The signals from the MOC would have carried "instructions" to decrease the gain of the active mechanism as the level of the noise in the "good" ear was increased. However, the abnormal activity in the auditory pathway that gave rise to the tinnitus would not have been affected by the signals from the MOC system. The unchanging tinnitus signal, in combination with MOC "instructions" to decrease the gain, may have resulted in the increasing loudness of the tinnitus with increasing background level.

In summary, for participants with "conventional" tinnitus, background noise does reduce the loudness of tinnitus, but the effect is small. For participants with a deaf ear following surgery for VS, noise presented to the "good" ear causes an increase of the loudness of tinnitus heard on the deaf side.

4.5 Residual Inhibition

As mentioned earlier, tinnitus can often be reduced in loudness, or even made inaudible for some time, after exposure to a sound that is capable of masking the tinnitus (Feldmann, 1971). The effect is known as residual inhibition (RI; Vernon, 1977), although the term residual suppression has also been proposed (Terry et al., 1983). It appears that about 75% of participants experience some degree of RI, although estimates vary across studies (Vernon & Meikle, 2003; Roberts et al., 2006). The duration of RI is typically in the range 5–45 seconds (Roberts et al., 2006), although there are some reports of RI lasting for several minutes (Terry et al., 1983; Vernon & Meikle, 2003) or even hours (Hazell & Wood, 1981).

Several studies have examined the factors that influence the duration of RI. Generally, the duration of RI has been found to increase with increasing masker intensity (Bailey, 1979; Terry et al., 1983; Tyler et al., 1984). However, Terry et al. (1983) found that little or no RI occurred when the masking sound did not completely mask the tinnitus when presented continuously.

Terry et al. (1983) studied some other factors that influenced the time course and magnitude of RI, including the center frequency, bandwidth, and duration of the masker. RI was estimated using two methods: (1) loudness estimation—where the participant varied the position of a pointer to indicate the loudness of his or her tinnitus; and (2) loudness balance—where the tinnitus was matched in loudness by adjusting the level of a tone presented to the ear opposite to that where the tinnitus was perceived. In addition, the absolute threshold in the frequency region of the tinnitus

(as determined by pitch matching) and in the frequency region of the masker was measured before and after masker presentation. Their main findings were as follows:

1. The frequency producing maximal RI was usually lower than the frequency that matched the tinnitus in pitch
2. For some participants a narrowband noise produced RI while a broadband noise did not.
3. For the masker durations used (in the range 10 s–10 min), the duration of RI was linearly related to the logarithm of the masker duration.
4. A second presentation of the masker during the time when RI was present did not lead to an increase in RI.
5. A masker presented in the ear opposite to the ear in which the tinnitus was perceived did not produce RI.
6. Maskers that produced RI also produced a TTS around the frequency matching the tinnitus pitch.
7. The magnitude and the time course of RI were positively related to the magnitude and time course of TTS

Roberts et al. (2006, 2008) studied the relationship between hearing loss, the "tinnitus spectrum" and the effectiveness of various maskers in producing RI. They initially asked participants to classify their tinnitus as "tonal," "ringing," or "hissing" by selecting one of three sounds with a center frequency (CF) of 5 kHz; the sounds were a pure tone, a noise with a bandwidth of 0.05 CF and a noise with a bandwidth of 0.15 CF. They then determined the "tinnitus spectrum" with the best-matching sound, using a method similar to that of Noreña et al. (2002), described in Section 9.2.3. The CFs of the sounds used for this ranged from 0.5 to 12 kHz. Finally, they measured RI using noise maskers with a bandwidth of 0.15 CF, for CFs with 11 values within the range 0.5–11 kHz. A white noise masker was also used. The masker duration was 30 s and the masker level was typically 10 dB above the level required to mask the tinnitus when the masker was presented continuously. RI was assessed using a subjective rating scale. As found by Noreña et al. (2002), the tinnitus spectrum fell mainly in frequency regions where the hearing loss was greatest. The amount of RI was also greatest for maskers with CFs in the region of hearing loss, and it tended to increase with increasing hearing loss, and with increasing contribution of that CF to the tinnitus spectrum. The narrowband noise maskers with CFs in the region of the tinnitus spectrum produced more RI than the white noise. Roberts et al. (2008) concluded that tinnitus and its suppression by RI "depend on processes that span the region of hearing impairment and not on mechanisms that enhance cortical representations for sound frequencies at the audiometric edge" (p. 417).

It has been proposed that RI might be used to provide temporary relief from tinnitus for those who are greatly distressed by it (Vernon & Meikle, 2003; Roberts, 2007); see Noreña, Chapter 10. However, the finding that maskers that are sufficiently intense to produce RI also cause TTS (Terry et al., 1983) suggests that it may be dangerous to use RI as a tool for alleviating tinnitus because sound exposures sufficient to produce TTS can have permanent long-term effects on hearing, even though the absolute threshold may return to normal (Kujawa & Liberman, 2009).

4.6 The Zwicker Tone and Tinnitus

When a noise with a spectral notch is presented and then abruptly turned off, some (but not all) listeners hear a weak tone, called the "Zwicker tone," whose pitch corresponds to a frequency close to the spectral region of the notch (Zwicker, 1964). The effect may occur because central auditory neurons with characteristic frequencies (CFs) within the passbands of the noise become adapted, and therefore produce less lateral inhibition of neurons with CFs within the notch. Increased spontaneous activity in those neurons may then lead to the phantom percept of a tone. Alternatively or additionally, central mechanisms may increase the gain for neurons with CFs within the notch relative to the gain for CFs within the noise passbands, and this imbalance in gain across CFs may give rise to the phantom percept.

Some researchers have proposed that tinnitus may be analogous to the Zwicker tone (Noreña et al., 2000; Parra & Pearlmutter, 2007). If the signal from the auditory periphery is reduced over a particular range of CFs, perhaps due to cochlear damage, gain adaptation in central mechanisms will enhance internal noise at those CFs, perhaps leading to tinnitus. Parra and Pearlmutter (2007) suggested a specific model for this process. The model predicted that the strength of both the Zwicker tone and of tinnitus should be increased by reduced compression in the cochlea and, due to variations in the strength of compression across participants, there should be a correlation between perception of the Zwicker tone and tinnitus. They tested this prediction using participants with and without tinnitus. They found that participants with tinnitus (11 out of 44) were significantly more likely to hear the Zwicker tone than participants without tinnitus, consistent with the predictions. Recent data also support the idea that the strength of tinnitus is related to the strength of cochlear compression as estimated from absolute thresholds and from input–output functions for distortion-product otoacoustic emissions (Zhou et al., 2011).

5 Summary

The percept of tinnitus is usually complex in quality. Although tinnitus can sometimes be matched in pitch by adjusting the frequency of a pure tone, the matches are often unreliable across sessions. The matching frequencies tend to fall in regions where the hearing loss is greatest and are usually high. Training to reduce octave confusions may result in pitch matches at lower frequencies, and may increase the reliability of the pitch matches, although more research is needed to determine whether this is the case. In cases where the tinnitus is described as tonal, and for people with sloping audiograms, the frequency that matches the tinnitus may correspond to an edge in the audiogram, where the hearing loss increases relatively abruptly. Again, more research is needed to confirm this finding. For temporary tinnitus produced by exposure to intense sounds, the frequency that matches the tinnitus may correspond to the upper edge of the region over which maximum TTS occurs.

It is still often stated that tinnitus is nearly always perceived as a soft sound, based on the finding that tones that are matched in loudness to the tinnitus usually

have a low SL. However, loudness matches do not give a direct indication of the loudness of the tinnitus in sones, whether the matching level is expressed as dB SL or dB HL. The results of loudness matching can be used to infer the loudness in sones based on additional measurements to infer how loudness changes with sound level, based on formula relating loudness to level, or based on a loudness model. When this is done, it becomes clear that tinnitus is not always perceived as soft. Calculations using a loudness model suggest that tinnitus typically has a loudness between 0.15 and 2 sones, but for a few individuals reaches values as high as 20 sones. The loudness of tinnitus can vary markedly over time, and estimates of loudness obtained in the laboratory or clinic may not be representative of the loudness of tinnitus in everyday situations. Tinnitus often coexists with hyperacusis, and this may contribute to distress caused by the tinnitus.

For some, but not all, people with tinnitus, the tinnitus can be reduced in loudness or even abolished completely by background sounds. The "masking" of tinnitus does not generally follow the "rules" for the masking of acoustic signals. The level of a background noise needed to mask tinnitus often increases over time when the noise is presented continuously, perhaps because the neural response to the noise adapts, while the neural response that leads to the tinnitus does not adapt. Thus, high noise levels may be needed to mask tinnitus for a long time. However, low-level background sounds may be effective in relieving tinnitus by distracting attention from the tinnitus, especially when the background sounds are time varying. There is some evidence that dynamic background sounds can reduce the loudness of tinnitus even when the sounds have low levels. For people who have had surgery to treat unilateral VS, which results in deafness and tinnitus on the treated side, the loudness of the tinnitus heard on the deaf side is usually increased by the presence of a noise presented to the "good" ear.

Tinnitus can often be reduced in loudness, or even made inaudible for some time, after exposure to a sound that is capable of masking the tinnitus, an effect known as residual inhibition (RI). However, maskers that are sufficiently intense to produce RI also often cause temporary threshold shift (TTS). This suggests that it may be dangerous to use RI as a tool for alleviating tinnitus, as sound exposures sufficient to produce TTS can have permanent long-term effects on hearing, even though the absolute threshold may return to normal.

It has been proposed that the perception of tinnitus may be related to perception of an auditory after-effect called the Zwicker tone. A model based on this idea leads to the prediction that the strength of tinnitus should be related to the strength of cochlear compression. Recent data are consistent with this prediction.

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Chapter 10
Stimulating the Auditory System to Treat Tinnitus: From Alleviating the Symptoms to Addressing the Causes

Arnaud J. Noreña

1 Introduction: The Two Paths of Tinnitus Research

The first important feature about tinnitus is that it is a symptom of a given cause (or disease). As for any disease, a prerequisite in developing any therapeutic approach to treat the causes of tinnitus is the understanding of these causes. When the cause of a cold is known (microbial infection) it is then straightforward to treat it with appropriate means (antibiotic). In parallel, the symptoms of the cold (fever, runny nose, muscle aches) can also be treated to prevent discomfort accompanying the cold.

A first view about the causes of tinnitus suggested that tinnitus might result from cochlear injuries, present in most if not all tinnitus subjects, leading to abnormal activity in the cochlear nerve which then could be interpreted as a sound by auditory centers. In this "peripheral" model, the auditory centers do not play any active role in the generation of tinnitus-related activity. The belief that the putative causes of tinnitus (cochlear injuries) might be irreversible has led researchers and clinicians to concentrate their efforts on approaches providing relief. In this context, stimulating the auditory system, the topic of this chapter, has become an important strategy for achieving this goal. The rationale of this approach was that partial or complete masking of tinnitus by another auditory perception induced by auditory stimulation, provided that it is less disturbing or more acceptable than tinnitus, may decrease tinnitus-related discomfort. The development of this approach went hand in hand with the progress of the technologies as different sorts of devices became available over time to stimulate the auditory system (hearing aids, portable noise generators, portable music players, cochlear implants). Finally, this approach was the first one to be implemented in a systematic way (Vernon, 1977); it has been refined over the years (Jastreboff, 1990) and it is still widely used today (Henry et al., 2006).

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In parallel with this view, new ideas gradually emerged in the early 1980s (Sasaki et al., 1980; Gerken et al., 1984) that had reached a broad consensus by the early 2000s (Eggermont & Roberts, 2004). While this new view also considered cochlear injuries as a necessary cause of tinnitus (just like the former view), the auditory centers were considered as an active and major player in generating the tinnitus-related activity. In brief, it was thought that plastic central changes induced by cochlear injuries resulted in the tinnitus-related activity (Sasaki et al., 1980; Gerken et al., 1984). It took nearly 20 years for this idea to replace the former "peripheral" model, and many authors who suggested that tinnitus was of "peripheral" origin in the 1980s became the fervent advocates of the "central" model in the 2000s. This new view represented a great step toward understanding the causes of tinnitus. Critically, it also provided a potential strategy to cure tinnitus: Although cochlear injuries cannot be repaired, the tinnitus-related central changes could be prevented or reversed by means of auditory stimulation.

The methods for alleviating tinnitus-related distress or treating the causes use the same instruments (portable music players, hearing aids, cochlear implants) or similar approaches (masking therapy vs. customized acoustic stimulation). As a consequence, it is often unclear whether auditory stimulation improved tinnitus through a reduction of distress or whether it interfered with the putative causes of tinnitus. However, a therapeutic approach interfering with the causes of tinnitus should change the psychoacoustic properties of tinnitus—pitch and loudness. The distinction between the two putative effects of auditory stimulation on tinnitus is a priori achievable through adequate measurement tools. Various questionnaires have been developed to assess the tinnitus-related distress or the impact of tinnitus on life quality (Kuk et al., 1990; Halford & Anderson, 1991; Newman et al., 1994).

For assessing the perception of tinnitus itself, several methods have been developed to determine the psychoacoustic properties of tinnitus (Henry & Meikle, 2000 for a comprehensive review; Moore, Chapter 9). Assuming that loudness is the most important dimension of tinnitus, many efforts have been devoted to estimating it. Loudness can be estimated through a matching procedure with an external acoustic stimulus, or visual analog scales (VAS). Visual analog scale is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end ("I can't hear my tinnitus"–"my tinnitus is extremely loud"). The patient marks on the line the point that he feels represents his perception of his current state. The VAS score is determined by measuring in millimeters from the left-hand end of the line to the point that the patient marks. Although VAS is convenient in clinical use (simple and quick), it has several drawbacks. First, tinnitus subjects have to be able to separate the dimensions of tinnitus-related distress and tinnitus loudness. This can be achieved by adequate explanation from the clinician/experimenter. Second, for hypothetical identical tinnitus loudness, subjects may scale the loudness of tinnitus differently according to internal criteria. In other words, subjects may have a different (scale) conception about what a loud percept is. However, this intersubject variability is somewhat minimized in studies in which subjects are their own controls (repeated measures when the effects of a given treatment are studied). A method has been recently developed to address these drawbacks, termed "constrained loudness scaling."

The method consists of training tinnitus subjects with a standardized loudness scale and using this scale to assess tinnitus loudness. The beauty of this method is that all tinnitus subjects estimate the loudness of tinnitus with the same scale, thus limiting intersubject variability. Interestingly, there was little correlation between tinnitus loudness, estimated either from constrained loudness scaling or from matching, and tinnitus-related distress as measured by the tinnitus handicap inventory (Ward & Baumann, 2009). This result points out the partial dissociation between the strength (loudness) of tinnitus percept and the tinnitus-related distress. Finally, in a few studies, the effects of auditory stimulation on tinnitus pitch have been evaluated (Norena et al., 2002; Moffat et al., 2009). Tinnitus pitch (or "spectrum") was thought to reflect the neural network involved in tinnitus perception. As a consequence, modifying the properties of this neural network by means of auditory stimulation is supposed to change the tinnitus spectrum.

Ideally, any study assessing the effects of auditory stimulation on tinnitus should estimate the effects on tinnitus-related distress and tinnitus loudness. Unfortunately, depending on the a priori of the authors, that is, whether they expected effects on the tinnitus-related consequences (distress) or causes (loudness) (see Section 10.4), only one dimension is usually assessed in the majority of studies. At this stage, therefore, when considering the many studies devoted to assessing the effects of auditory stimulation on tinnitus, one notes that the same approaches (acoustic stimulation, hearing aids, cochlear implants) have been motivated by different rationales (treating the symptom or the causes) and that usually only one dimension of the effects is estimated (distress or loudness). Overall, this emphasizes the difficulty (or the impossibility) of classifying the different methods of auditory stimulation to treat tinnitus based on their rationale. In this context, I have chosen to present (in Section 10.4) independently the effects of each approach (hearing aids, acoustic stimulation, electrical stimulation).

The next two sections present a short history of tinnitus research. The view is presented that tinnitus research has followed two paths. These sections are aimed at giving the reader the necessary background to interpret the studies presented in Section 10.4.

2 Tinnitus of Cochlear Origin: Achieving Tinnitus Relief When Suppression Was Thought to Be Out of Reach

2.1 Generation of Tinnitus-Related Activity

Until around the mid-1990s, and while the proposed mechanisms remained largely speculative (see 10.2), the dominant model to account for tinnitus was peripheral; that is, an aberrant activity in the cochlear nerve was thought to propagate all the way up to auditory cortex and ultimately result in tinnitus perception. This aberrant activity was first suggested to be an increase of spontaneous firing rate (Evans &

Borerwe, 1982; Salvi & Ahroon, 1983). One proposed mechanism to account for this increase in activity is the existence of discordant damage between outer and inner hair cells. It was suggested that a collapse of the tectorial membrane (due to injuries affecting outer hair cells [OHCs]), decreasing the distance between inner hair cell (IHC) stereocilia and the tectorial membrane to the extent of bending of the stereocila, might induce a tonic depolarization of intact IHCs and therefore an increase in cochlear nerve firing rate (Jastreboff, 1990).

However, the hypothesis suggesting that tinnitus is related to an increase in firing rate at the cochlear level was questioned by studies showing that cochlear injuries were accompanied by a decrease of spontaneous activity in the cochlear nerve (Liberman & Dodds, 1984). In this context, it has been proposed that tinnitus could result from an abrupt change in spontaneous activity as a function of characteristic frequency. The resulting "edge effect," induced by the reduced spontaneous activity in the frequency region affected by cochlear damages, would result in tinnitus (Kiang et al., 1970). Alternatively, it has been suggested that tinnitus could result from an increase in synchrony between cochlear nerve fibers, due to ephaptic connections, for instance (Moller, 1984; Eggermont, 1990).

In summary, tinnitus was thought to result from cochlear injuries, tinnitus-related activity was assumed to be present in the cochlear nerve, and the auditory centers were suggested to play a passive role in "interpreting" tinnitus-related activity as a sound. This view had considerable importance especially for clinical management of tinnitus. Indeed, the fact that most cochlear injuries are known to be irreversible (Wang et al., 2002; Kujawa & Liberman, 2006, 2009) led clinicians to acknowledge that there might be no cure for tinnitus. The view that dominated tinnitus management at that time is well illustrated by Vernon (1977, p. 126):

> Keeping in mind that there is no cure for tinnitus let us then turn to some attempts to relieve tinnitus. Admittedly, this action means the treatment of a symptom and not treatment of the disease. Tinnitus is not a disease but rather one symptom among others of some kind of disease or damaged state. Perhaps in this case it is admissible to treat a symptom, providing no harm comes to the patient, and providing that by such treatment some relief of distress will be produced.

2.2 The Beginnings of Alleviating Tinnitus Distress: Tinnitus Masking Therapy

For a long time, the salience of the tinnitus percept was known to be decreased by external acoustic stimulation. Environmental noise (Aristotle 384 BC, Problemata Book 32, para 9, cited in Hazell et al., 1985), piano chords (Spaulding, 1903), masking devices (Jones & Knudsen, 1928), or hearing aids (Saltzmann & Ersner, 1947) have been reported to decrease the tinnitus percept. The first systematic study investigating tinnitus masking was published by Feldman (1971) (see Moore, Chapter 9).

