CHAPTER 9

General conclusions, discussion and future perspectives
Introduction

This thesis describes new insights into pathophysiology, diagnosis and treatment of chronic, subjective tinnitus. In this final chapter general conclusions concerning the main objectives of this thesis are formulated. Implications for further research and clinical practice are described.
General conclusions

The results of the seven chapters have provided answers concerning the main objectives of this thesis as stated in the introduction paragraph. These objectives concern new insights into tinnitus pathophysiology, diagnosis and treatment.

Objective 1. Pathophysiology
The first objective was the evaluation of current ideas about the manifestations of neural plasticity in generating tinnitus in order to improve our knowledge about tinnitus pathophysiology. The tonotopically organized receptive fields of the auditory pathways can be dynamically modified because of early and late-onset neural plastic processes, in order to adapt to altering afferent input and compensate for the effects induced by injury or diseases at peripheral level. Unmasking of dormant synapses, reduced (surround) inhibition and initiated creation of new connections through axonal sprouting are early manifestations of neural plasticity. Extended axonal sprouting and reorganization of tonotopic receptive fields are late effects of neural plasticity. Our hypothesis is that maladaptive neural plasticity and reorganization of the auditory pathways lead to hyperactivity and hypersensitivity of the central auditory pathways, with the perception of tinnitus as a consequence.

Neuroimaging techniques, like PET and fMRI, demonstrated to enable us to visualize tinnitus-related neural activity in the central nervous system. By objectifying tinnitus-related neural activity, neuroimaging techniques improve our knowledge about tinnitus pathophysiology.

Objective 2. Diagnosis
The second objective was the development of a clinical, multidisciplinary approach in diagnosing tinnitus. Guidelines for clinical evaluation consist of a multidisciplinary, individually applicable, set of assessment tools for chronic subjective tinnitus patients visiting an outpatient clinic. Some parts of the protocol are indicated in clinical evaluation of every patient, other parts are recommended to be performed only on indication. Besides interview, physical and otological examinations, audiological evaluation, laboratory and radiological assessments, our results underline the role of questionnaire assessments in the clinical evaluation of chronic, subjective tinnitus. Advantage of the suggested set of questionnaires is the individual applicability of each questionnaire by means of presented cut-off scores. The proposed questionnaires assess personality traits, psychological distress and tinnitus severity. According to our results from questionnaire evaluation we have formulated the following recommendations for investigating personality characteristics and psychological distress associated with tinnitus:

- Type D personality turned out to be strongly associated with having tinnitus, with a substantial greater impact than previously investigated personality traits neuroticism, extraversion and social inhibition. In addition to this, type D directly influences mental and physical health-related quality
of life and tinnitus severity. Even more important is the mediating role of type D personality on the implications of psychological distress on impairing health-related quality of life and increasing tinnitus severity.

- For its substantial role on impairing health-related quality of life and enhancing tinnitus severity, we recommend investigating *vital exhaustion* as indicator of psychological distress besides anxiety and depression.

- The additive, and sometimes synergistic, effect of anxiety and depression underlines the assessment of both indicators of psychological distress in the clinical evaluation of tinnitus.

The multidisciplinary character of the protocol enables the clinician to identify the etiological problems related to the onset of tinnitus, to differentiate between different forms of tinnitus, and to describe medical, audiological and psychological tinnitus characteristics.

**Objective 3. Treatment**

The third objective of this thesis was the evaluation of innovative techniques for tinnitus modulation via chronic electrical stimulation of the vestibulocochlear nerve and transcranial magnetic stimulation. Neuromodulation via electrical stimulation of the vestibulocochlear nerve shows to be able to alter the tinnitus perception successfully. Restoring the afferent input in unilaterally deaf subjects by means of continuously, electrical stimulation of the most peripherally located part of the auditory pathways, is presumably able to manipulate the effects of neural plasticity responsible for tinnitus.

The inhibiting effect of low frequency TMS located at the auditory cortex, turns out to transiently modulate tinnitus in a few tinnitus subjects. Therefore, TMS seems to be capable of diagnosing tinnitus location. Nevertheless, major limitations currently contributed to TMS (no consensus about stimulation parameters, interindividual variety, depth of penetration and site of stimulation) need to be improved before successfully applying TMS as a possible treatment modality.