In this context, it has been proposed that the use of acoustic or electric instruments delivering (noise generators, portable music players, cochlear implants) or

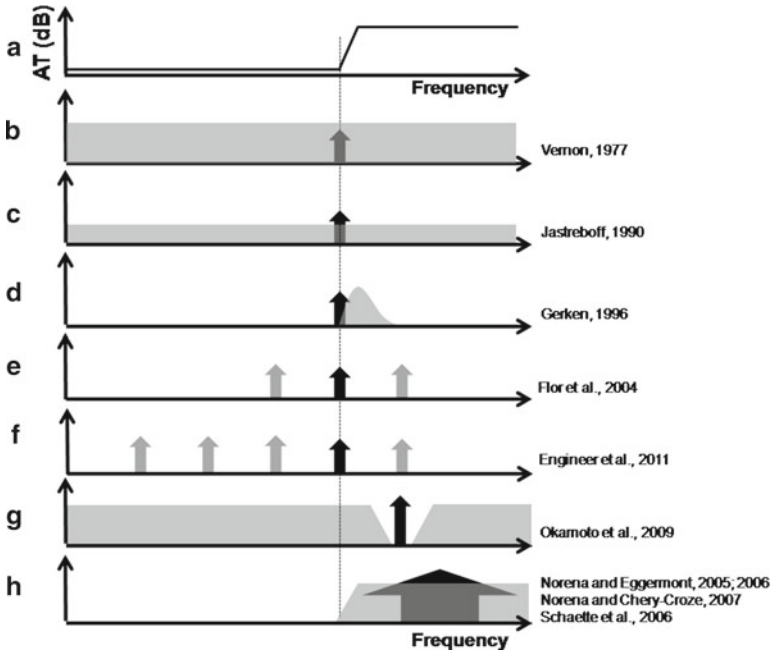

Fig. 10.1 Spectrum of the acoustic stimuli used in the different methods developed to provide relief or reverse tinnitus-related central changes. Tinnitus frequency is represented by black arrows. The vertical dotted line represents the edge frequency of hearing loss. Spectra of acoustic stimulation are shown in gray. (**a**) Hypothetical audiogram presenting a high-frequency hearing loss (AT: absolute threshold). (**b**) Complete masking of tinnitus as advocated by TMT. (**c**) Partial masking of tinnitus as advocated by TRT. (**d**) The acoustic stimulus is aimed at preventing the occurrence of an "edge effect," that is, local increase of firing rate tonotopically located at the edge frequency of hearing loss. (**e**) Sensory training with narrowband stimuli at frequencies different from tinnitus frequency aiming at reducing the cortical representation of tinnitus frequency (which is thought to be "over-represented"). (**f**) Presentation of narrowband stimuli (coupled with vagal nerve stimulation) at frequencies different from tinnitus frequency. This method is aimed at reducing the cortical representation of tinnitus frequency (which, again, is thought to be "over-represented"). The rationale for both methods illustrated in **e** and **f** is not corroborated by the literature: Tinnitus frequency is usually found above the edge frequency of hearing loss. This suggests that tinnitus frequency is "under-represented" in the auditory cortex (see text). (**g**) The acoustic stimulus presents a "notch" centered on the tinnitus frequency. This method is aimed at inhibiting the tinnitus-related activity by promoting lateral inhibition (provided by the stimulation at the adjacent frequencies of the notch). (**h**) The spectrum of the acoustic stimulus matches the audiogram. This method postulates that tinnitus-related activity (increase of spontaneous activity and/or increase of synchrony) results from central changes caused by sensory deprivation. In this context, this method is aimed at compensating for the sensory deprivation resulting from cochlear injuries, namely stimulating the frequency range of hearing loss

amplifying (hearing aids) background noise or both (noise generators implemented in hearing aids) could provide some relief to subjects with tinnitus (Vernon, 1977). This approach, called tinnitus masking therapy (TMT), was aimed at providing tinnitus relief through the substitution of the tinnitus percept by a (hopefully) more acceptable auditory percept (Fig. **10.1**). Hearing aids were favored over other

devices because they added the benefit of improving hearing in hearing-impaired subjects in addition to amplifying background noise. However, all tinnitus subjects are not eligible for hearing aid fitting (subjects with near normal or mild hearing loss). For these subjects, a dedicated device (hearing aid-like) designed to generate broadband noise in the ear has been developed. Ultimately, as emphasized by Hazell and Wood (1981, p. 223): "The most important therapeutic consideration is how the tinnitus can be masked and by what."

This method advocated using the lowest level of masking sound that is capable of masking or relieving tinnitus. For the 20% or so of patients in whom tinnitus cannot be completely masked, the clinician should reassure them that complete masking is not absolutely necessary, and that tinnitus relief is also achieved with partial masking (Vernon & Meikle, 2003). A second potential benefit of this approach was that it can result in a temporary decrease or suppression of tinnitus (residual inhibition). When residual inhibition is experienced by tinnitus subjects, it gives patients the realization of the possibility of somewhat "controlling" their tinnitus.

As early as the end of the 1980s, the emotional component involved in tinnitus severity was emphasized (Hallam, 1989). It was suggested that the natural course of tinnitus includes eventual habituation, except when tinnitus is associated with some negative beliefs, that is, that tinnitus is the symptom of some severe disease. These beliefs would then be accompanied by stimulation of emotional centers, prevent habituation from occurring, and result in tinnitus-related distress. In this context, it was quickly recognized that tinnitus masking required counseling, namely a sort of "psychoeducational" approach, to be efficient (Sheldrake et al., 1985). At the very least, counseling is aimed at providing the subjects with the reassurance that tinnitus is not the symptom of some severe disease (brain tumor, for instance) (Hazell & Wood, 1981, p. 226): "Many tinnitus sufferers require repeated reassurance that their tinnitus is not a symptom of serious intra-cranial disease. For many with tinnitus of low intensity, this reassurance will be all that is needed, especially when it is supported by adequate investigation and full explanation as far as that is possible."

In summary, TMT was considered as the "best of the various possible managements that are directed at palliation of the tinnitus relief" (Coles et al., 1985) until the end of the 1980s. This approach was empiric and its main postulate was that the auditory percept induced by background noise or tinnitus maskers will be more tolerable than tinnitus itself. The method has been refined over the years and the role of appropriate counseling has been emphasized. As described in the next section, Jastreboff developed tinnitus retraining therapy (TRT), which borrowed some key ideas from the tinnitus masking method (use of sound device and counseling) but organized them into a synthetic and structured theoretical framework.

2.3 A Standardized Method for Alleviating Tinnitus Distress: TRT

In 1990, Jastreboff published an influential paper in which he developed a synthetic model of tinnitus called "the neurophysiological model of tinnitus" (Jastreboff, 1990).

The main postulate (and advance) of this model is that nonauditory central areas, in addition to the auditory system, are involved in the clinical manifestations of tinnitus (the idea had been proposed earlier by Hallam, 1989). More specifically, the model differentiates between mechanisms involved in tinnitus perception (or generation) and those resulting in tinnitus-induced suffering. At a first stage, tinnitus is thought to result from an abnormal activity generated in the auditory system and then interpreted as a percept by the auditory centers. When tinnitus is perceived it is evaluated: if the perception of tinnitus is not associated with any emotion, tinnitus is classified as being irrelevant information and is not accompanied by suffering. On the other hand, if tinnitus is associated with any negative connotations (tinnitus is the symptom of severe disease, for instance), this will activate the limbic and autonomic nervous system, will attract attention toward tinnitus, and will result in tinnitus-related distress. The model suggests that the functional connections between tinnitus and limbic and autonomic nervous system are partly governed by the principles of conditioned reflexes. The negative connotations about tinnitus could simply result from the fact that subjects do not have sufficient knowledge about the benign nature of tinnitus (Jastreboff, 2007).

Jastreboff elaborated a comprehensive clinical approach, tinnitus retraining therapy (TRT), to achieve tinnitus relief. This method was aimed at "changing specific functional connections between the auditory and the limbic and autonomic nervous systems without the attempt to change the abnormal neural activity that causes the tinnitus" (Jastreboff, 2007, p. 420). In other words, TRT was aimed at reversing the conditioned reflex connecting tinnitus perception to the activation of limbic and autonomic nervous systems (assuming that any kind of conditioned reflex can be reversed). Ultimately, TRT is aimed at inducing and facilitating habituation of tinnitus so that tinnitus does not interfere with the patient's life (Jastreboff, 2007). This is achieved by counseling and sound therapy. One notes that, as for TMT, the TRT targets tinnitus-related symptoms and not the causes.

The aim of counseling is to reassure subjects about their tinnitus, that is, classify tinnitus into a category of neutral stimuli, while the role of sound therapy is to decrease the strength of abnormal neural activity that causes the tinnitus (Fig. **10.1**). We have emphasized earlier that counseling was already advocated in TMT (Section 10.2.2). However, no specific counseling protocol has been published for TMT (counseling was informal), in contrast to the use of a standardized counseling protocol for TRT. On the other hand, the way sound therapy is used in TRT is somewhat different compared to what is advocated by TMT. Whereas sound therapy is used to provide (and maximize) immediate relief from the patient's distress in TMT, the purpose of TRT is to facilitate long-term habituation to tinnitus (Henry et al., 2002). More specifically, whereas complete masking of tinnitus is recommended for TMT, partial masking is mandatory for TRT (Fig. **10.1**). Indeed, according to TRT, tinnitus must always be audible to promote the reversion of the conditioned reflex connecting tinnitus perception to the activation of limbic and autonomic nervous system tinnitus, which is the sine quo none condition to reach habituation (Jastreboff, 2007).

Some studies have been carried out on the potential refinements that can be added to these methods (TMT and TRT) to improve their efficacy. One approach consisted of adapting the spectrum of the masking sound to the subject's audiogram (Davis et al.,

2007, 2008; Hanley et al., 2008; see Section 10.4). Moreover, the masking sounds themselves have been the subject of few studies; as masking sounds are used to provide some relief to tinnitus subjects, some studies have investigated the degree of annoyance they themselves produce (Terry & Jones, 1986; Henry et al., 2004).

2.4 Conclusion

This section developed the view that, in the absence of an efficient cure, tinnitus management should provide relief to tinnitus subjects. In this context, much effort has been devoted to developing methods to help subjects cope with their tinnitus. Briefly stated, Vernon was first to propose the systematic use of noise maskers or hearing aids to provide tinnitus relief. Shortly after these seminal studies, it was acknowledged that counseling was an important aspect of the clinical strategy (in addition to sound therapy). A few years later, Jastreboff proposed a synthetic framework to account for and treat tinnitus (the neurophysiological model of tinnitus and the TRT, respectively). Today, a branch of the tinnitus field is examining the mechanisms of tinnitus-related distress (Schlee et al., 2009; Vanneste et al., 2010).

As TMT and TRT were aimed at providing relief to tinnitus subjects, the effects of these methods were estimated through the dimension of tinnitus-related distress (with specific questionnaires). It is easily understandable that counseling alone can have a large positive impact on tinnitus-related distress once subjects are reassured that tinnitus is not the symptom of a serious illness. In this context, it is not always clear whether auditory stimulation further improved the tinnitus relief and disagreements have arisen about the usefulness of sound stimulation. Although it is recognized that sound therapy can provide a means of escape "as it allows some people a greater sense of control over their tinnitus," the usefulness, and even the rationale, for using sound therapy is questioned (McKenna & Irwin, 2008, pp. 21–22):

> It has been suggested that sound therapy plays a particular role in facilitating habituation to tinnitus because it provokes reorganization of neural pathways responsible for tinnitus generation and perception (Folmer & Carroll, 2006). Overall, the evidence from the papers reviewed does not lend support to this idea. The findings from one study (Eysel-Gosepath et al., 2004) suggest that sound therapy is no more effective than distraction through imagination assisted by light and heat, and the evidence from the other studies reviewed strongly suggests that habituation is initiated through psychological interventions rather than sensory ones.

Finally, these authors attempted to treat the anxiety of tinnitus patients by exposing them to silence (p. 22): "The present authors have used the opposite of sound therapy when responding to some patients' anxieties about tinnitus leading to psychological crises. Anxiety is removed in some of our patients by having them carry out a behavioral experiment using a silent environment to listen to tinnitus and observe that psychological breakdown does not occur."

The point I wish to make here is that this latter view, suggesting that auditory stimulation provides only marginal effects on tinnitus severity, is mainly a criticism of TRT. This is healthy and necessary, and suggests that treating tinnitus-related

distress has become a research field, with (like other research fields) ideas, rationales, debates, and conflicts. However, it is important to not lose sight that these methods, although useful in providing tinnitus subjects with some relief, are not aimed toward curing tinnitus. As emphasized by Jastreboff and Jastreboff (1999, p. 87): "Note, that even when a very high level of habituation of the reaction and perception is achieved it is still not a cure for tinnitus, as patients can hear their tinnitus anytime when they focus their attention on it; and the tinnitus pitch, loudness are the same as at the beginning of the treatment."

Finally, even when tinnitus does not induce a significant impairment of life quality, many tinnitus subjects admit that their life would be better without tinnitus at all. In conclusion, although TMT and TRT have been useful to provide relief to tinnitus subjects, the ultimate goal remains to find a cure that would completely suppress tinnitus. In this context, the next section is dedicated to the view suggesting that tinnitus may result from central changes accompanying cochlear injuries. Assuming that these central changes are reversible, this view opens the possibility of treating the causes of tinnitus (at least in theory) and therefore to suppress it.

3 From a "Peripheral" to a "Central" Origin of Tinnitus: When the Causes of Tinnitus Become Reversible

The previous section presented the view, dominant until the mid-1990s, that tinnitus may result from an aberrant neural activity already present in the cochlear nerve and induced by cochlear injuries. The rise of the auditory neurosciences over the recent years changed not only this view, but also our conceptions about the central nervous system and especially about its ability to change (neural plasticity) when facing/adapting to different sensory environments (for a review see Noreña, 2011). In this context, the view that tinnitus could result from the central changes induced by cochlear injuries has gradually grown. This section is aimed at giving a brief history on how this view has come to prevail over the peripheral hypothesis of tinnitus.

First, the observation of a decrease of spontaneous firing rate in the cochlear nerve after cochlear injuries (Kiang et al., 1970; Liberman & Dodds, 1984) was inconsistent with the proposed peripheral location of tinnitus-related activity. Second, although cochlear nerve section can suppress tinnitus in some cases, it has been shown that tinnitus can remain in other cases, suggesting that at least in some cases, tinnitus-related activity does not originate in the cochlear nerve (Silverstein et al., 1986; Pulec, 1995). In parallel, some studies, published as early as early as the 1980s, showed that sensory deprivation was followed by central hyperactivity. Namely, the effects of cochlear injuries decreased the detection thresholds of pulsate electrical stimuli delivered at subcortical nuclei (cochlear nucleus, superior olivary complex, inferior colliculus, and the medial geniculate body) (Gerken, 1979; Gerken et al., 1984). Gerken et al. (1984, pp. 258–259) concluded: "It is clear that hearing loss cannot be viewed only as a reduction of input to a fixed central processor. Rather, it seems that the central auditory processes are themselves altered following

peripheral damage, which in turn may have consequences at the perceptual or psychophysical level."

In another early study, neural activity in auditory centers after cochlear removal was estimated from 2-deoxyglucose (2-DG) metabolic studies (Sasaki et al., 1980). This study showed that sensory deprivation resulted in an increase of glucose uptake, suggesting that the lack of sensory inputs resulted in neural hyperactivity. The temptation to mention the following paragraph extracted from Sasaki's paper (p. 512), which sounds so modern today, cannot be resisted:

> A disturbance in suppressive influences on auditory neurons may be etiologically significant in the origin of such spontaneous neural discharge, and it is hypothesized that the functional integrity of the cochlea is in some way essential to the generation of these suppressive influences within the auditory system. Accordingly, when afferent auditory signals are altered or interrupted due to cochlear injury or injury to the cochlear nerve, inhibitory influences in turn may be diminished, thus releasing higher auditory structures into tonic hyperactivity. Such spontaneous neuronal activity along the afferent auditory pathway may be interpreted at the subject's cortical level as a sound, just as the activity of neurons in the visual pathway be perceived as light without direct photostimulation of the sensory epithelium of the retina.

Many subsequent results are simply the confirmation of these previous findings, namely that sensory deprivation is accompanied by central (stimulus-induced and spontaneous) hyperactivity. These central changes were shown to occur weeks or minutes after hearing loss and at virtually all stages of the auditory system from cochlear nucleus to auditory cortex (Noreña, 2011). These latter results, that is, neural hyperactivity after cochlear injuries, together with the fact that cochlear nerve section does not always abolish tinnitus and that spontaneous activity in the cochlear nerve is decreased after cochlear injuries, underlie the view that tinnitus may result from the central changes accompanying cochlear injuries, or in other words that tinnitus has a "central" origin. Today, this view has reached a broad consensus and is dominant over the former view suggesting that tinnitus is of "peripheral" origin. Of course, it could be that several subtypes of tinnitus exist, some of "peripheral" origin (Ruel et al., 2008, Chapter 4) and others of "central" origin. Nevertheless, it is well known that the majority of tinnitus subjects, if not all, present cochlear injuries, suggesting that the most prevalent form of tinnitus is "central."

Although a central origin of tinnitus is widely accepted, the fine mechanisms of tinnitus remain to be elucidated. Nevertheless, several "central" models have been proposed. The next paragraphs present these different "central" models and their clinical implications; these models are not necessarily mutually exclusive from each other.

3.1 Tinnitus as a Result of a Release from Central Inhibition

A simple hypothesis proposed to account for tinnitus generation is that tinnitus may result from an increase of spontaneous activity in the auditory centers induced by sensory deprivation. As suggested by Sasaki et al. (1980), sensory inputs may

contribute to preserving a certain balance between excitatory and inhibitory activity. More precisely, it is thought in the sensory systems that inhibitory activity (at least a certain type of inhibitory activity, "tonic") depends on the mean level of sensory inputs. By sensory inputs is meant the spontaneous activity as well as activity induced by the sensory environment in the cochlear nerve. The removal or decrease of sensory inputs (which are excitatory) due to cochlear injuries may induce a corresponding decrease of inhibition (Calford, 2002; Garraghty et al., 2006) and ultimately an increase of spontaneous activity.

A simple neural model proposed by Gerken (1996) suggested that a sharp decrease of sensory inputs within the frequency range of hearing loss could induce, through a release from inhibition, an "edge effect," that is, a local increase of spontaneous activity in the auditory centers at the edge frequency of hearing loss (Fig. **10.1**). Gerken (1996) was first to propose an acoustic stimulus aiming at "smoothing" the spontaneous activity over frequencies, that is, at reducing spontaneous activity at the edge frequency of hearing loss (Fig. **10.1**). This model, however, is not consistent with the pitch of tinnitus, which is found well above the edge frequency of hearing loss (see Section 10.3.2.2) (Henry et al., 1999; Norena et al., 2002; Roberts et al., 2006).

3.2 Tinnitus as the Result of the Reorganization of the Tonotopic Map

One of the well-known and dramatic central changes after cochlear injuries restricted to a limited frequency range (usually high frequencies) is the reorganization of the tonotopic map (Robertson & Irvine, 1989; Kamke et al., 2003; Noreña & Eggermont, 2005). Namely, thalamic and cortical neurons, which were responding to high frequencies before the cochlear lesions, become sensitive to the edge frequency of the hearing loss (Fig. **10.2**). As a result of these plastic changes, the edge frequency of hearing loss is said to be "over-represented" in the sense that more neurons are dedicated to this frequency. Salvi (1996, p. 464) was the first to propose a potential link between these central changes and tinnitus:

> One of the most profound changes seen in the auditory cortex is the rearrangement of the tonotopic map which leads to an over-abundance of neurons tuned to frequencies near the "edge" of the hearing loss. It is conceivable that the overabundance of neurons tuned to frequencies near the "edge" of the hearing loss would make the neural activity in this region much more salient relative to the under represented regions. Significantly, pitch matches to subjective tinnitus are often made to frequencies located above or below the maximum hearing loss. Large clusters of cortical neurons tuned to a narrow frequency range could give rise to phantom auditory sensations, particularly if the neural activity in these clusters were to become synchronized, as often happens in cases of epilepsy.

Assuming that tinnitus may result, at least in part, from the cortical reorganization of the tonotopic map (through an increase of synchrony within the reorganized area, for instance), it has been suggested that normalizing the tonotopic reorganization in

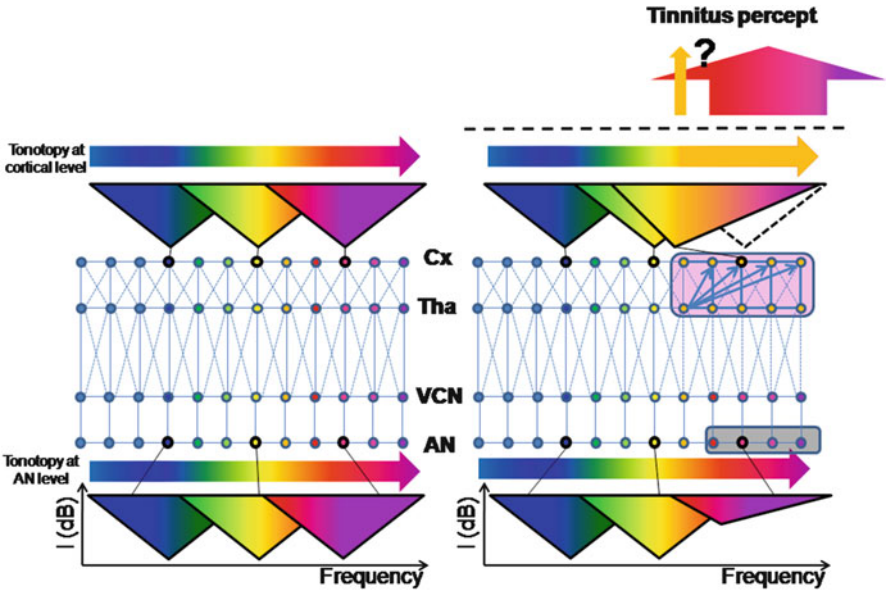

Fig. 10.2 Highly simplified schematic of the auditory system, from the auditory nerve (AN) to auditory cortex (Cx), via the ventral cochlear nucleus (VCN) and the auditory thalamus (Th), without (left) and with cochlear injuries (right). Each circle corresponds to neurons and the color represents their characteristic frequency. Neurons are connected to each other (dotted lines = weak connections; full lines = medium connections; thick lines = strong connections). The tuning curves of some neurons in the auditory nerve and auditory cortex are shown (circles with thick contours). Without cochlear injuries (left), the tuning curves present the classic "V-shape" and all frequencies are (roughly) equally represented at each stage of the auditory system, that is, the tonotopic map is normal. In presence of cochlear injuries (right), the tuning curves of cochlear neurons corresponding to the frequency band of hearing loss are modified. These tuning curves result from the sensory inputs remaining after cochlear injuries ("residual responses"): characteristic frequency can be shifted toward lower frequencies and neural thresholds are elevated. At the cortical level, high frequencies are no longer represented (in terms of characteristic frequency). The characteristic frequency of neurons in the reorganized area has shifted toward the edge frequency of hearing loss. Importantly, this shift in CF is not accompanied by an increase in neural threshold, which suggests that these changes result from a plastic process. The functional connections are thought to be increased between neurons presenting a CF at the edge frequency of hearing loss and neurons with a "native" CF within the frequency band of hearing loss (thick arrows). In addition, the functional connections between neurons in the reorganized region (orange region in the figure) are thought to be high, which could account for the increase in synchrony reported in some studies. In summary, the edge frequency of hearing loss is over-represented, whereas frequencies above the edge frequency of hearing loss are under-represented. The tinnitus frequency being located within the frequency range of hearing loss, this suggests that tinnitus frequency is "under-represented" in auditory cortex

auditory centers may improve or suppress tinnitus. Interestingly, this goal has led to two different therapeutic strategies according to whether tinnitus frequency is thought to be "over-represented" or "under-represented" in auditory cortex.

3.2.1 Is Tinnitus Frequency "Over-Represented" in Auditory Centers?

As suggested in the previous paragraph, tinnitus could result from some aberrant activity within the reorganized cortical region after hearing loss. Assuming that tinnitus pitch corresponds to the frequency tuning of the reorganized cluster of neurons, tinnitus may therefore correspond to the edge frequency of hearing loss, that is, the new characteristic frequency of neurons in the reorganized cortical area (Fig. **10.2**). This view was advocated by Eggermont (2000, p. 87): "Hence, these edge-tuned neurons might fire very similarly and more or less synchronously even in the absence of sound (Salvi et al., 1996). This synchrony would be analogous to that caused by stimulation with edge-frequency tones or narrow-band noise. Hence, tinnitus with a pitch resembling that of such a stimulus will result."

Importantly, the belief that tinnitus frequency matched the edge frequency of hearing loss implied that tinnitus frequency was "over-represented" in the auditory centers. The results from a study carried out in magnetoencephalography are often interpreted as corroborating this view (Mülnickel et al., 1998). However, this study was conducted on subjects with normal or near-normal hearing. It is unclear what the mechanisms accounting for the reported reorganization of the tonotopic map are and how the results of this study can be extended to subjects with hearing loss (which represent the vast majority of cases). The view that tinnitus frequency may be "over-represented" in the auditory centers has led to the development of approaches aiming at decreasing the cortical representation of the tinnitus frequency (Flor et al., 2004; Herraiz et al., 2007; Engineer et al., 2011). These approaches were based on previous studies showing that the tonotopic map could be manipulated. Namely, a frequency discrimination task at a given frequency induced an over-representation of that trained frequency at the expense of the neighboring frequencies (Recanzone et al., 1993). Therefore, training the neighboring frequencies of tinnitus may "over-represent" the trained frequencies and reduce the cortical representation of the tinnitus frequency (Flor et al., 2004; Herraiz et al., 2007). The rationale of this approach is summarized as follows by Flor et al. (2004, p. 114):

> Frequency discrimination training in the neighboring zones of the area affected by tinnitus may "capture" cortical neurons from the tinnitus-generating network and allocate them to the network supporting the representation of the training frequencies. If patients are presented tone frequency discrimination tasks close to their tinnitus frequency, a spreading of the representation area of these tone frequencies would be expected, diminishing the representation area of the tinnitus frequencies.

This approach has been refined recently by pairing auditory stimulation with vagal nerve stimulation so as to promote central plasticity (Engineer et al., 2011) (Fig. **10.1**).

3.2.2 Is Tinnitus Frequency "Under-Represented" in Auditory Centers?

The view developed in Section 10.3.2.1 suggested that tinnitus frequency is "over-represented" in the auditory centers. However, in the somatosensory system, it is well known that the phantom percept after limb amputation often corresponds to the missing limb, suggesting that the reorganized neural cluster is still associated with its initial (before amputation) perception (for reviews, see Doetsch, 1998; Ramachandran & Hirstein, 1998). It is also important to point out that, while characteristic frequencies (CFs) of neurons in the reorganized area have been shifted toward the edge frequency of hearing loss, these neurons are still responding to the frequency range of hearing loss at moderate to high levels (Fig. **10.2**).

In the auditory system, the exact location of the tinnitus pitch, measured from a matching procedure with a tone pip, was found to be located within a relatively broad frequency band (between the edge frequency of hearing loss and 1 or 2 octaves above it) and variable across sessions within the same subjects (Loeb & Smith, 1967; Atherley et al., 1968; Henry et al., 1999). This variability was likely due to the fact that tinnitus has a reduced pitch strength compared to a tone pip, and/or does not present a unitary pitch as a tone pip does (Penner, 1993). In this context, we devised and used a method allowing us draw a more complete portrait of the internal tinnitus "spectrum" by capturing the various pitch components that contribute to the whole tinnitus sensation. This method assumed that the tinnitus percept presented a pitch but not that it presented a dominant pitch. Broadly speaking, the tinnitus "spectrum" obtained from this method can be seen as a sort of probability density function of frequency components of tinnitus. Releasing the subject from the task of finding the dominant frequency of his tinnitus, we thought that this method would settle whether the tinnitus pitch is at, or above the edge frequency of hearing loss (Norena et al., 2002). In broad agreement with previous studies, the study showed that the dominant pitch of tinnitus was located well above the edge frequency of hearing loss. This result has two important implications for models trying to account for the mechanisms of tinnitus and for their related therapeutic approaches. First, it suggests that the activation of the reorganized cluster of neurons is still associated with their initial (before hearing loss) perception, which is consistent with what has been reported in the somatosensory system (Doetsch, 1998, for a review). Second, because tinnitus is located within the frequency range of hearing loss (Henry et al., 1999; Roberts et al., 2006; Schaette & Kempter, 2009), the tinnitus frequency can thus be considered as "under-represented" in the auditory centers (Fig. **10.2**).

Ultimately, the functional connectivity between cortical neurons in the reorganized area may be increased, which could result in an increase in synchrony between these neurons. This increase in synchrony has been interpreted as a putative "neural sign" of tinnitus (Noreña & Eggermont, 2003, 2005). The cause of the cortical reorganization being the sensory deprivation induced by cochlear injuries, it has been suggested that compensating for the sensory deprivation may reverse the cortical reorganization and the changes in the pattern of spontaneous activity (Norena et al., 2002; Noreña & Eggermont, 2005). In brief, this approach consists of stimulating the frequency band of hearing loss.

3.3 Tinnitus as a Result of an Increase of Central Gain

Another view considered tinnitus-related activity as the result of an increase of central gain. This idea has been first proposed by Jastreboff (1990) and later developed by Jastreboff and Hazell (1993, p. 10):

> Plasticity in the auditory system has been clearly demonstrated (…). Importantly, even a temporal decrease in auditory input results in an increase of sensitivity of neurons within the subcortical centres (..). These observations provide an explanation to the well-recognized phenomenon that if a person with normal hearing is deprived of auditory input in an anechoic chamber, the person will experience increased hearing sensitivity, start to hear extremely weak sounds, and frequently experience tinnitus. The implication of these findings and the postulate of the involvement of subcortical processing in tinnitus is that in certain cases tinnitus might be due to such an increased gain within the subcortical centres of the auditory system. As such it can be treated by a method aimed at decreasing this gain; that is, hearing aids or white noise generators incorporated into a protocol which employs a very gradual increase of such auditory input over prolonged periods of time. (…). Another ramification of this hypothesis is that hyperacusis can be regarded as a pretinnitus state. Hyperacusis is a manifestation of increased central gain.

A major conceptual advance has been achieved by Schaette et al. (2006), who implemented the concept of "gain" in a computational model designed to mimic the auditory system facing a sensory deprivation. The first important assumption of the model is that central neurons maintain their mean firing rates around a set point value. Second, the key idea of the model is that mean firing rate is maintained constant through the adaptation of neural sensitivity or "gain." It is hypothesized that neural sensitivity or gain is controlled by a homeostatic plasticity mechanism (Turrigiano et al., 1998). The model suggests that when the auditory system (cochlear nucleus, for instance) is facing a decrease in sensory inputs due to cochlear injuries, the gain of central neurons is increased, which can result in an increase of spontaneous activity, and ultimately tinnitus. This model also proposed that this mechanism can "amplify" the nonauditory inputs coming from other sensory modalities (for review see Dehmel et al., 2008).

The involvement of central gain in sensory deprivation and tinnitus mechanisms was suggested subsequently by others (Parra & Pearlmutter, 2007; for review see Noreña, 2011). In particular, Noreña (2011) proposed that the central gain might preserve the stability of neural firing around a set point value (the key idea proposed by Schaette et al., 2006) and preserve the neural coding efficiency (infomax principle: Laughlin, 1981) (Fig. **10.3**). Ultimately, when the sensory inputs are decreased by cochlear injuries, the model suggests that the price to pay for maintaining neural homeostasis and neural coding efficiency (through an increase of central gain) is an increase of the spontaneous firing rate. This increase in firing rate could result in tinnitus. This model suggests that spontaneous activity in the cochlear nerve plays a key role in tinnitus generation, as a "peripheral drive" that is abnormally amplified, and distinguishes tinnitus originating from ventral cochlear nucleus (moderate hearing loss, amplification of "residual" inputs coming from the cochlear nerve) or dorsal cochlear nucleus (extensive hearing loss, amplification of inputs coming from other modalities—the somatosensory system).

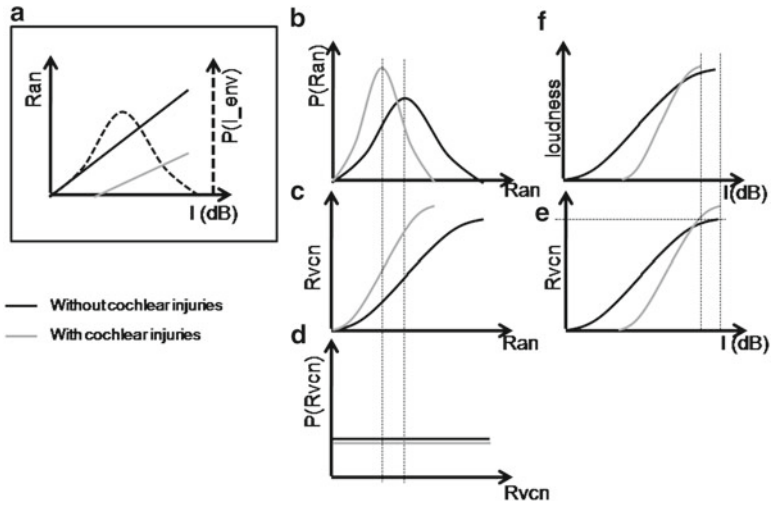

Fig. 10.3 Central gain in the auditory system. (**a**) The distribution of intensity levels of the environment (P(I_env) as a function of level I) and the (simplified) input–output function (IOF) of auditory nerve are shown in the left panel. Cochlear injuries are accompanied by a decrease of the slope of the IOF and a decrease of the maximum response of the auditory nerve. (**b**) Distribution of firing rate of fibers in the auditory nerve (P(Ran)). Cochlear injuries are associated with a shift of the distribution toward lower values. (**c**) Input–output function of neurons in the ventral cochlear nucleus (VCN) (firing rate of VCN neurons as a function of their inputs, in terms of firing rate in the auditory nerve). The shape of the IOF results from the infomax principle (the distribution of firing rate of VCN neurons is uniform: **d**), it corresponds to the cumulative distribution of inputs (see text for details). (**e**) The firing rate of VCN neurons is represented as a function intensity level (I). (**f**) Putative loudness functions assuming that loudness is proportional to the firing rate of VCN neurons. The model accounts for loudness recruitment and for the decrease of loudness discomfort level (hyperacusis)

Assuming that loudness perception is roughly proportional to neural activity in auditory centers (Cai et al., 2009), an implication of these latter models is that loudness perception should be, at least in part, "recalibrated" as a function of the distribution of sensory inputs (Fig. **10.3**). Namely, an enriched acoustic environment is thought to decrease auditory sensitivity, while sensory deprivation is thought to increase auditory sensitivity. These predictions are broadly consistent with the literature. Acoustic stimulation or sensory deprivation induced by noise generators or earplugs have been shown to decrease or increase auditory sensitivity, respectively (Formby et al., 2003; Philibert et al., 2005; Hamilton and Munro, 2010). Interestingly, the threshold of the acoustic reflex was significantly decreased after 7 days of sensory deprivation induced by unilateral earplugs, likely reflecting an increase of auditory sensitivity (Munro and Blount, 2009). Moreover, the comfortable loudness level in cochlear implant subjects has been found to rise significantly over time; this may be due to a decrease of central gain and neural sensitivity (Kubo et al., 1996; Hughes et al., 2001). The "acclimatization" effect, first described by Gatehouse

(Gatehouse, 1989), may be accounted for by changes in central gain. Finally, loudness recruitment (abnormally rapid growth of loudness as a function of level in hearing-impaired subjects) may also be accounted, at least in part, by an increase of central gain. This model suggests that tinnitus may result from an "amplification of neural noise." In our opinion, this view can reconcile many facets of tinnitus and in particular two "families" of results that may, at first, appear contradictory. Moreover, two different clinical approaches can be derived from these models.

On one hand, tinnitus accompanying sensory deprivation, that is, after cochlear injuries or in normal-hearing subjects in profound silence, can be accounted for by an increase of central gain (Knobel & Sanchez, 2008; Del Bo et al., 2008). These results suggest that an approach consisting of reducing the central gain may suppress tinnitus. This approach is similar to that developed in Section 10.3.2.2 and consists of restoring the "pre-hearing loss" distribution of sensory inputs. According to this model, an "ideal" hearing aid (compensating perfectly the loss of inputs up to high frequencies), cochlear implants, or customized acoustic stimulation could therefore decrease tinnitus loudness through a reduction of central gain (Fig. **10.1**).

On the other hand, it has been shown that cochlear nerve section (in some cases) and positive current applied at the promontory or round window could suppress tinnitus (Cazals et al., 1978). Electrical stimulation with positive current has been suggested to hyperpolarize cochlear nerve fibers and decrease their spontaneous firing rate (Schreiner et al., 1986). Here, in apparent contradiction with the hypothesis suggesting that the increase of central gain, due to sensory deprivation, results in tinnitus, a further decrease of spontaneous activity in the cochlear nerve is found to suppress tinnitus. The spontaneous activity in the cochlear nerve is very large in the intact cochlea, as 1 million of spikes/s is roughly discharged in the silence of a soundproof room. In this context, the "residual" spontaneous cochlear nerve activity, namely the reduced spontaneous activity after cochlear injuries, has been proposed to be the "peripheral drive" of tinnitus. Tinnitus could result from the "amplification" (due to the increase in central gain) of this peripheral drive (Noreña, 2011). This hypothesis is consistent with a study carried out in animals showing that neural hyperactivity in inferior colliculus induced after sensory deprivation is strongly dependent on cochlear nerve activity (Mulders et al., 2009). As a consequence, any means of reducing cochlear nerve spontaneous activity could suppress tinnitus. However, although this approach may provide subjects with immediate release from their tinnitus, which already can be very helpful for patients, it is unclear whether this approach would be efficient when used chronically. Indeed, the risk of decreasing cochlear nerve activity is that it may also further increase the central gain, resulting in a worsening of tinnitus. Nevertheless, this electrical stimulation is meant to reduce cochlear spontaneous activity and not stimulus-induced activity; this may prevent an increase of central gain. In this context, it has been reported that auditory perception was not affected by electrical stimulation with positive current (Portmann et al., 1979). Moreover, cochlear nerve sectioning can improve tinnitus in more than 50% of subjects (Silverstein et al., 1986; Pulec, 1995), suggesting that further reducing peripheral inputs is not necessarily accompanied by a worsening of tinnitus.

3.4 Conclusion from the Central Models

This section develops the hypothesis that tonotopic reorganization after cochlear injuries may play an important role in tinnitus generation, through an increase of synchrony within the reorganized area. Two different approaches have been proposed to reverse tinnitus-related central changes. Based on the assumption that tinnitus was over-represented in the centers, one view suggested to stimulate at frequencies around tinnitus frequency and avoiding tinnitus frequency to decrease the central representation of the tinnitus frequency. On the other hand, another view suggested that tinnitus-related central changes were caused by the sensory deprivation accompanying cochlear injuries. As a consequence, compensating for the sensory deprivation (by stimulating the frequency range of hearing loss) was proposed to reverse the tinnitus-related central changes.