**General discussion and future perspectives**

**Pathophysiology**

The pathophysiological processes associated with tinnitus are only partly understood, mainly caused by the subjective character of tinnitus. A review of literature about tinnitus and related manifestations of neural plasticity in other disorders (mainly chronic phantom pain) was used as basis for answering the first objective of this thesis. The increasing role of neuroimaging and animal studies have increased the fundamental insight into tinnitus pathophysiology. Consequently, it is nowadays generally accepted that chronic subjective tinnitus is generated along the auditory pathways, somewhere from cochlea up to auditory cortex, as a result of early and late effects of neural plasticity.
Although scientific research markedly increased the fundamental insight into tinnitus pathophysiology up to now, many questions remain unsolved. Why are some individuals affected with tinnitus and others with comparable etiology aren’t? For what reason does tinnitus consist of taxonomy of (non-meaningful) sounds without inter individual uniformity? Is there a difference in pathophysiological mechanisms between chronic, subjective tinnitus with an acute or gradual onset? Are all manifestations of neural plasticity finally reversible if the disturbed pattern of input is completely restored? Which areas of the central nervous system are mainly responsible for the generation of tinnitus and are these areas inter individually comparable? Is tinnitus really generated via the nonlemniscal system and does that really explain some tinnitus subjects to be able to modulate their tinnitus perception by stimulating visual or somatosensory systems?

Overall, we can estimate that, in order to improve our knowledge about tinnitus pathophysiology, more scientific research is essential. This scientific research can be based on the following developments;

a) increasing role of neuroimaging techniques, like fMRI and PET
b) development of tinnitus animal models, based on tinnitus-inducing mechanisms like noise-trauma or pharmaceutical manipulations
c) scientific research performed on other manifestations of hyperexcitability of the central nervous system, diseases or symptoms in analogy with tinnitus

The increasing role of neuroimaging techniques (like fMRI and PET) in objectifying tinnitus-related neural activity was described in Chapter 8 of the thesis. Preliminary results of these studies showed tinnitus-related neural activity in a variety of areas in the central nervous system. By means of fMRI, tinnitus-related neural activity in normal-hearing, unilateral tinnitus patients was demonstrated at the level of both inferior colliculi. PET was used for visualizing the effects on cerebral perfusion when comparing ON and OFF conditions of electrical neurostimulation of the vestibulocochlear nerve via an implanted device (Chapter 7). Although these PET-images predominantly concern the effects induced by the neurostimulation system (ON minus OFF), the results of this study demonstrate that tinnitus-related neural activity probably concerns more neural circuits than the auditory system alone.

Unfortunately, current quality of neuroimaging devices is not sufficient to visualize tinnitus-related neural activity images in detail. Tinnitus-related neural activity can nowadays only be visualized by the subtraction of cerebral perfusion of two conditions. Therefore, tinnitus subjects who are able to modulate their tinnitus, thereby creating two conditions of neural activity, have already proved to be particularly useful for these studies.

The first group of patients suitable for neuroimaging studies are patients with unilateral or lateralized tinnitus as presented in the fMRI study of Chapter 8 and Melchers study (2). Since the results of our study were contradictory to Melchers results, further investigation of unilateral tinnitus subjects is indicated. In order to improve future research, investigating more uniform patient groups with...
comparable tinnitus characteristics might be indicated. These tinnitus characteristics can be grouped according to tinnitus location, acute versus gradual onset, tonal versus noise-like tinnitus, and continuous versus intermittent tinnitus. A difference in pathophysiological mechanisms can be responsible for this variety in tinnitus characteristics, possibly identifiable with improved neuroimaging devices.

The second group useful for neuroimaging studies are those patients who are able to modulate their tinnitus sensation by a voluntary act, already described in several studies (3-8). The modulation of tinnitus by voluntary act can presumably be explained by cross-modal plasticity along the non-classical pathway (as described in Chapter 1). Since on and off situations of tinnitus perception can be created in these patients, they can function as their own control group. Unfortunately, since the ability of modulating tinnitus is present in a few patients, previously performed studies only concern a small number of patients. The use of uniform scanning procedures and evaluation techniques, creates opportunities for addition of tested results determined in various clinics. Consequently, larger patient numbers can be generated and more fundamental conclusions can be drawn.