The hypothesis that tinnitus may result from the tonotopic reorganization and an increase in synchrony can be questioned or may not hold in all cases. Indeed, subjects with flat and severe hearing loss (cochlear implant candidates for instance: Quaranta et al., 2004) and normal hearing subjects in the silence of a soundproof room often present tinnitus (Del Bo et al., 2008). In absence of "contrast" in sensory inputs (flat hearing loss or normal hearing in silence), tonotopic reorganization is unlikely. In this context, it has been proposed that an increase of central gain may be involved in the generation of tinnitus. Neural hyperactivity and the "recalibration" of loudness perception (increase of sensitivity) when the auditory system is facing a sensory deprivation is broadly consistent with the model. The introduction of the concept of gain reconciled the apparent paradox between the causal effect of sensory deprivation on tinnitus (i.e., increase in central gain) and the suppressive effects of cochlear nerve section and extracochlear stimulation with positive current on tinnitus. The two hypotheses (cortical reorganization and increase of central gain) are not necessarily exclusive of each other. The respective contribution of tonotopic reorganization and central gain in the generation of tinnitus remains to be clarified.

In summary, all the central models developed in Section 10.3 suggest that tinnitus-related activity could be generated in the auditory centers. From a clinical point of view, this hypothesis was a major conceptual advance, as it suggested that tinnitus-related mechanisms could be reversed by means of adequate stimulation, assuming that tinnitus-related central changes are reversible (but see Section 10.4.1.6). Finally, the fact that tinnitus could result from central changes and that these central changes can be reversed by means of auditory stimulation can account for part of the beneficial effects of TMT and TRT, in which the use of sound devices (hearing aid, noise generator, or custom acoustic stimulation) are advocated. In other words, in addition to an immediate relief provided by the masking of tinnitus (TMT), and/or facilitating the habituation of tinnitus (TRT), the use of stimulating device may have interfered with the tinnitus-related central changes.

4 Effects of Auditory Stimulation on Tinnitus

4.1 Acoustic Stimulation

4.1.1 TMT and TRT

Many studies have shown that TMT and TRT can provide some relief to tinnitus subjects, suggesting that auditory stimulation is efficient in helping tinnitus subjects to cope with their tinnitus. However, only a few of the studies included placebo controls (for review see Hobson et al., 2010) and the different studies are not always comparable, as they used different questionnaires and protocols, with some studies even using their own custom questionnaires.

An interesting study carried out by Henry et al. (2006) compared the efficacy of TMT and TRT. Tinnitus severity was estimated from the tinnitus handicap inventory, tinnitus handicap questionnaire, and tinnitus severity index. Both methods induced a relief of tinnitus, but TRT was largely superior to TMT in reducing tinnitus-related distress, especially in the group "tinnitus is a very big problem." The superiority of TRT was significant when tinnitus-related distress was assessed with all the questionnaires used. In addition, the authors estimated the percent of the awake time during which the subjects were aware of their tinnitus (tinnitus awareness). Eighteen months after the beginning of the protocol, subjects treated with TRT showed a larger decrease of tinnitus awareness. Finally, the time course of improvement was different between the two methods. Indeed, most of the improvement induced by TMT was achieved during the first 3– 6 months of treatment, while TRT induced a steady improvement over the course of the treatment (18 months).

4.1.2 Restoring Lateral Inhibition

A recent approach investigated the effects of notched music on tinnitus, the notch (1 octave width) being chosen to correspond to the pitch of tinnitus (Okamoto et al., 2010). The notched music was intended to reduce tinnitus-related cortical activity within the notch, possibly through increasing lateral inhibition (Pantev et al., 1999). After 12 months of regular listening, this approach was reported to reduce tinnitus loudness, estimated from VAS, by around 20% on average (eight subjects were treated with the notched music). Tinnitus reduction correlated with the reduction of auditory steady-state responses (obtained at the tinnitus frequency).

This approach was interpreted by the authors as reversing the "maladaptive cortical reorganization by the notched music training (p. 1209)." Since the meaning of "maladaptive cortical reorganization" was not defined, the mechanisms which could have accounted for tinnitus reduction are unknown. Above all, it is unclear how the notched music could have impacted the auditory system and tinnitus. Indeed, the tinnitus frequency is usually relatively high (6 kHz on average in this study).

Importantly, the energy of music is usually low at high frequencies (Jansson & Sundberg, 1972), where in addition hearing loss can be large, which decreases even more the contribution of high frequencies. In conclusion, it is unclear whether the notched music effectively induced a notched pattern of excitation at the cochlear nerve level, and therefore whether the effects of notched music on tinnitus can be attributed to lateral inhibition.

4.1.3 Diminishing the Cortical Representation of Tinnitus Frequency

Although it is not consistent with the literature, some authors defended the idea that tinnitus could result from an over-representation of the tinnitus frequency (Mülnickel et al., 1998; Flor et al., 2004; Engineer et al., 2011). They proposed that tinnitus could be suppressed by decreasing the cortical representation of the tinnitus frequency (for reviews see Hoare et al., 2010 and Roberts & Bosnyak, 2010). Tinnitus subjects were then trained or stimulated with tones close to or remote from the tinnitus frequency. Overall, the effects of this approach were relatively small (Flor et al., 2004; Herraiz et al., 2007, 2010).

4.1.4 Compensating for Reduced Sensory Inputs

Some tinnitus models developed in Section 10.3 suggest that tinnitus may result from the central changes accompanying hearing loss. This model suggests that hearing loss act as a trigger for the generation of tinnitus-related activity. An implication of this model is that compensating for the sensory deprivation may reverse the central changes due to hearing loss, including those involved in tinnitus generation (increase of spontaneous activity and/or increase of neural synchrony). In other words, this approach is aimed at restoring the "pre-hearing loss" sensory inputs. Interestingly, the model is corroborated by studies reporting that tinnitus is abolished when hearing is restored, namely after middle ear surgery in patients with chronic otitis media (Kim et al., 2011) or after removing excessive ear wax from the ear canal (Midani et al., 2006).

This idea was tested in a very preliminary study in which one subject was trained in a frequency discrimination task (Norena et al., 2002). The aim of this study was to reverse the central changes putatively resulting in tinnitus. The active sensory training was thought to promote the reversion of these central changes. Specifically, the trained frequencies were chosen to fall in the frequency range of hearing loss. The subject took part in seven frequency discrimination training sessions, with two or three sessions per week, over 3 weeks. During each of these training sessions, which lasted around 2 hours, the subject repeatedly performed the frequency discrimination task using four test frequencies. The effects of this approach were assessed on the "tinnitus spectrum." As tinnitus spectrum may reflect the neural network involved in tinnitus generation, any changes in this network caused by the sensory training was thought to result in changes in the frequency content of tinnitus.

The study revealed that the training significantly reduced the contribution of high-frequency components of tinnitus. Unfortunately, the effects of sensory training on tinnitus loudness (through VAS, for instance) were not reported.

Although it is thought that sensory training involving the active participation of subjects (attention, for instance) may promote sensory plasticity through neuromodulation (acetylcholine release, for example: Kilgard & Merzenich, 1998), it is unclear whether active versus passive training will be more efficient in reversing central changes due to hearing loss. Indeed, it has been shown that tonotopic reorganization accompanying hearing loss does not depend on the basal forebrain cholinergic input (Kamke et al., 2005). In this context, passive stimulation with customized acoustic stimulation has been used as a means to compensate for sensory deprivation and to reverse tinnitus-related central changes. The principle of this method has been studied in cats that were placed in an enriched acoustic environment immediately after noise trauma (see Eggermont, Chapter 7 for further details) (Noreña & Eggermont, 2005, 2006). This study showed that the enriched acoustic environment reduced noise-induced hearing loss and prevented the reorganization of the cortical tonopic map and the emergence of the putative neural signs of tinnitus.

In human subjects, this approach was investigated in subjects presenting hyperacusis (Noreña & Chery-Croze, 2007). Subjects were stimulated (a few hours per day) over a period of 15 weeks with a multitone stimulus whose spectrum was specifically adapted to each subject's audiogram. In other words, subjects were stimulated specifically in the frequency range of hearing loss (no stimulation was provided below the edge frequency of hearing loss); the stimulus was aimed at normalizing (across frequency) the sensory inputs provided to the auditory centers. Auditory sensitivity was assessed from a loudness categorizing test (derived from the loudness growth in one-half octave band). The results showed that the enriched acoustic environment significantly decreased the auditory sensitivity at all tested frequencies (even at frequencies below the edge frequency of hearing loss which were not stimulated); on average, the auditory sensitivity was reduced by 15 dB. Interestingly, 2 weeks after stopping the acoustic stimulation, the auditory sensitivity showed a slight but significant increase of sensitivity compared to the sensitivity estimated at the end of the stimulation period. This result is in broad agreement with the hypothesis suggesting that auditory sensitivity depends on the distribution of sensory inputs (for review see Noreña, 2011). Overall, this method showed that stimulating the sensory deprived region was efficient for reducing auditory sensitivity. However, this study did not assess the effects of varying the spectrum of the acoustic stimulation. Namely, it is unclear whether stimulating the frequency range of hearing loss is more efficient than stimulating the frequency range below the edge frequency of hearing loss or stimulating with a broadband noise. In this context, broadband noise has been shown to decrease the loudness discomfort level by around 10–20 dB after a stimulation period of 9–12 months (Wolk & Seefeld, 1999; Gold et al., 1999).

The approach of stimulating the frequency range of hearing loss with customized stimulation has been tested in subjects with tinnitus. Neuromonics treatment is one

of these methods and can be viewed as a mixture between the concepts derived from the TRT and the need to compensate for reduced sensory inputs (Davis et al., 2007, 2008; Hanley & Davis, 2008). The method consists of an acoustic stimulation combining music and broadband noise. The spectrum of this combination is customized so as to provide an equalized stimulation over the audible frequency range. In addition to providing stimulation within the deprived sensory region, the acoustic stimulation is also designed to promote relaxation and relief. Indeed, the use of relaxing music provided a sense of relief from the tinnitus perception. These effects are reinforced and complemented by benefits arising from the broader counseling and support program. In contrast to the approach advocated in the TRT, in the neuromonics tinnitus treatment patients are permitted to completely mask their tinnitus in the early stages of the treatment to maximize relief and relaxation (2 months). This initial stage is also intended to maximize the amount of stimulation of the deprived sensory region. In a second stage (4 months), the patients are then discouraged to mask their tinnitus to facilitate desensitization. This method has been reported to significantly improve tinnitus: 86% of the subjects reported more than 40% of improvement in tinnitus disturbance as measured by the TRQ (vs. 47% and 23% of the subjects treated with broadband noise + counseling and counseling, respectively). The method reduced sound intolerance (loudness discomfort level was decreased by 10 dB on average) and minimum masking level. It is worthwhile to mention that this high "success rate" of the method was obtained in subjects who did not display "complicating factors," such as a high level of psychological disturbance and/or hearing loss in the worse-hearing ear greater than 50 dB at frequencies of 0.5, 1, 2, and 4 kHz.

4.1.5 Effects of Hearing Aids on Tinnitus

The effects of hearing aids on tinnitus have been reviewed elsewhere (Del Bo & Ambrosetti, 2007). The use of hearing aids has been advocated by both TMT and TRT to achieve tinnitus relief and habituation. Moreover, hearing aids are also thought to act at the level of tinnitus causes by compensating for the sensory deprivation (Schaette et al., 2010). Overall, hearing aids have been reported to improve tinnitus (Surr et al., 1985; Folmer & Carroll, 2006; Trotter & Donaldson, 2008). Recently, it has been shown that hearing aids plus counseling induced a larger relief than counseling alone (Searchfield et al., 2010).

Schaette et al. (2010) suggested that hearing aids should reduce tinnitus in subjects with tinnitus frequency within the range of frequencies amplified by the device (Schaette & Kempter, 2009). Interestingly, subjects with a tinnitus pitch less than 6 kHz and fitted with hearing aids showed a significant reduction of tinnitus loudness (from 73.4 before to 56.4 after treatment), whereas subjects with a tinnitus pitch higher than 6 kHz did not show any decrease in tinnitus loudness. In another attempt to assess whether hearing aids could interact with the putative causes of tinnitus (central changes induced after hearing loss), the effects of hearing aids on the "tinnitus spectrum" were studied (Moffat et al., 2009). Two different regimens

of amplification were tested: a "conventional" amplification and "high-bandwidth" amplification. The conventional amplification was shown to reduce the tinnitus components at low frequencies.

4.1.6 Conclusion Regarding Methods Based on Acoustic Stimulation

The effects of acoustic stimulation on tinnitus are modest, at least on the tinnitus percept itself. It is therefore unclear whether acoustic stimulation improves tinnitus through some interaction with tinnitus mechanisms or through the partial or complete masking of tinnitus. Moreover, hearings aids may improve tinnitus through the improvement of life quality due to the increase in speech understanding. However, it has been found that there was no significant correlation between the benefits induced by hearing aids on speech understanding and the benefits on tinnitus severity (Surr et al., 1999). This suggests that tinnitus improvement does not depend on the improvement of speech understanding.

The relatively modest effects of acoustic stimulation on tinnitus may be accounted for by several reasons. First, the "central" model of tinnitus assumes that the central changes due to sensory deprivation and involved in tinnitus generation are reversible. This assumption is supported by a study, albeit in a different sensory modality, reporting the effects of bilateral hand transplantation in a subject who sustained a traumatic amputation of both hands 4 years earlier. Indeed, the hand transplantation reversed the reorganization induced after amputation, which was paralleled by a suppression of phantom perceptions (Giraux et al., 2001). However, among the many changes resulting from sensory deprivation, some of them might be difficult to reverse, namely axonal sprouting, cross-modal reinnervation, and reactive neurogenesis (Darian-Smith & Gilbert, 1994; Florence et al., 1998; Dutheil et al., 2009). These structural changes may account for, at least in part, why tinnitus is so resistant to clinical approaches, especially when sensory deprivation has been present for many years. In this context, any therapeutic approach aimed at treating tinnitus should apply the slogan "the sooner, the better" (De Ridder et al., 2005).

Moreover, while hand transplantation has been associated with suppression of phantom perception (Giraux et al., 2001), acoustic stimulation does not replace an intact cochlea (basically, the customized acoustic stimulation is meant to mimic an intact cochlea providing the auditory centers with "normal" inputs). In other words, it may not be possible to compensate fully for deprived inputs by means of acoustic stimulation. Indeed, the cochlea (and/or cochlear nerve) can have nonfunctional areas, which are called "dead regions" (Moore & Alcántara, 2001). The presence of "dead regions" would prevent any acoustic stimulation from activating the auditory centers within the corresponding projecting areas. In this context, by bypassing the cochlea, electrical stimulation delivered by cochlear implants may be more efficient than acoustic stimulation to reverse tinnitus-related central changes (see Section 10.4.2.1).

Finally, the properties of the acoustic stimulation (frequency of amplitude modulation, for instance), other than simply the long-term spectrum of the acoustic sequence, may be critical for suppressing tinnitus over the long term. It is well

known that the auditory cortex, the ultimate "recipient" of auditory stimulation, acts as a low-pass filter with a corner frequency at around 20 Hz. On the other hand, auditory cortex is also known to respond only weakly to unmodulated stimuli (for review see Eggermont, 2001). A stimulus presenting a relatively high frequency of amplitude modulation may then reduce cortical activity and possibly induce synaptic depression (Noreña et al., 2006). In this context, it can be suggested that customized acoustic stimulation should result in low-frequency amplitude modulation; periods of silence could even be interleaved to avoid neural habituation/synaptic depression (Nakahara et al., 2004). One can also wonder whether the acoustic stimulus should be presented at a regular rate to maximize the effects of the stimulation. Finally, one also wonders if there is any frequency of presentation at which information flow toward the cortex is maximized.

4.2 Electrical Stimulation

4.2.1 Intracochlear Stimulation (Cochlear Implants)

Tinnitus is experienced by 60–100% of adult cochlear implant (CI) candidates, with an average of around 80%. The effects of CIs on tinnitus are well known and have been reviewed elsewhere (Quaranta et al., 2004; Baguley and Atlas, 2007; Punte et al., 2010).

The simple surgical procedure (electrode insertion) has been reported to suppress or exacerbate tinnitus in some cases. In a series of 42 patients, Gibson (1992) reported after surgery but before switch-on CI, that tinnitus was abolished or reduced in 5% and 33% of tinnitus subjects, respectively. In a series of 15 patients, Kim et al. (1995) reported (before using the device, while the implant was off) complete relief in five implanted ears; no worsening of tinnitus was reported. Finally, in two other studies, tinnitus was abolished postoperatively (before switch-on CI) in 18.7% and 4.3% of the patients (Aschendorff et al., 1998; Greimel et al, 2002, respectively). On the hand, CI insertion can be accompanied by an increase of tinnitus loudness in subjects with preoperative tinnitus and even by tinnitus in subjects without preoperative tinnitus (McKerrow et al, 1991; Miyamoto et al., 1997; Aschendorff et al., 1998). However, this risk is usually small (from 0% to 26%).

The great majority of studies assessing the effects of CI on tinnitus over time reported complete or partial suppression of tinnitus (Van de Heyning et al., 2008; Pan et al., 2009). Interestingly, tinnitus suppression has been noted in both the ipsilateral and contralateral ear to the CI. In a recent study carried out on a series of 41 implanted patients, tinnitus severity was evaluated at least 3 months after cochlear implant activation (Quaranta et al., 2008). With CI off, tinnitus was abolished in 56% and 54% of the subjects in the implanted ear and in the contralateral ear, respectively. With the CI on, tinnitus was abolished in 66% in the ipsilateral and contralateral ear. The suppression of tinnitus when the CI is switched off and the reduction of tinnitus in the contralateral ear are both consistent with an effect of electrical stimulation on the central mechanisms underlying tinnitus.

The effects of cochlear implants on tinnitus are of great value to challenge the different models of tinnitus. The high prevalence of tinnitus in CI subjects is consistent with a critical role played by sensory deprivation in tinnitus generation. At first sight, the reasons why complete suppression of tinnitus after electrode insertion and before CI is switched on are unclear. One interpretation is that, in some cases, tinnitus in CI subjects may result from amplification (increase of central gain) of the residual spontaneous activity in the cochlear nerve (Noreña, 2011). By damaging further the cochlea, electrode insertion may have suppressed the residual spontaneous activity in the cochlear nerve, which could have therefore abolished tinnitus. It would be interesting to know whether this tinnitus suppression is maintained over time (there is, however, no indication in the literature that tinnitus can be suppressed after electrode insertion and reappear weeks or months thereafter).

The decrease in tinnitus loudness (up to complete suppression) in both the implanted and the contralateral ear, with the device on and off, strongly suggests that the effects of CI on tinnitus cannot be accounted for only by masking or habituation. The reader is reminded here that habituation is thought to leave the psychoacoustic properties of tinnitus unaffected (see Section 10.2). The prevalent and large reduction of tinnitus loudness induced by CI suggests that CI indeed interacts with the causes of tinnitus. One interpretation is that the stimulation provided by the implant decreased the central gain, which in turn decreased tinnitus loudness.

On the other hand, it is unclear whether tinnitus in deaf subjects (before CI implantation) can be related to an increase of neural synchrony in auditory cortex. Indeed, as hearing loss is usually flat across the audible spectrum, it is unknown whether clusters of cortical neurons are tightly synchronized with each other, as has been proposed when hearing loss is restricted to high frequencies (“contrast” in sensory inputs). However, although it has not been studied in detail, and may vary among subjects, it seems that tinnitus could correspond to a pitch in at least some deaf subjects (Dauman & Tyler, 1993; Demajumdar et al., 1999; Akdogan et al., 2009). This result suggests that tinnitus in deaf subjects may result, at least in some cases, from neural “aberrant” activity (increase in spontaneous activity and/or synchrony) of a given neural cluster restricted tonotopically. Further studies are needed to clarify this interesting question.

4.2.2 Extracochlear Stimulation

It has been known for 200 years that anodal direct current can suppress tinnitus (Rubinstein & Tyler, 2004). The first report in “modern” times was published by Hatton et al. (1960). This study consisted of providing (in 33 subjects) anodal or cathodal current on the zygomatic arch on the side ipsilateral to tinnitus. In 15 subjects, anodal current delivered on the tinnitus side resulted in tinnitus reduction, and even resulted in suppression in some cases at high current strengths. The suppression lasted the duration of the electrical stimulation and as the current was gradually reduced to zero, tinnitus gradually returned to its former intensity. The current strength at which tinnitus was suppressed varied from 1.5 mA to 8.8 mA. On the other hand, when cathodal current was delivered on the tinnitus side, the opposite

effect was obtained: tinnitus increased in loudness as the strength of the current was increased and tinnitus loudness returned to its former level as the strength of the current was reduced gradually to zero. This effect was subsequently fortuitously rediscovered by another group (Cazals et al., 1978, p. 209): "In this study our aims were the determination of in how many cases of severe hearing loss additional information could be obtained to discriminate sensory from neural lesions and to evaluate the eventual auditory sensations with respect to possible rehabilitation procedures. In the course of the experiments, unexpected effects were observed: very often, when tinnitus was present, it could be completely suppressed by specific stimuli." In this series of studies, stimulating electrodes were positioned on the promontory or the round window. Tinnitus suppression was obtained with positive rectangular pulses (from 20 μA to 500 μA) presented at frequencies greater than 50 Hz (usually from 50 Hz to 500 Hz). Tinnitus suppression lasted the duration of the stimulation and the patients often reported a short sound at the end of the stimulation. On the other hand, a negative current was found to elicit an auditory percept. Tactile sensations were much less frequently associated with negative than with positive pulses (Aran et al., 1983). Although tinnitus suppression could be achieved with an electrode positioned on the promontory or the round window, stimulation at the round window was found to be more effective to suppress tinnitus. Interestingly, it was observed in subjects with residual hearing that speech understanding was not affected by the simultaneous stimulation suppressing tinnitus.

These promising results of anodal direct current on tinnitus did not lead to a clinical approach, as electrical current using nonbalanced charges is known to induce detrimental effects on biological tissues (Shepherd et al., 1991). Only alternating currents, such as those used in cochlear implants, are safe for chronic stimulation (Rubinstein & Tyler, 2004). In this context, few studies have assessed the effects of alternating (balanced-charge) currents provided by extracochlear stimulation on tinnitus (Hazell et al., 1993; Okusa et al., 1993; Ito & Sakakihara, 1994). Some of these studies have shown some efficacy of electrical stimulation in suppressing tinnitus. However, it is not always clear whether the suppressive effects are obtained by a masking effect or by a "true" suppression of tinnitus. In a study carried out by Rubinstein et al. (2003) in 11 tinnitus subjects with high-frequency hearing loss, extracochlear electrical stimulation was used to restore normal spontaneous activity in the cochlear nerve. The frequency of the electrical stimulation was relatively high (4800 Hz, well above the refractory period of neurons) to make the cochlear fiber discharges random and therefore to provide the auditory centers with what the authors call the "code for silence." The stimulation electrode was positioned on the round window niche. In three subjects, electrical stimulation did not elicit any auditory percept, or the stimulation induced pain. In three other subjects, electrical stimulation could suppress tinnitus but only in the presence of a stimulus percept, suggesting that the suppression of tinnitus was attributed to a "masking" effect. Finally, in the remaining five subjects, tinnitus could be suppressed in the absence of a stimulus percept, or after complete or nearly complete adaptation to the stimulus percept. The suppression of tinnitus was usually achieved after several minutes of stimulation (5–15 minutes), and the residual inhibition of tinnitus could last from minutes to days.

It has been shown that a decrease in neural activity can be achieved by electrical stimulation (Konishi et al., 1970). More specifically, positive currents applied to the round window in cats suppressed stimulus-evoked and spontaneous activity, estimated from the whole nerve response (Schreiner et al., 1986). The suppression lasted throughout the duration of the electrical stimulation, but a rebound effect (brief increase in spontaneous activity) was sometimes observed at the offset of the electrical stimulation. The strength of the suppression was a function of the applied current level. On the other hand, negative current induced an increase in the amplitude of driven and spontaneous responses. However, prolonged stimulation with negative current (>30 s) resulted in a progressive reduction of cochlear nerve activity until a profound suppression of spontaneous activity and evoked activity was achieved. As developed in Section 10.4.2.2, tinnitus suppression can be achieved by extracochlear stimulation with positive current. It is tempting to interpret these findings (tinnitus suppression and the following "rebound" of tinnitus) as resulting from the modulation of activity in the cochlear nerve (Schreiner et al., 1986). Finally, the progressive reduction of cochlear nerve activity over time during a prolonged electrical stimulation might provide an explanation for the residual inhibition of tinnitus reported in some studies (Souliere et al., 1992; Kim et al., 1995; Rubinstein et al., 2003).

5 Summary

This chapter briefly reviewed the history of tinnitus and the various models of tinnitus generation to give the necessary background to comprehend the rationale and expected effects of auditory stimulation, which is one of the most widely used methods to provide tinnitus subjects with relief.

The author has suggested that the tinnitus field had taken two distinct paths (Fig. **10.4**). First, tinnitus was thought to result from cochlear injuries and aberrant neural activity already present in the cochlear nerve. Knowing that most of the cochlear injuries are irreversible, some authors have doubted in the possibility of finding an efficient method to suppress tinnitus. Although no efficient cure was available to treat tinnitus, strategies were proposed to help patients cope with their tinnitus. In this context, TMT was developed, followed by TRT. These methods have been shown to provide tinnitus subjects with some relief. However, none of these techniques were aimed at targeting the causes of tinnitus, and as a consequence, tinnitus was usually not abolished after the treatment.

In parallel with the peripheral model of tinnitus, the view that tinnitus may result from central changes after cochlear injuries has progressively emerged. The observations that cochlear injuries were associated with a decrease of spontaneous activity in the cochlear nerve, that cochlear injuries were accompanied by neural hyperactivity in auditory centers, and that cochlear nerve section was not always followed by tinnitus suppression were interpreted as arguments supporting a central origin of tinnitus. In brief, central models suggest that sensory deprivation due to cochlear injuries induces central changes including those related to tinnitus.

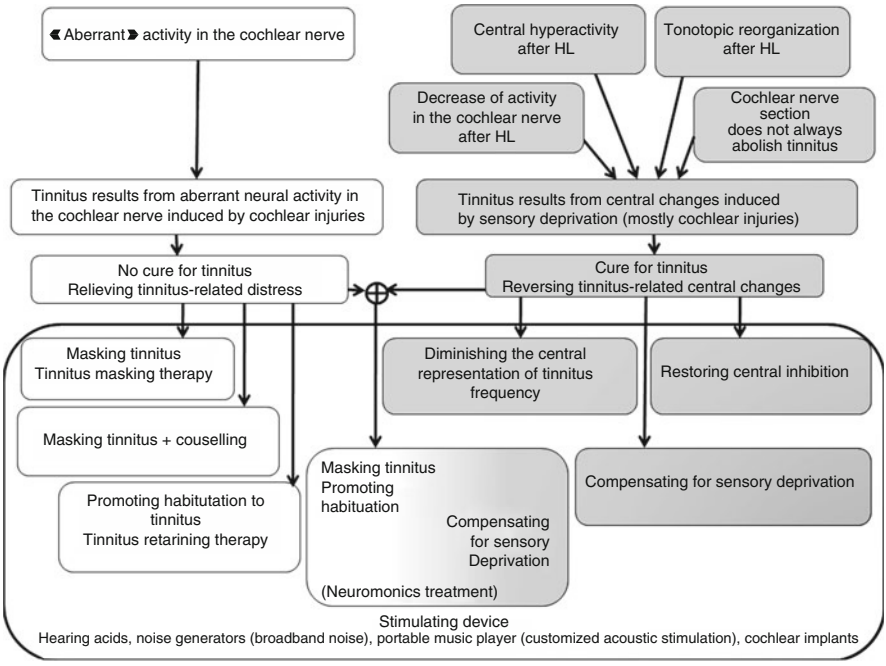

Fig. 10.4 Summary of tinnitus history. The pathway suggesting that tinnitus results from irreversible cochlear damages is shown in white. This view proposed that there may be no cure for tinnitus and promoted the research of methods aiming at reducing tinnitus-related distress. The pathway suggesting that tinnitus results from central changes after cochlear injuries is shown in gray. This view proposed that reversing the tinnitus-related central changes may cure tinnitus. Both types of methods have advocated the use of auditory stimulation and the same stimulating device

This view had a great impact in the field as it suggested that tinnitus may be cured, by preventing or reversing the tinnitus-related central changes. Briefly stated, two different types of methods have been proposed. One method was aimed at reducing the cortical representation of the tinnitus frequency (which was thought to be over-represented in auditory cortex) by means of sensory training (the frequency of acoustic stimuli were close but different from the tinnitus frequency). However, the validity of this rationale is questionable, as the tinnitus frequency, usually located within the frequency range of hearing loss, might actually be under-represented in auditory cortex. Another family of methods resulted from the view that the critical event triggering tinnitus-related central changes is a sensory deprivation (usually induced by cochlear injuries), and therefore suggested compensating for the sensory deprivation by auditory (acoustic or electrical) stimulation. Finally, a more recent model stressed the importance of the residual spontaneous activity in the cochlear nerve for tinnitus generation. The model suggested that tinnitus may result from the "amplification" (increase of central gain) of this residual spontaneous activity. As already developed in Section 10.4.1.4, this model suggests that compensating for sensory deprivation should decrease the central gain and reduce tinnitus loudness.

Moreover, this model suggests that reducing the residual activity in the cochlear nerve should suppress tinnitus. This latter prediction is consistent with tinnitus suppression induced by extracochlear electrical stimulation with positive current and by cochlear nerve section. One notes, however, that cochlear nerve section does not always abolish tinnitus, suggesting that the tinnitus-related activity can be independent from the cochlear nerve inputs. In this context, it has been proposed that the dorsal cochlear nucleus may play a crucial role, where nonauditory inputs could compensate for the loss of auditory inputs.

Ironically, the two different views on the origins of tinnitus have both advocated the use of auditory stimulation (auditory and electrical stimulation). Whereas auditory stimulation is used as a kind of "distracter" in the methods aiming at reducing tinnitus consequences, auditory stimulation is meant to reverse tinnitus-related central changes in the second class of methods. In brief, it was found that acoustic stimulation resulted in modest effects on tinnitus, while it more significantly suppressed hyperacusis. This result points to a partial dissociation between the mechanisms causing tinnitus and those inducing hyperacusis. Overall, electrical stimulation (cochlear implants) is far superior to acoustic stimulation in reducing tinnitus. The efficiency of cochlear implants in suppressing tinnitus over time, in the implanted ear as well as the contralateral ear, is broadly consistent with a model suggesting that tinnitus results from the central changes induced by sensory deprivation. The superiority of electrical stimulation over acoustic stimulation in suppressing tinnitus may result from the fact that it bypasses the cochlea, which could have "dead regions" (cochlear region that function poorly, if at all). Indeed, "dead regions" prevent acoustic stimulation from compensating for sensory deprivation and therefore from interfering with the central causes of tinnitus.

In summary, tinnitus is now thought to result from central changes due to sensory deprivation, which result in increased spontaneous activity and/or synchrony in auditory centers. These central changes have been suggested to involve modulation of central gain, homeostatic plasticity, structural plasticity, and multimodel plasticity. The central changes after cochlear injuries are often interpreted as being "maladaptive" because their functional role is unclear or even deleterious (they are accompanied by "aberrant" perceptions such as hyperacusis and tinnitus). However, it has been recently suggested that they may actually result from a normally adaptive process, which under typical circumstances allows the system to maintain neural homeostasis in the sensory environment, which itself is constantly changing (i.e., cochlear injuries result in a chronic reduction of sensory inputs). Under those circumstances, the central changes may preserve the mean neural activity around a set point level and optimize the neural coding efficiency when the distribution of input levels in the sensory environment changes. However, in the case when the auditory system is facing an abnormal sensory deprivation, these adaptive central changes may come at a price: the overall increase of neural sensitivity may "amplify" the neural background and then induce tinnitus.

Tinnitus has evolved from a simple symptom restricted to audiology and studied in the context of medical sciences to a challenging question worthwhile for studying in auditory neurosciences. Clear models accounting for many facets of the tinnitus

phenomenon have recently been proposed and the techniques are available (the techniques of the neurosciences) for testing these models and invalidating or refining them. The field of tinnitus may have been slowed down for two reasons. First, although tinnitus can be accompanied by significant distress, in the vast majority of cases, it is not the symptom of a severe disease. Thus, medicine and science have therefore often focused on other topics. Second, there is no means to record tinnitus-related neural activity in individual subjects. As science is more amenable to examining salient and reproducible phenomena, the absence of a reliable neural correlate of tinnitus has been (and still is) a great handicap. In our opinion, a broad consensus about the neural correlates of tinnitus would help focusing the research on the mechanisms of tinnitus, that is, how the neural correlates of tinnitus are generated, what is the neural circuitry involved in tinnitus generation. For comparison, the great "chance" when studying epilepsy is that epilepsy seizures are caused by abnormal neural activity that is very salient and therefore easily detectable. Studying the dynamic of this activity, or its modulation by any treatment is then achievable; this gives a great "window" to understand the mechanisms of epilepsy. In this context, finding a reliable neural correlate of tinnitus would give an "anchor point" for studying the mechanisms of tinnitus, which would be a great step for the field. Animal studies have revealed that tinnitus may result from increase of spontaneous activity and/or increase in synchrony. However, there is no agreement between studies carried out in animals with those carried out in tinnitus subjects. Indeed, the possible neural correlates of tinnitus or "abnormal" activity accompanying it found in tinnitus subjects (increase in gamma activity, increase in delta activity, decrease of alpha activity) (Weisz et al., 2007, for a review; Ortmann et al., 2011) have not been corroborated by animal studies (even in awake preparation, Noreña et al., 2011).

In conclusion, the tinnitus field is still in its adolescence and advances and new treatments based on auditory stimulation should appear in the future as our understanding of the mechanisms progress.

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Chapter 11
Treatment: Pharmacological, Repetitive Transcranial Magnetic Stimulation, Epidural Stimulation, and Deep Brain Stimulation

Berthold Langguth, Dirk De Ridder, Tobias Kleinjung, and Ana Belén Elgoyhen

1 Introduction

Available treatments for the management of tinnitus are diverse. These include counseling and cognitive–behavioral therapies; different forms of sound therapies; methods that attempt to increase input to the auditory system, such as hearing aids and cochlear implants (for use in patients whose tinnitus is caused by deprivation of signals to the auditory nervous system); pharmacological treatment; neurobiofeedback; and various forms of electrical stimulation of brain structures, either through implanted electrodes or by inducing electrical current in the brain with transcranial magnetic stimulation. The existence of many different treatment approaches derives from the fact that there exist different subgroups of tinnitus that differ in their

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pathophysiology and their response to treatment. In clinical practice it is frequently difficult to choose the optimal treatment approach for an individual patient. The treatment approaches presented in this chapter (pharmacological, magnetic, or electrical brain stimulation) are all at early stages of development. The further development of these new treatment options will depend on the extent to which we understand the pathophysiology of the different forms of tinnitus.

Even if most of the presented approaches cannot yet be recommended for routine application, their use in specific cases may be clinically beneficial. However, they should be performed in the context of a comprehensive management of the tinnitus patient. To guide clinicians in the diagnostic and therapeutic follow-up of individual patients, a *Flowchart for the Diagnostic and Therapeutic Management of Tinnitus* has been proposed recently (Langguth et al., 2011; http://www.tinnitusresearch.org/en/projects/flowchart_en.php).

1.1 The Role of Neuroimaging

Functional and structural imaging techniques (functional magnetic resonance imaging [fMRI], single-photon emission computed tomography [SPECT], positron emission tomography [PET], MRI) have been successfully applied to identify brain structures involved in tinnitus (Landgrebe et al., 2009; Lanting et al., 2009). Electro- and magnetoencephalography (EEG, MEG) provide information regarding abnormal neural synchronization and connectivity (Weisz et al., 2005; Schlee et al., 2009a). Through the contribution toward a better characterization of the brain areas and networks involved in tinnitus and the identification of new targets for treatment, these methods are essential in the development of both pharmacological and brain stimulation approaches. A further potential application of these approaches is the differentiation between different forms of tinnitus. By contributing to differential diagnosis, imaging may also serve as outcome predictor for specific treatments. Further, neuroimaging can be used for the assessment of the neuronal mechanisms by which specific treatments exert their effects. This knowledge, in turn, can be useful for improving efficacy of treatment interventions. (For more information about neuroimaging of tinnitus see Eggermont, Chapter 7 and Melcher, Chapter 8.)

1.2 Pathophysiology of Tinnitus

Subjective tinnitus is defined as the perception of sound in the absence of an internal or external sound source. Current concepts assume that tinnitus results from maladaptive plastic changes in the structural and functional organization of the auditory system at several levels as a consequence of reduced auditory input

(for more information see Eggermont, Chapter 7). In people with tinnitus these changes of neuronal activity can be visualized by functional imaging techniques such as fMRI, PET, EEG, or MEG (Adjamian et al., 2009; Melcher, Chapter 8). The focus of most research in this area has been the central auditory pathways. However, data from patients in persistent vegetative state suggest that activation of primary auditory cortex by an auditory stimulus is not sufficient for conscious perception (Laureys et al., 2000). Rather, synchronized coactivation of the inferior parietal cortex, the hippocampus, the anterior cingulate cortex (ACC), and the posterior cingulate cortex (PCC) seems mandatory for conscious auditory perception (Boly et al., 2004). Taken together, these results indicate that the function of the primary sensory cortices is mainly to generate an appropriate neural discriminatory representation of the sensory input, but a stimulus becomes conscious only when functionally connected to a network of higher order brain areas. This concept is analogous to the global workspace model elaborated for the visual system (Dehaene et al., 2006; Baars & Franklin, 2007).

MEG and EEG studies are aiding toward delineating the network connectivity underlying the affective components of tinnitus suggesting that the presence of distress in tinnitus is related to a network activity, lateralized to the right hemisphere (Schlee et al., 2008b). The amount of distress in tinnitus patients is reflected by functional alterations in a network consisting of the medial temporal lobe (amygdala and hippocampus), parahippocampal areas, insula, and subgenual and dorsal ACC (Vanneste et al., 2010a). Enhanced activity of the amygdale has been shown by PET imaging and by transient tinnitus diminution after suppression of the amygdalo–hippocampal complex by amytal (De Ridder et al., 2006b). Hippocampal deficits have been documented in animal models of tinnitus (Goble et al., 2009; Kraus et al., 2010), and structural imaging (voxel-based morphometry of MRI data) in tinnitus patients has demonstrated a decrease in gray matter in the hippocampus (Landgrebe et al., 2009). Structural deficits have also been observed in the subgenual cingulate cortex/nucleus accumbens area (Muhlau et al., 2006; Leaver et al., 2011) and, based on these findings, it has been postulated that some forms of tinnitus may be the result of a deficient sensory attentional gating mechanism, originating in the subgenual cingulated cortex/nucleus accumbens area and acting on the reticular thalamic nucleus, thereby modulating thalamocortical processing in the auditory system (Rauschecker et al., 2010).

Further, it has been shown that the tinnitus related network changes over time. A MEG study looking at phase-locked connectivity in the tinnitus network found that in patients with a tinnitus history of less than 4 years, the left temporal cortex is predominant in the gamma band network, whereas this network is more widely distributed, including more frontal and parietal regions, in patients with tinnitus duration of more than 4 years (Schlee et al., 2009a). This might account for the reported increased resistance to treatment the longer the duration of tinnitus, both for TMS (De Ridder et al., 2005; Plewnia et al., 2007b; Khedr et al., 2008) and surgical procedures such as microvascular decompressions (Møller et al., 1993; De Ridder et al., 2010).

1.3 Methodological Considerations

1.3.1 Tinnitus Measurement

For evaluation of any therapeutic intervention the measurement of outcome is critical in the design of a clinical trial. As tinnitus is a purely subjective phenomenon, definition of outcome measurements is not trivial. A comprehensive evaluation includes the assessment of (1) tinnitus loudness, either by visual analogue scales or by psychoacoustic measurements and (2) of tinnitus severity, which is usually assessed by validated questionnaires. Tinnitus loudness can be assessed by psychoacoustic methods and by subjective rating scales (VAS), with both measurements providing complementary information. Several validated questionnaires are available for assessment of tinnitus severity. However, these questionnaires have not been designed to be sensitive for evaluating treatment-induced changes (Meikle et al., 2007). Moreover, most of the questionnaires have been validated by using the Beck Depression Inventory (BDI) and therefore their scores correlate highly with the BDI scores. Hence, in a sample of tinnitus patients with comorbid depression, a drug that has an antidepressant effect, but no effect on tinnitus would probably result in reduced tinnitus scores, just by reducing depressive symptoms (Newman & Sandridge, 2004). (For more information about tinnitus measurement see also Moore, Chapter 9 and Noreña, Chapter 10).

1.3.2 Heterogeneity of Tinnitus

An important step toward designing a successful strategy in the search for tinnitus drugs should include criteria to classify tinnitus patients included in trials. Different triggering events can lead to tinnitus, such as noise exposure or administration of specific pharmacological agents, ear or head injuries, some diseases of the ear, and ear infections. In some cases the causative agent remains unknown. Thus, identification of triggering causes might be important for selecting the most adequate treatment. Moreover, the manifestation of tinnitus can vary, ranging from intermittent tinnitus perception with little impact on daily life to a very bothersome tinnitus that occurs 24 hours a day, preventing sleep, leading to the inability to do intellectual work and to social isolation. Tinnitus is also often associated with other symptoms, such as hyperacusis and distortion of sounds (Møller, 2007) and several affective disorders, such as anxiety, phonophobia, and depression. With such differences in etiology and symptoms, heterogeneity within tinnitus patients is expected. Specific underlying pathophysiological mechanisms have already been identified for specific clinical factors such as the perceived localization (Melcher et al., 2000; Weisz et al., 2007b; Vanneste et al., 2010c), the duration (Schlee et al., 2009a), or the frequency composition (Vanneste et al., 2010d). Differential diagnosis of triggering events and temporal onset should allow for a more rational and effective pharmacological approach. The fact that a subgroup of patients who have intermittent tinnitus that sounds like a typewriter, popped corn, or ear clicking receive

significant relief from the use of carbamazepine (Mardini, 1987), indicates that stratifying tinnitus patients benefits treatment. Efforts toward establishing tinnitus subgroups are underway (Tyler et al., 2008; Landgrebe et al., 2010), and will most likely aid the identification of responders to specific drugs and the selection of patients in future clinical trials. Thus the most probable future scenario is that there will be different treatment approaches for the different forms of tinnitus.

2 Brain Stimulation for the Treatment of Tinnitus

2.1 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is an experimental tool for stimulating neurons via brief magnetic pulses delivered by a coil placed on the scalp (Barker et al., 1985). In brief, the stimulator delivers a short lasting, high-intensity current pulse through an insulated stimulating coil. This induces a magnetic field perpendicular to the coil that penetrates the scalp with little attenuation (Fig. **11.1**a). The magnetic field reaches a maximum of approximately 1.5–2 Tesla in about 100 μs and then decays back to zero (Hallett, 2000). Because the field changes rapidly with time, it induces an electrical current in the brain area under the coil. This electrical current in turn depolarizes axons in the stimulated brain area.

Whereas single magnetic pulses do not seem to have longer lasting effects on the brain, the rhythmic application of multiple pulses, called repetitive TMS (rTMS), can induce changes in neuronal excitability that outlast the duration of the stimulation. These effects resemble those seen in animal experiments in which repeated electrical stimulation has been shown to produce changes in the effectiveness of synapses in the same circuits (Hoffman & Cavus, 2002). These changes include the phenomena of long-term potentiation (LTP) and long-term depression (LTD), which have been shown to be important for learning and memory processes (Wang et al., 1996). But repetitive TMS can also be used to transiently disturb ongoing neural activity in the stimulated cortical area, thus creating a transient functional lesion. Such an approach can help to identify whether a given brain area is critically involved in a specific behavioral task

Magnetic coils with different shapes are used. For therapeutic use in general, figure-eight-shaped coils are elected because they produce a more focal magnetic field than round coils. Their maximal current is delivered at the intersection of the two round components (Hallett, 2000) (Fig. **11.1**b). Due to the strong decline of the magnetic field with increasing distance from the coil, the direct stimulation effect is limited to superficial cortical areas. However, stimulation effects propagate transsynaptically to functionally connected remote areas and thus modulate brain network activity (Siebner et al., 2003).

Because of these unique and powerful features, rTMS has been widely used in various fields, including cognitive neuroscience and several clinical applications (for review see Pascual-Leone et al., 2000; Slotema et al., 2010).

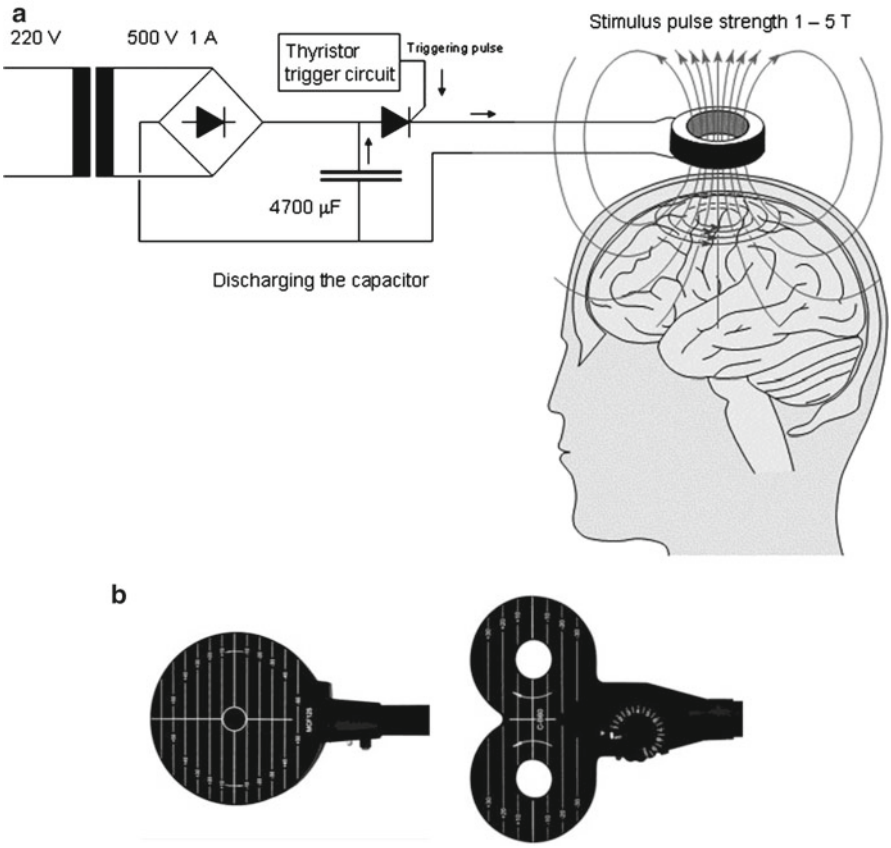

Fig. 11.1 **(a)** The underlying principle of TMS: The strong current in the coil produces a magnetic field perpendicularly to the plane of the coil. The magnetic field passes unimpeded through the skull and induces oppositely directed electric current in the brain. (Adapted with permission from the web version of the book: Jaako Malmivuo & Robert Plonsey: *Bioelectromagnetism–Principles and application of bioelectric and biomagnetic fields*, Oxford University Press, New York, 1995.) **(b)** Schematic diagrams of different coil types used for TMS

2.1.1 Rationale for the Application of TMS in Tinnitus

As mentioned in the introduction, tinnitus is related to altered activity of cortical networks involving also central auditory areas. Because rTMS has the ability to modulate cortical activity focally, it has been assumed that it can interfere with the tinnitus-related abnormal neural network activity and thereby influence the perception of tinnitus. If this is the case, repeated applications of rTMS might represent a potential treatment for some forms of tinnitus by producing longer lasting modulation of cortical activity. Additional support for this approach comes from clinical trials in which rTMS was used in an attempt to treat other pathological conditions

with potential cortical hyperactivity, such as auditory hallucinations (Hoffman et al., 2003), writers' cramp (Siebner et al., 1999), and obsessive–compulsive disorders (Mantovani et al., 2006).

2.1.2 Studies Using Single Sessions of rTMS in Tinnitus

Within the last few years, results of several studies using single sessions of rTMS have been published. The goal of these studies was to reduce tinnitus perception transiently. In this kind of studies, rTMS was preferentially administered at high frequencies (10–20 Hz). In a pilot study, stimulation of the left temporoparietal cortex with high-frequency rTMS (10 Hz) resulted in a transient reduction of tinnitus in 57% of the participants (Plewnia et al., 2003). This result has been confirmed in a large series of 114 patients with unilateral tinnitus (De Ridder et al., 2005). In this study, repetitive TMS at frequencies between 1 and 20 Hz was applied over the auditory cortex contralateral to the site of tinnitus perception. The best transient tinnitus suppression was achieved using higher stimulation frequencies for tinnitus of recent onset and lower frequencies for tinnitus of longer duration. Patients who had their tinnitus for a shorter duration had the best results. These results suggest that rTMS may be a valuable diagnostic tool for differentiating different forms of chronic tinnitus. This approach has been used for screening purposes to select patients for surgical implantation of cortical electrodes (De Ridder et al., 2004, 2007b) (see Section 11.2.2).

Two studies (Folmer et al., 2006; Fregni et al., 2006) confirmed the result of transient tinnitus reduction after high-frequency stimulation of the left temporoparietal cortex, whereas one study (Londero et al., 2006b) demonstrated reliable tinnitus suppression in only 1 out of 13 subjects after a single session of high-frequency rTMS. One of these studies also suggests that the participants with significant tinnitus reduction after rTMS also respond to anodal transcranial direct current stimulation (tDCS) (Fregni et al., 2006). It should be noted that different target areas have been used in the various studies and also different methods for identifying the target for stimulation. In one study, changes of cerebral blood flow were determined before and after lidocaine injection (Plewnia et al., 2007a). Single sessions of low-frequency (1 Hz) rTMS with the coil navigated to individually determined areas in the temporoparietal cortex resulted in tinnitus reduction in 6 out of 8 participants lasting up to 30 minutes, which is much longer than the usual seconds-long transient tinnitus suppression induced by single sessions rTMS.

2.1.3 Studies Using Repeated Sessions of rTMS in Tinnitus

The application of low-frequency rTMS in repeated sessions followed the hypothesis that longer lasting improvement of tinnitus complaints can be achieved by reducing auditory cortex hyperactivity. An increasing number of studies using this approach as a treatment for tinnitus have been published. Most rTMS treatment

studies applied low-frequency rTMS in long trains of 1200–2000 pulses repeatedly over 5–10 days. In all controlled studies, a statistically significant improvement of tinnitus complaints has been documented. However, the degree of improvement and its duration varied across studies, probably due to differences in study design, stimulation parameters, and selection criteria of the participants.

Repetitive TMS has been applied over temporal or temporoparietal cortical areas. One placebo-controlled study with 14 participants used [^{18}F]deoxyglucose ([^{18}F]DG) PET and a neuronavigational system for the exact positioning of the TMS coil over the site of maximum activation in the auditory cortex (Kleinjung et al., 2005). After active treatment, the participants experienced a significant decrease in their tinnitus, as reflected by the score of the tinnitus questionnaire, whereas sham treatment showed no effect. Treatment effects were still detectable 6 months after treatment. Another study concerned the effects of 2 weeks of rTMS applied over the cortical area where lidocaine-induced activity change was largest as determined by [^{15}O]H_2O PET (Plewnia et al., 2007b). This approach also resulted in moderate, but significant effects after active stimulation. Placing the coil over the left temporal area according to the 10–20 EEG coordinate systems (Langguth et al., 2006) resulted in a significant reduction of tinnitus severity after 10 sessions of 1-Hz rTMS. Beneficial effects of low frequency rTMS have been confirmed by several further controlled studies (Rossi et al., 2007; Smith et al., 2007; Anders et al., 2010; Marcondes et al., 2010).

Although some studies demonstrated effects that outlasted the stimulation period for several months (Kleinjung et al., 2005; Khedr et al., 2009, 2010) and even up to 4 years (Burger et al., 2011), others were not able to achieve long-lasting effects (Plewnia et al., 2007b; Rossi et al., 2007).

A recent case report showed that rTMS may be used as a maintenance treatment to manage chronic tinnitus (Mennemeier et al., 2008). In this patient, tinnitus could be reduced by rTMS each time it reoccurred using one to three sessions of rTMS; it finally remained stable on a low level after the third stimulation series. The positive effect of this maintenance stimulation could also be confirmed by reduced cerebral metabolism in PET imaging after treatment. The approach to use rTMS for maintenance treatment of tinnitus is further supported by the observation that those patients who respond once to rTMS treatment also experience further positive effects from a second series of rTMS (Langguth et al., 2008c).

2.1.4 Enhancement Strategies

When repeated sessions of rTMS were introduced as a therapeutic approach, stimulation was performed at a frequency of 1 Hz (Londero et al., 2006a). This was motivated by the finding that 1-Hz rTMS reduces neuronal excitability over the motor cortex (Chen et al., 1997) and by the successful use of low-frequency rTMS in treatment of neuropsychiatric disorders, which are associated with focal hyperexcitability (Hoffman & Cavus, 2002). This concept has been challenged by recent studies with a relatively large sample size that compared effects of 1 Hz, 10 Hz, and 25 Hz

rTMS (Khedr et al., 2008). Whereas sham rTMS treatment had no effect, active stimulation over the left temporoparietal cortex resulted in a reduction of tinnitus irrespective of the stimulation frequency. A follow-up assessment 1 year after treatment suggested a trend for higher efficiency of stimulation at 10 and 25 Hz, as compared to 1 Hz (Khedr et al., 2009).

Experimental data from motor cortex stimulation in healthy subjects indicates that the effect of low-frequency rTMS can be enhanced by high-frequency priming stimulation (Iyer et al., 2003). However, in a clinical trial, high-frequency priming stimulation failed to enhance the therapeutic efficacy of low-frequency rTMS for the treatment of tinnitus (Langguth et al., 2008a).

Repetitive TMS can be applied in a tonic and a burst mode. The burst stimulation technique has been proposed for enhancing rTMS effects. In detail, bursts of 3 stimuli at a frequency of 50 Hz (interval of 20 ms between each stimulus), applied every 200 ms (5 Hz, theta burst) have been shown to induce more pronounced and longer lasting effects on human motor cortex than tonic stimulation (Huang et al., 2005). Single sessions of continuous theta burst stimulation (3 pulses at 50 Hz, repeated at 200-ms intervals for up to 600 pulses for 40 s continuously) over the temporal cortex in tinnitus patients resulted in only short-lasting reduction of tinnitus loudness, comparable to effects achieved with single sessions of tonic stimulation, whereas other theta burst protocols had no effect at all (Poreisz et al., 2009; Lorenz et al., 2010). In two other studies, single sessions of burst stimulation were compared with tonic stimulation (De Ridder et al., 2007c,d). Burst stimulation had effects similar to those of tonic stimulation in patients with pure tone tinnitus but was superior in patients with noise-like tinnitus. It was hypothesized that pure tone tinnitus may be due to increased neuronal activity in the classical (lemniscal) tonotopically organized auditory pathways, which mainly fire tonically, whereas noise-like tinnitus may be the result of increased activity in the nonclassical (extralemniscal) non- (or less) tonotopically organized auditory pathways, characterized by burst firing (Hu et al., 1994; De Ridder et al., 2007c, 2010). A follow-up study of the same group could replicate this result for bilateral tinnitus, but not for unilateral tinnitus (Meeus et al., 2009). Further, this study suggests that higher stimulation intensity may result in slightly better tinnitus suppression.

The optimal target for stimulation and the method for coil positioning are still a matter of debate (Langguth et al., 2010). Various neuroimaging methods reveal slightly different areas of abnormal neuronal activity in tinnitus and accordingly different targets have been chosen for stimulation. Based on [^{18}F]DG–PET data that reveal increased neuronal activation predominantly of the left auditory cortex independent of tinnitus laterality (Arnold et al., 1996), this area has been chosen as treatment target in many studies. Other imaging studies identified abnormalities predominantly in temporoparietal areas (Reyes et al., 2002; Plewnia et al., 2007a). Based on fMRI studies (Smits et al., 2007), MEG (Muhlnickel et al., 1998; Llinas et al., 1999; Weisz et al., 2007b), EEG (van der Loo et al., 2009), and implanted electrode studies (De Ridder et al., 2007a, 2009) the primary involvement of the auditory cortex contralateral to the perceived tinnitus has been hypothesized (De Ridder, 2011b). A recent study confirmed this notion by demonstrating that

rTMS over temporoparietal areas is more efficient when applied contralaterally to the perceived tinnitus than ipsilaterally (Khedr et al., 2010). However this is somewhat contradictory to another recent finding that showed lower efficacy of left temporal rTMS in right-sided tinnitus as compared to left-sided tinnitus (Frank et al., 2010).

Based on recent imaging findings stressing the relevance of nonauditory areas in tinnitus, stimulation protocols have been extended to the frontal cortex. In one pilot study, 32 patients received either low-frequency temporal rTMS or a combination of high-frequency prefrontal and low-frequency temporal rTMS (Kleinjung et al., 2008). Directly after therapy, there was an improvement of the tinnitus questionnaire score for both groups, but there were no differences between groups. Evaluation after 3 months revealed a remarkable advantage for combined prefrontal and temporal rTMS treatment. These data indicate that modulation of both frontal and temporal cortex activity might represent a promising enhancement strategy for improving TMS effects in tinnitus patients.

Combination of rTMS with pharmacological intervention has been suggested for potentiating rTMS effects. It is known from animal experiments that neuronal plasticity can be enhanced by dopaminergic receptor activation (Bao et al., 2001). However, in pilot studies the administration of neither 100 mg of levodopa nor 150 mg of bupropion before rTMS was successful in enhancing rTMS effects in tinnitus patients (Kleinjung & Langguth, 2009).

There is some evidence from several studies that the clinical characteristics of patients who are treated may affect the therapeutic outcome of rTMS in tinnitus patients. Several studies reported that patients who have had their tinnitus for a short duration have better treatment outcomes (De Ridder et al., 2005; Kleinjung et al., 2007; Khedr et al., 2008). Normal hearing was also identified as a positive clinical predictor for good treatment response (Kleinjung et al., 2007; Marcondes et al., 2010). Interestingly, short tinnitus duration and normal hearing have been demonstrated to be positive predictors in other treatment options for tinnitus as well (Møller et al., 1993; Ryu et al., 1998).

2.1.5 TMS: Neurobiological Mechanisms

The mechanisms by which rTMS exerts its clinical effects on tinnitus are still incompletely understood. Low-frequency rTMS was initially introduced for the treatment of tinnitus based on the assumptions that tinnitus is related to increased neuronal activity in the auditory cortex and that 1-Hz rTMS can reduce cortical excitability by LTD-like effects (Hoffman & Cavus, 2002). This concept, however, has been challenged by many findings. First it has been shown that tinnitus is reduced by both low- and high-frequency rTMS (Khedr et al., 2008, 2010). Further, strategies that have been successful in enhancing LTD effects such as high-frequency priming stimulation (Iyer et al., 2003) or dopaminergic medication (Lang et al., 2007) were not successful in enhancing 1-Hz rTMS effects in tinnitus patients (Langguth et al., 2008a; Kleinjung et al., 2009).

The exact cortical region in which rTMS exerts clinical effects in tinnitus patients is still a matter of debate (Langguth et al., 2008b). It has been argued that the primary auditory cortex is difficult to reach by TMS because it is located far from the brain surface in the Sylvian fissure in the lateromedial direction. Further, patients with low-pitch tinnitus (cortical activation is expected to be more superficially located) do not respond better to rTMS than those with high-frequency tinnitus (Frank et al., 2010). In analogy to direct electrical stimulation, it has been assumed that rTMS might exert direct effects on the superficial secondary auditory cortex that then further propagate to the primary auditory cortex, analogous to what has been described for electrical stimulation of the secondary auditory cortex in tinnitus (De Ridder et al., 2004). A recent study that used MEG to record auditory evoked potentials demonstrated that rTMS induces changes in both primary and secondary auditory cortex activity (Lorenz et al., 2010). The auditory steady-state response, which is supposed to be generated in the primary auditory cortex, was more consistently influenced by rTMS and its changes also correlated with perceptual changes (Lorenz et al., 2010). This result is in line with findings from a tinnitus treatment study using specific auditory stimulation (Okamoto et al., 2010).

Spontaneous neuronal activity in the auditory cortex is known to be driven to some extent by thalamic activity (Llinas et al., 1999; Weisz et al., 2007a). Accordingly it is assumed that rTMS exerts the observed changes in cortical activity by interfering with thalamocortical processing (Langguth et al., 2007; May et al., 2007).

2.1.6 TMS: Conclusion

In summary, there are an increasing number of studies investigating rTMS for the treatment of tinnitus. Though encouraging, results 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 are still controversial. Effects outlast the stimulation period up to 4 years in some patients; in other studies, no long lasting after-effects were found. Replication in multicenter trials with many patients and long-term follow-up are required before firm conclusions can be drawn (Landgrebe et al., 2008). Further clinical research is also needed to obtain a clear definition of which subgroups of tinnitus patients benefit most from rTMS and how their medical histories affect the outcome. Better understanding of the pathophysiology of the different forms of tinnitus and the neurobiological effects of rTMS will be critical for optimizing or even individualizing treatment protocols.

2.2 Direct Electrical Brain Stimulation

Neuronal activity in the auditory cortex can be also modified by direct electrical stimulation via implanted electrodes. In contrast to rTMS, which can be applied for only a limited amount of time, electrical stimulation via implanted electrodes can be

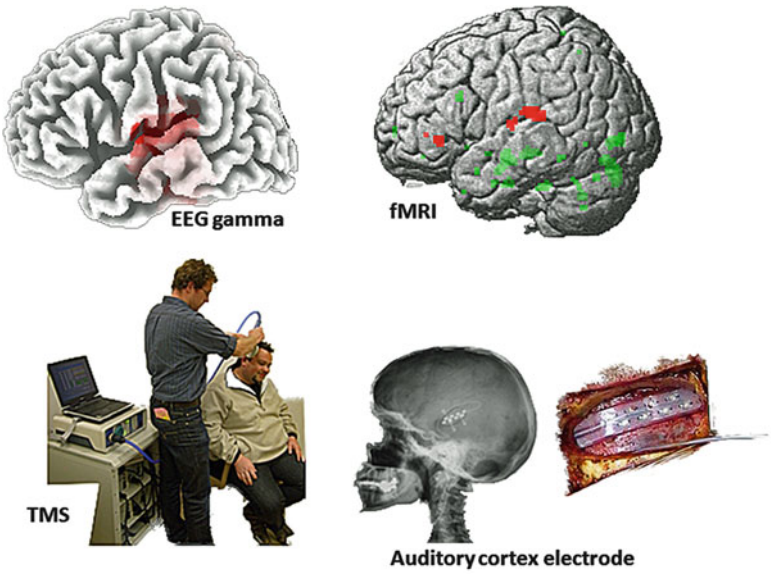

Fig. 11.2 Rationale for auditory cortex implants in the treatment for tinnitus. Tinnitus is related to gamma band activity (30–80 Hz) in auditory cortex, which can be demonstrated by EEG (upper left). This gamma band activity correlates with the BOLD effect on fMRI (upper right). This gamma band and BOLD activity can be used as a target for noninvasive TMS (lower left). If tinnitus can be successfully suppressed by TMS an electrode can be implanted on the same target (lower right)

performed permanently. Several different techniques for electric brain stimulation can be differentiated: epidural cortical stimulation, subdural cortical stimulation, and intracerebral electrical stimulation by deep brain electrodes.

2.2.1 Electrical Cortical Stimulation

Rationale and Practical Application of Auditory Cortex Stimulation

The procedure for auditory cortex stimulation has been developed based on the following four-step rationale (Fig. **11.2**):

1. Tinnitus is related to increased gamma band synchronous activity in the auditory cortex,
2. The anatomical location of the tinnitus generator can be determined by fMRI,
3. The abnormal neuronal activity can be modulated by neuronavigated transcranial magnetic stimulation resulting in transient tinnitus reduction,
4. If TMS can transiently suppress the tinnitus, electrical stimulation through an electrode implanted on the same area can provide permanent tinnitus suppression.

Both MEG (Seidman et al., 2008) and fMRI (De Ridder et al., 2007b) have been used for exactly localizing the auditory cortical hyperactivity. After performing a tinnitus matching in the MRI, the matched tone is presented during fMRI via ear phones in three ways: as a tone, a narrowband noise centered around the tone and as a wideband noise. Depending on the patient's individual tinnitus characteristics, the tone, narrowband noise (NBN) or wide band noise (WBN) evoked blood oxygenation level–dependent (BOLD) response is selected as a target for implantation. It is assumed that the localization of the evoked activity—as determined by fMRI—corresponds to the anatomical location of the tinnitus generator (De Ridder et al., 2011a). In a similar way, MEG can be fused with an MRI scan to identify the magnetic source of the auditory evoked potential (Seidman et al., 2008).

Subsequently, the exact area of the auditory cortex that is processing the tinnitus tone is stimulated by TMS. A neuronavigation system is useful for exactly localizing the target area for TMS on the patient's head. If tinnitus can be transiently suppressed by TMS of this area, an electrode is placed extradurally, overlying the secondary auditory cortex exactly at the site where fMRI demonstrated hyperactivity and where TMS was successful. Human auditory cortex consists of six different areas (Galaburda & Sanides, 1980; Rivier & Clarke, 1997) that are characterized by tonotopy (Talavage et al., 2000, 2004), one of which is the superior temporal gyrus (Talavage et al., 2000, 2004). In addition, intradural and intracerebral electrode placements have been performed. However, complication risks are much higher and treatment results are not superior to the epidural approach (De Ridder et al., 2007b). The electrode is activated by an internal pulse generator, similar to a cardiac pacemaker, placed subcutaneously in the abdomen. The stimulation parameters (frequency, amplitude, and pulse width) can be changed postoperatively by remote control to find the best parameters for maximal tinnitus control. The electrodes that are implanted can have 4–16 electrode contacts (De Ridder et al., 2007b, 2011b).

The surgery for an extradural electrode placement has been described in some detail (De Ridder et al., 2004, 2007b) and has minimal risk of complications.

Stimulation is not performed continuously because of the risk of eliciting an epileptic seizure. Switching the stimulator 5 s on and 5 s off is usually sufficient for continuous tinnitus suppression. As the patient does not feel the electrical impulses, he or she does not know whether the stimulator is on or off. With a given stimulation program the tinnitus reoccurs after a certain amount of time in most cases. Tinnitus recurrence can be prevented by running alternately several different stimulation programs using different electrode contacts (De Ridder et al., 2004, 2006a).

During the first period after the implantation the tinnitus returns very quickly when the stimulator is turned off. However, it has been observed that after years of stimulation it may take weeks before the tinnitus returns full scale when the stimulator is switched off or the battery has become drained (De Ridder et al., 2011b). It can only be hoped that after many years of stimulation the tinnitus might be absent for longer and longer periods and finally forever, even without further stimulation.

Results of Epidural Stimulation of Auditory Cortex

The largest sample comes from the TRI Tinnitus Clinic in Antwerp, Belgium, where 43 patients with severe treatment resistant tinnitus (grade 3 and 4 tinnitus according to the tinnitus questionnaire [Goebel & Hiller, 1994]) were implanted with a cortical electrode overlying the secondary auditory cortex (De Ridder et al., 2011b). Before implantation, all patients underwent tests in two TMS sessions on separate dates performed by a person not involved in the surgery. If TMS resulted in suppression of the tinnitus (>20% improvement on a visual analog scale [VAS]) on two separate occasions, the patients were considered eligible for implantation. Although all patients reacted to TMS, one out of three patients did not respond to the cortical stimulation after implantation. Among the responders to cortical stimulation there was an average decrease in the perceived tinnitus loudness of 51.3%. There was a significant but weak positive correlation ($p<0.05$) between the amount of the suppression effect from the test TMS and cortical stimulation after implantation (De Ridder et al., 2011b).

With respect to stimulation protocols, it has been observed that burst stimulation (5 stimuli of 1 ms pulse width, 1 ms interpulse interval delivered 40 times per second) is more efficient. With tonic stimulation only one in three patients responded to stimulation. With burst stimulation, half of the nonresponding patients benefitted. Burst stimulation was specifically superior to tonic stimulation for suppressing noise-like tinnitus (De Ridder et al., 2011b), analogous to what has been described for TMS (De Ridder et al., 2007c,d; Meeus et al., 2009). In contrast to TMS, in which the suppression effect decreases with longer tinnitus duration, no correlation was found between the effect of electrical cortical stimulation and tinnitus duration for the same study population, suggesting that electrical cortical stimulation acts on tinnitus by a different mechanism than TMS. Further, all patients responded to TMS, as this was an inclusion criterion for implantation, and not all patients responded to the implant.

Further, treatment effects depended on tinnitus type. Pure tone tinnitus can be suppressed better than NBN or the combination of pure tone and NBN, and unilateral tinnitus better than bilateral tinnitus, irrespective of the electrode location. This approach has been replicated by other centers with similar or different results. A French study obtained persisting 65% tinnitus reduction in a woman using an fMRI-based extradural auditory cortex implant (Litre et al., 2009, 2010). Another study of eight patients using a similar technique but different hardware found no permanent tinnitus suppression (Friedland et al., 2007). In six out of the eight patients, temporary effects on tinnitus perception were observed. However, tinnitus distress decreased slowly over time, even without suppression of tinnitus intensity. This may be related to the fact that an electrode with only two contacts was used, which limits the way the electrodes can be programmed. The finding of decreased tinnitus distress with unchanged tinnitus intensity could possibly be explained by disruption of the phase synchronization between the "general distress network" and the tinnitus-related activity in the auditory cortex (De Ridder et al., 2008). Intracortical microstimulation in the auditory cortex of animals disrupts not only local ongoing activity but also long-range connections in a larger network (Deliano

et al., 2009), similarly to findings in humans using TMS of auditory cortex (Langguth et al., 2007; May et al., 2007).

In some patients, tinnitus suppression can be obtained but only for short times (1–3 days) after which the effect wears off, even after reprogramming the stimulation several times. This might be due to plasticity of the secondary auditory cortex. In four patients an intradural electrode on the primary auditory cortex was inserted in the Sylvian fissure, stimulating gray matter of primary auditory cortex (De Ridder et al., 2004, 2006a). In two patients the purpose was to obtain stabilization of tinnitus suppression, because the stimulus parameters had to be reprogrammed every 2–3 days. In both patients the intradural positioning resulted in a stabilized suppression of their tinnitus, suggesting a different reaction pattern of primary auditory cortex to electrical stimulation.

Another approach has been proposed, inserting a wire electrode in the white matter beneath layer 6 of the primary auditory cortex. This has been performed successfully, using magnetic source imaging for target localization, resulting in tinnitus suppression (Seidman et al., 2008).

Recent animal studies, using electrical stimulation of the auditory cortex significantly suppressed behavioral evidence of tinnitus and enhanced hearing detection (Zhang et al., 2011). Such suppression of tinnitus and enhancement of hearing detection were respectively demonstrated by a reversal of tone exposure compromised gap detection and compromised prepulse inhibition. On the contrary, auditory cortex stimulation did not induce behavioral changes in animals that did not manifest any behavioral evidence of tinnitus and compromised hearing detection after the same tone exposure. The results point out that tinnitus may be more related to compromised central auditory processing than hearing loss at the peripheral level. Thus, the induced suppression of behavioral evidence of tinnitus by electrical stimulation of auditory cortex may involve restoration of abnormal central auditory processing (Zhang et al., 2011).

Mechanisms of Direct Electrical Stimulation of Auditory Cortex

There is consensus in the scientific community that tinnitus develops as a consequence of reduced auditory input (see also Noreña, Chapter 10). Restoring auditory input by hearing aids (Moffat et al., 2009; Schaette et al., 2010) or cochlear implants (Van de Heyning et al., 2008) reduces tinnitus. In this context, one may speculate that direct electrical stimulation exerts its therapeutic effect by providing input to the deafferented area of auditory cortex (De Ridder et al., 2004, 2007b). It is also known from animal studies that electrical simulation through an electrode that is placed on the area of cortical hyperactivity can normalize reorganized tonotopic maps in auditory cortex through egocentric selection (Suga et al., 2000) of the entire tonotopic pathway all the way to the cochlea (Perrot et al., 2006).

Auditory cortex stimulation may also result in suppressing the tinnitus by interfering with hypersynchronous gamma band activity (De Ridder et al., 2011a), which is thought to code tinnitus intensity (van der Loo et al., 2009), and which is an

important hub in the tinnitus related network (Schlee et al., 2008a, 2009a). In a recent study using MEG during electrical stimulation of auditory cortex, the stimulation increased spectral correlation across low and high gamma band activity; between alpha and beta activity, but delta/theta activity decreased, suggesting that auditory cortex stimulation does indeed affect thalamocortical dysrhythmia (Ramirez et al., 2009). This has been confirmed by recordings from electrodes overlying the secondary auditory cortex. Maximal tinnitus suppression was obtained by current delivery exactly at the BOLD spot, elicited by tinnitus-matched sound presentation in the MRI machine, which colocalizes with increased gamma and theta activity, in contrast to the other electrode poles. These spectral changes normalize when stimulation induces tinnitus suppression, both on electrode- and source-localized EEG recordings. Further, only at the BOLD area autocorrelations of the current densities for each frequency showed theta–gamma coupling, meaning that theta and gamma current densities co-occur at the area of BOLD activation. This spatial co-occurrence does not mean the theta and gamma are temporally or phase coupled or nested. This confirms the hypothesis that theta–gamma might be causally related to a conscious auditory phantom percept, as proposed by the model of thalamocortical dysrhythmia (Llinas et al., 1999; De Ridder et al., 2011a). These findings support the idea that electrical stimulation reduces tinnitus perception by interfering with the abnormal thalamocortical dysrhythmia embedded in a larger tinnitus network.

One difficulty of the thalamocortical dysrhythmia model is that it proposes that the tinnitus pitch is at the edge frequency, which is not in accordance with clinical data (Noreña et al., 2002), suggesting that the tinnitus pitch matches the deafferented frequencies. Some hypothetical explanations have been offered for this contradiction requiring the unproven presence of dendritic sprouting in the deafferented areas (De Ridder & Van de Heyning, 2007).

2.2.2 Deep Brain Stimulation

Rationale for Deep Brain Stimulation

Tinnitus-related changes in neural activity encompass both auditory and nonauditory brain areas. It is assumed that tinnitus related pathological activity can be best conceptualized as an altered neuronal network (Schlee et al., 2008b, 2009a,b). This tinnitus-related network involves the auditory system, frontoparietal awareness–related areas, an unspecific distress system, and memory-related brain areas. Superficial parts of this network such as the temporal cortex, the dorsolateral prefrontal cortex, or the temporoparietal cortex can be modulated by rTMS or epidural stimulation and these approaches have demonstrated some promise in altering tinnitus perception and distress (see Sections 11.3 and 11.4.1). However, the limited effects of the superficial stimulation techniques may be due to the fact that they are not sufficient to efficiently disturb tinnitus-related network activity. Most efficient interruption of the “tinnitus networks” is expected when network hubs are targeted. This could be achieved by targeted deep brain stimulation. The challenge of this

approach is the identification of the critical hubs in the individual patient. In a pilot study the involvement of the amygdohippocampal area was investigated by selective amobarbital injection (De Ridder et al., 2006b). Recently, the subgenual cingulated cortex/nucleus accumbens area, a target area for deep brain stimulation of treatment-resistant depression (Mayberg et al., 2005), has been suggested to represent a potential target for tinnitus treatment as well (Rauschecker et al., 2010).

Studies Investigating Deep Brain Stimulation for the Treatment of Tinnitus

To our knowledge, there are no published reports of patients who received deep brain stimulation (DBS) for the treatment of tinnitus. However, results are available from patients who received DBS in the ventralis intermedius nucleus of the thalamus (Shi et al., 2009) or in the caudate nucleus (Cheung & Larson, 2010) for movement disorders who also reported having tinnitus.

Thalamic DBS has been used to treat multiple neurological symptoms, one of which is chronic pain. Because tinnitus may share mechanisms similar to those of other neurological symptoms such as chronic pain, DBS may also be effective for treating tinnitus (Shi et al., 2009).

In one study, seven patients implanted with DBS systems for movement disorders who also reported having tinnitus were interviewed and asked about their tinnitus conditions. Three of the seven patients reported reduced tinnitus loudness when DBS was turned on. Of the four patients tested in a specialized tinnitus clinic, results indicated that DBS of the ventralis intermedius nucleus of the thalamus decreased tinnitus loudness in two patients with relatively prolonged residual inhibition (Shi et al., 2009).

The caudate is routinely traversed during DBS implantation of the subthalamic nucleus and ventral intermediate nucleus in awake patients for treatment of Parkinson's disease and essential tremor, respectively. In six tinnitus patients who underwent DBS for movement disorders the effect of DBS in the locus of caudate neurons (area LC) was evaluated with respect to the patients' tinnitus. In five subjects tinnitus loudness in both ears was suppressed to an intensity level 2/10 or less. In one subject, where the DBS lead was outside the area LC tinnitus was not modulated. Hearing thresholds were unchanged by area LC stimulation.

These results suggest that DBS of nonauditory thalamus and caudate structures may provide tinnitus relief for some patients. The mechanisms involved in tinnitus suppression by DBS are yet unknown, but should be explored further.

2.2.3 Conclusion and Outlook of Direct Electrical Brain Stimulation for Tinnitus

Direct electrical brain stimulation for the treatment of tinnitus is currently still at a very early stage of development. Nevertheless, extradural stimulation of secondary auditory cortex has demonstrated preliminary promising results in patients with

severe and otherwise intractable tinnitus. The subgroup of patients in whom the tinnitus is completely suppressed by electrical stimulation is an especially impressive proof of the principle of this approach. Recent advances in the understanding of the pathophysiology of tinnitus suggest good alternative targets to auditory cortex. Development of new stimulation designs as well as the application of network science might, in the near future, improve results of neurostimulation techniques. Based on advanced neuroimaging methods it should be possible to identify the essential hubs of the tinnitus related neuronal network in an individual patient, which then can be targeted by neuromodulation.

Moreover, the results from brain stimulation, both successful tinnitus suppression and treatment failures, are important complementary information to neuroimaging for understanding the mechanisms of tinnitus generation and maintenance. Further, recordings from implanted electrodes provide a unique possibility for deciphering the neural code of tinnitus.

3 Pharmacologic Treatment

The market for a drug that specifically targets tinnitus is huge. The Royal National Institute for Deaf People (RNID) in the United Kingdom estimates that a novel tinnitus drug could have a product value of U.S.$689 million in its first year of launch (Vio & Holme, 2005). However, currently there is still no drug on the market that is approved by the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) for the treatment of tinnitus. More than 4 million prescriptions are written each year for tinnitus relief in Europe and the United States, but these are all off-label prescriptions from a wide variety of compounds (Vio & Holme, 2005).

3.1 Tinnitus Can Be Pharmacologically Treated

Neuronal excitability can be modulated by different neurotransmitters, neuromodulators, and compounds acting on voltage-gated channels. Thus, there is no a priori reason to believe that tinnitus cannot be pharmacologically treated. The best proof is the transient disappearance of tinnitus in up to 70% of patients after intravenous application of the voltage-gated sodium channel blocker lidocaine (Melding et al., 1978; Trellakis et al., 2007).

Unfortunately, the lidocaine effect on tinnitus occurs only after intravenous application, it is short-lasting and side effects are considerable (Gil-Gouveia & Goadsby, 2009). Oral antiarrhythmic drugs such as tocainide, flecainide, and mexiletine have been investigated for tinnitus, however, without much success (Dobie, 1999; Darlington & Smith, 2007).

3.2 Treatment of Acute Tinnitus

There is a consensus among clinicians and researchers that the pathophysiology underlying the onset of tinnitus may differ from that of chronic tinnitus. Therefore, treatment approaches will probably vary with the duration of the disease. There is no pathophysiologically founded border between "acute" and "chronic" tinnitus. The currently used distinction is arbitrary and varies between 3 and 6 months.

Immediately after tinnitus onset, more causally oriented treatment approaches might be possible and involvement of the cochlea might still be important. In case of abrupt-onset tinnitus associated with sudden hearing loss or noise trauma, treatment strategies that restore hearing function are expected to have beneficial effects on tinnitus. A special form of acute tinnitus is that associated to sudden hearing loss. No specific sound frequency region in the cochlea appears to be preferentially affected, and the severity of hearing loss ranges from mild to profound. Up to 65% of patients experience spontaneous recovery of pre-loss hearing; others experience no recovery at all. The high variability suggests that there are different forms of sudden hearing loss with different etiologies. Among others, vascular, inflammatory, and infectious mechanisms are probably involved.

Another specific form of acute tinnitus is that associated to noise-induced hearing loss produced by exposure to a blast or after a rock concert. Noise at levels of 85 A-weighted decibel (dBA) and higher can lead both to mechanical and metabolic damage of the cochlea (Lim, 1986). Single, repeated, or continuous exposure to high levels of noise can cause noise-induced hearing loss and tinnitus. Excessive noise can cause immediate and direct irreversible structural damage to the hair cell bundles and can generate in a second phase potentially reversible or preventable excitotoxic effects on the sensory nerve terminals (Puel et al., 2002). Hair cells die by apoptosis and cannot be replaced. Loss of hair cells leads to loss of spiral ganglion neurons, which depend on hair cells for the production of survival factors such as the neurotrophin NT-3 and brain-derived neurotrophic factor. Accumulation of free radicals, excitotoxicity mediated by glutamate receptors, and activation of apoptosis are predictable factors in the loss of cells (Holley, 2005). Animal experiments show that growth factors and drugs directed against apoptosis, excitotoxicity, and oxidative stress can provide valuable protection from hearing loss and tinnitus if applied during exposure (Lynch & Kil, 2005) and also probably immediately after exposure.

Various otoprotectants are in clinical development for preventing noise-induced hearing loss and associated tinnitus. Daily supplements of 4 g of oral magnesium granulate (6.7 mmol of magnesium aspartate) significantly reduced hearing loss after noise compared to placebo in a double-blind placebo-controlled study involving 300 young and healthy military recruits (Attias et al., 1994). In contrast, 900 mg of the glutathione prodrug *N*-acetylcysteine 30 minutes before exposure to 2 hours of loud music (mean noise level of 98.1 dB) had no beneficial effects on temporary threshold shifts compared to placebo (Kramer et al., 2006). In animal models, high doses of

N-acetylcysteine are required to effectively prevent noise-induced hearing loss. Several ongoing trials are being performed to test the efficacy of this compound (Kopke et al., 2007). SPI-1005 (ebselen), an antioxidant developed by Sound Pharmaceuticals is currently tested in phase II trials with the Navy/Marine Corps. AM-101, an *N*-methyl-D-aspartate (NMDA) antagonist for the treatment of tinnitus after noise trauma has been developed by Auris Medical and shown to be safe in a phase II trial (Muehlmeier et al., 2011). Summarizing, there is consensus among clinicians that acute tinnitus deserves specific attention and that there might be a short therapeutic window for specific pharmacological interventions, even if there are yet no treatments available that have shown repeated efficacy in controlled trials.

3.3 Treatment of Chronic Tinnitus

There is no specific pharmacological compound that has been approved for the treatment of tinnitus. But a large variety of drugs that are approved for other indications are used for the treatment of chronic tinnitus in clinical practice. Some of these compounds have also been investigated in clinical trials. Here we discuss the most relevant results, sorted by the type of drugs tested.

3.3.1 Antidepressants

Antidepressants are frequently proposed for the management of chronic tinnitus (Robinson et al., 2007). The main reason for the large use of antidepressants is the comorbidity between depressive disorders and tinnitus. Among all antidepressants that have been investigated for tinnitus, a particular interest has been paid to tricyclic antidepressants, mainly because of their beneficial effects on chronic pain syndromes (Mico et al., 2006). In a small-scale, single-blind placebo-washout study involving patients with severe tinnitus and major depression, nortriptyline significantly reduced depression and tinnitus loudness (10 dB reduction) (Sullivan et al., 1989). In a follow-up double-blind placebo-controlled study involving subjects with severe tinnitus and depressive symptoms, nortriptyline significantly reduced depression scores, tinnitus disability scores, and tinnitus loudness (6.4 dB reduction) relative to placebo (Sullivan et al., 1993). There was a significant correlation between the reduction in tinnitus disability scores and depression scores, suggesting that nortriptyline is especially effective in severely depressed tinnitus patients, but has less benefit in nondepressed individuals with tinnitus (Katon et al., 1993). One study compared amitriptyline with placebo and after treatment for 6 weeks with 100 mg amitriptyline found a significant reduction of tinnitus complaints and tinnitus loudness compared to the placebo group (Bayar et al., 2001). A small double-blind placebo crossover study did not demonstrate a difference between trimipramine and placebo treatment (Mihail et al., 1988). It should also be noted that the induction and worsening of tinnitus with tricyclic antidepressants has been reported (Tandon et al., 1987).

Among the selective serotonin reuptake inhibitors (SSRIs), paroxetine and sertraline were tested in tinnitus. In a randomized double-blind placebo-controlled study of patients without severe hearing loss, but with depression, anxiety, and a high risk for developing severe tinnitus, sertraline was significantly more effective than placebo in reducing tinnitus loudness and tinnitus severity (Zoger et al., 2006). In a double-blind, placebo-controlled study involving chronic tinnitus patients, few of whom suffered from depression, the paroxetine group showed little difference from placebo on tinnitus loudness matching, Tinnitus Handicap Questionnaire (THQ) scores, and other measures; however, the paroxetine group showed a significant improvement on tinnitus aggravation compared to the control group (Robinson et al., 2007).

It has to be considered that the scales used for the measurement of tinnitus correlate highly with depression scales (Crocetti et al., 2009). Thus, the observed reduction of tinnitus severity under antidepressant treatment might—at least to some extent—be a pure consequence of the antidepressant effect of the investigated drugs. Nevertheless, available data provide converging evidence that tinnitus patients with depression and anxiety may gain benefit from antidepressant treatment and clearly suggest that the use of an antidepressant in this patient group is highly indicated. However, available results do not allow for determining whether one specific compound is superior to others (Robinson et al., 2007). Therefore, in clinical practice, selection of the antidepressant drug should be guided by the patient's comorbidities and the side effect profile of the specific drug.

3.3.2 Benzodiazepines

Because benzodiazepines are allosteric potentiators of the γ-aminobutyric acid A ($GABA_A$) receptor and tinnitus is thought to be the result of an imbalance between excitatory and inhibitory neurotransmission toward the former, benzodiazepines should have a positive effect on tinnitus by increasing inhibitory neurotransmission. Further, owing to their anxioloytic and sleep-inducing properties, benzodiazepines should have beneficial effects on comorbid anxiety and insomnia.

In a small double-blind placebo-controlled study, 12 weeks of alprazolam administration at an individually adjusted dosage reduced tinnitus loudness in 76% of subjects —measured with a tinnitus synthesizer and a visual analog scale—whereas only 5% showed a reduction in tinnitus loudness in the control group (Johnson et al., 1993). However, emotional aspects of tinnitus were not assessed and the data were never replicated. Diazepam, evaluated in a double-blind triple crossover trial involving 21 tinnitus patients, had no effect on tinnitus loudness (Kay, 1981). In a prospective, randomized, single-blind clinical trial involving 10 patients per group, clonazepam significantly reduced tinnitus loudness and annoyance (visual analog scale) relative to the control group (Bahmad, et al., 2006). A potential beneficial effect of clonazepam is further suggested by a retrospective study analyzing medical records from more than 3000 patients taking clonazepam (0.5–1 mg/day, 60–180 days) for vestibular or cochleovestibular disorders, in which 32% reported

an improvement in their tinnitus (Gananca et al., 2002). Summarizing, given the side effect profile of benzodiazepines, especially the risk of drug dependency, the available data are by far not sufficient to recommend the use of benzodiazepines for the treatment of tinnitus. Moreover, caution is warranted because protracted tinnitus has been reported after discontinuation of benzodiazepines (Busto et al., 1986, 1988).

3.3.3 Non-benzodiazepine Anticonvulsants

Anticonvulsants are increasingly used in the treatment of several non-epileptic conditions, including various psychiatric disorders and pain syndromes. Some of them have also been investigated for the treatment of tinnitus. Diverse pharmacological mechanisms of action are responsible for the therapeutic effects of antiepileptics; among them, effects on voltage-gated sodium and calcium channels, and on synaptic transmission—mainly mediated by $GABA_A$ receptors. Because antiepileptics reduce neuronal excitability, in principle they should be beneficial for the treatment of tinnitus.

Carbamazepine reduces neural firing by binding to voltage-gated sodium channels and stabilizes the sodium inactivation state. Based on the assumption that carbamazepine resembles lidocaine in its mechanism of action, several studies have investigated the effect of carbamazepine in tinnitus patients who previously had responded to intravenous lidocaine (Shea & Harell, 1978; Melding & Goodey, 1979). However, placebo-controlled studies did not reveal any positive effects (Donaldson, 1981; Hulshof & Vermeij, 1985). In contrast, a significant benefit from carbamazepine has been reported for a rare group of patients who have intermittent tinnitus that sounds like a typewriter or ear clicking and that is caused by a neurovascular conflict (Mardini, 1987; Levine, 2006).

Gabapentin is an anticonvulsant that acts on voltage-gated calcium channels and is used for the treatment of seizures, neuropathic pain, and migraine. One controlled trial has shown a significant improvement in tinnitus annoyance and loudness for a subgroup of participants with tinnitus related to acoustic trauma (Bauer & Brozoski, 2006). A second study did not detect improvement in tinnitus handicap, but did report a significant improvement in tinnitus annoyance when compared to placebo (Witsell et al., 2007). However, further controlled trials did not report any benefit of the compound on tinnitus annoyance or loudness (Piccirillo et al., 2007; Bakhshaee et al., 2008). Thus, gabapentin might benefit a subpopulation of patients in whom tinnitus is associated with acoustic trauma (Bauer & Brozoski, 2007).

Lamotrigine inhibits voltage-sensitive sodium channels and is a membrane stabilizer. It has been investigated in a double-blind placebo-controlled crossover clinical trial of 33 tinnitus patients and failed to demonstrate a beneficial effect (Simpson et al., 1999). Valproic acid is one of the most frequently prescribed antiepileptic drugs and acts by multiple mechanisms. It has not been systematically investigated for tinnitus and has been reported as useful only in isolated case reports (Mansbach & Freyens, 1983; Menkes & Larson, 1998).

3.3.4 Antiglutamatergic Compounds

Glutamate receptor antagonists have been tried in tinnitus sufferers with the goal to reduce excitatory neurotransmission in the auditory pathway. Blocking glutamatergic neurotransmission after noise overexposure is thought to prevent noise-induced excitotoxic injury of hair cells (Guitton et al., 2004). The putative nonselective NMDA receptor antagonist acamprosate has been tried in a double-blind study (Azevedo & Figueiredo, 2007). Acamprosate had no beneficial effects after 30 days of treatment, a modest benefit at 60 days, and a significant effect at 90 days. Approximately 87% of the subjects in the acamprosate group showed some improvement, compared to 44% in the placebo group. A larger clinical trial is currently underway (http://clinicaltrials.gov/ct2/show/NCT00596531).

Treatment with intravenous caroverine, an antagonist of non-NMDA and NMDA receptors, has been analyzed with contradictory results (Denk et al., 1997; Domeisen et al., 1998). The nonselective NMDA antagonist memantine was no more effective than placebo in a prospective randomized double-blind crossover 90-day treatment study using the Tinnitus Handicap Inventory to assess efficacy (Figueiredo et al., 2008). The memantine analogue neramexane, which blocks both NMDA and $\alpha 9\alpha 10$ nicotinic cholinergic receptors (Plazas et al., 2007), has shown beneficial effects on tinnitus in a phase II study (Suckfuell et al., 2011) and is currently investigated in several phase III clinical trials (http://clinicaltrials.gov/ct2/show/NCT00405886).

3.3.5 Dopaminergic/Antidopaminergic Drugs

Dopaminergic pathways in limbic and prefrontal areas may be involved in mediating emotional aspects of tinnitus. Dopamine also has an inhibitory function in the cochlea suggesting a potential role in the early phase of tinnitus. Thus, both dopaminergic and antidopaminergic drugs have been proposed for the treatment of tinnitus. In one double-blind placebo-controlled study, the dopamine antagonist sulpiride significantly reduced subjective ratings of tinnitus and tinnitus visual analogue scores. Effects were more pronounced when sulpiride was combined with either hydroxyzine (an antihistamine and anxiolytic) or melatonin (Lopez-Gonzalez et al., 2007a,b). The dopamine agonist piribedil was investigated in a double-blind placebo-controlled crossover study. Piribedil was not superior to placebo; however, a post hoc analysis suggested that a subgroup of patients with specific findings in the electrocochleography may benefit from the drug (de Azevedo et al., 2009). Although these results are preliminary and to some extent contradictory, they warrant further exploration of the modulation of the dopaminergic system.

3.3.6 Drug Combinations

One should also consider that a combination of different drugs may be more effective than a single drug alone. Such a combination treatment could consist of different

drugs, even if each one in isolation has shown only some limited benefit for tinnitus suppression. Thus, further specific clinical trials for drug combinations are needed. One such example is the combination of a neuroleptic drug, a tricyclic antidepressant, and a benzodiazepine. The use of Deanxit (neuroleptic flupentixol + tricyclic melitracen) as add-on treatment to clonazepam has been recently investigated in a pilot study using a double-blind placebo-controlled crossover design. Deanxit was superior to placebo with respect to the time patients are aware of the tinnitus ($p = 0.026$) and the visual analogue scale for tinnitus annoyance ($p = 0.024$) (Meeus et al., 2011). It is unknown whether flupentixol or melitracen or both exert the tinnitus improving effect, as both tricyclic and dopamine-blocking compounds have been suggested to have beneficial effects.

3.4 Pharmacological Treatment: Developmental Issues

Why do no approved tinnitus drugs exist in spite of the existence of such a huge market for a clinically unmet need? One reason is probably that the lack of serendipitous discoveries of effective treatments has severely limited insight into tinnitus pathology. An additional challenge in the design of drugs for the treatment of tinnitus derives from the fact that the underlying neural substrates are far from being understood. In addition, modern drug discovery mainly focuses on the identification of new chemical entities interacting with discrete molecular targets. This is a reductionist approach that requires the knowledge of defined sites of drug action with a known clinical relevance but is not the scenario faced in the case of tinnitus. The absence of a fully determined neuronal correlate/s for tinnitus makes research into this area potentially very high risk. However, the empirical approach that has been used for most central nervous system (CNS) disorders should not be precluded in the case of tinnitus. Most innovative CNS-acting drugs were discovered serendipitously (Howland, 2010). Advances in the understanding of tinnitus pathophysiology reveal a large number of similarities with other disorders of the CNS, such as chronic pain. Thus, any new compound under development for any of these conditions should also be tested in the case of tinnitus patients.

Another drawback is the lack of in vitro bioassays or validated animal models in which to test or screen for compounds. The basic dilemma faced by animal researchers is whether animals have tinnitus (Turner, 2007; Lobarinas et al., 2008). An additional challenge is imposed by the fact that, in humans, tinnitus is accompanied by the activation of a distress network that involves the limbic system (Vanneste et al., 2010a), which is probably not recapitulated in the animal models. Different animal models have been developed for acute tinnitus perception (Jastreboff et al., 1988; Bauer & Brozoski, 2001; Lobarinas et al., 2004). However, it is questionable to which extent results from the currently available animal models can predict effectiveness of a drug on severity of chronic tinnitus in humans. Thus, there is a clear need for developing animal models of chronic tinnitus that also include detection of the extent of tinnitus-evoked emotional or cognitive changes. However, even in

diseases in which there is a greater mechanistic understanding, there are still significant disparities between the animal models used in discovery validation and the human diseases being targeted for treatment (Hurko & Ryan, 2005). Thus, the search for drugs to treat tinnitus should not wait for a complete understanding of the neural correlates of tinnitus or the refinement of the animal models.

Finally, because the first tinnitus drugs are yet to be approved, regulatory agencies such as the FDA or the EMA lack standardized protocols for their approval process. Therefore, the first pharmaceutical industry to develop a tinnitus drug will have to lead the way. This will be most successful as a collaborative effort with tinnitus researchers providing informed direction to drug companies and developing better lines of communication.

3.5 Pharmacologic Treatment: Conclusions

Despite the significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA-approved drug on the market. Although the available treatments for the management of the tinnitus patient are diverse, most patients and clinicians are waiting for a drug than can suppress or significantly reduce tinnitus. Thus, there is a pressing need to develop a drug or a combination of drugs for tinnitus relief. A wide variety of drugs with different therapeutic uses have been used off-label with some effect in a limited subset of patients. Tinnitus-related comorbidities such as depression or anxiety can especially be addressed successfully with pharmacological treatment. Because pharmaceutical companies are slowly entering the tinnitus field, this scenario most likely will change in the near future.

4 Outlook

Our understanding of phantom perception has evolved from a "peripheral" to a "primary sensory cortex," into a "static network," reaching a "dynamic multiple parallel network" problem. Possibly different and pathophysiologically separable mechanisms might lead to the same phantom percept, explaining why treatment is so difficult. Animal research, psychophysiological studies, and neuroimaging have contributed to these advances in the understanding of the generation and the maintenance of tinnitus. But an important contribution has come also from interventional studies both with pharmacological compounds and with brain stimulation. Assessing intervention effects both on a behavioral and on a neuronal level will be essential for a more detailed knowledge of tinnitus and for the further development of treatment approaches.

New pharmaceutical compounds for tinnitus are under development, and new brain stimulation techniques such as vagus nerve stimulation (VNS) (Engineer et al., 2011) and transcranial direct current stimulation (tDCS) (Vanneste et al., 2010b, 2011)

are currently being tested. Hypothesis-driven combination of different treatment methods might result promising (Engineer et al., 2011). Thus, pharmacological treatment or specific brain stimulation may be powerful in enhancing the therapeutic effects of sound stimulation or cognitive behavioural therapy. Given the fast advancement during the last decade both in understanding of the underlying mechanisms generating tinnitus and in treatment strategies, more efficient therapies are expected to appear in the near future.

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