The third group of patients suitable for neuroimaging studies, are those by whom tinnitus can be modulated, for example via electrodes positioned at the auditory cortex (9;10) or around the vestibulocochlear nerve (Chapter 7). According to this point of view we have developed a PET study described in Chapter 8. Besides visualizing tinnitus-related neural activity, neuroimaging techniques can objectify the effects induced by neuromodulation. In contrast to implanted devices, neuromodulation can noninvasively be achieved by means of transcranial magnetic stimulation (TMS). Especially the combination of neuroimaging during TMS can be useful for determining tinnitus-related neural activity. Therefore, more precise positioning of the TMS-coil can be achieved.

These three groups of patients will still be of great value in future tinnitus neuroimaging research, especially as long as neuroimaging techniques need two conditions of neural activity for visualizing tinnitus-related neural activity. Whenever neuroimaging techniques improve and a straight comparison between two conditions is no longer needed, other tinnitus subjects may be of value in these studies, as well. Consequently, the value of neuroimaging techniques in tinnitus research will markedly increase and they might even become keystones in future diagnosing of tinnitus location.

b) During the last decades, physiological and behavioral animal models of tinnitus have been developed that have significantly increased our understanding about pathophysiological processes associated with the risk of getting tinnitus. Previously performed animal studies have described the dorsal cochlear nucleus and inferior colliculus as important sites for the generation and modulation of tinnitus-producing signals. Intense tone exposure and pharmacologically decreased GABA-mediated inhibition created increased spontaneous activity in both neural structures in several species (11-20). Animal models are currently used for development of
new therapies by means of administration of drugs and application of electrical modulation (21-25)

The main constraint of the use of animal models is the subjective character of tinnitus. Although we assume to be able to induce and measure tinnitus in animals, objectification of induced mechanisms remains a problem; conclusions about the effect on tinnitus are drawn from behavioral alterations or neurophysiological measurements. Nevertheless, the use of animal models in tinnitus research has two major advantages compared to using human models instead. These advantages determine their great value in tinnitus research. First, single tinnitus inducing mechanisms can be investigated, like noise trauma or medication-induced tinnitus. In humans often more than one mechanism seems frequently responsible for tinnitus generation, creating difficulties in studying tinnitus mechanisms. Second, repeated application of noise-trauma or pharmaceuticals and implantation of neuromodulation devices may cause definitive harm in humans, which also justifies the use of animal models.

c) Many similarities have been described between the pathophysiological processes of tinnitus and other hyperexcitability manifestations like neuropathic pain, muscle spasm, phantom pain, phonophobia and hyperpathia (26). In accordance to tinnitus, phantom limb sensations and phantom pain are believed to be generated in the central nervous system, since neural activity causes symptoms that do not originate from the peripheral location at which the symptoms are perceived (27). Currently developed scientific research programs about diagnosing and treating other hyperexcitability disorders can improve our knowledge about pathophysiological tinnitus mechanisms. Development of new treatment modalities based on analogy with these disorders, will be described in the section ‘treatment’.

**Diagnosis**

Because of its high prevalence and frequent major implications on perceived quality of life and daily functioning, tinnitus can nowadays be assumed as a major problem. In a wealthy and economically growing society, the implications and limitations associated with a chronic condition like tinnitus are not generally accepted and understood. This may cause major impairments for tinnitus sufferers, who frequently end up in a vicious circle with tinnitus, its associated complaints, psychological distress and impairment of quality of life. Early diagnosing of tinnitus-associated psychological, personality and cognitive-behavioral problems seems essential. Unfortunately, several medical centers use different collections of assessments and questionnaires. Clearly defined comparisons between the different tinnitus populations of the different medical clinics are therefore impossible. Variety of scientific purposes of research and the lack of uniform tinnitus severity questionnaire are possible explanations for this diversity in diagnostic approaches.

The proposed guidelines for clinical evaluation of chronic, subjective tinnitus turned out to be capable of multidisciplinary evaluating an individual tinnitus patient at the outpatient clinic (chapter 3). For scientific purposes, the
proposed protocol can be extended with other assessments. In our institution the clinical evaluation protocol is currently extended with studies, investigating residual inhibition, phase out syndrome and tinnitus spectrum tests. By means of the clinical evaluation protocol, specific patient groups can be selected for scientific purposes; e.g. those patients who are able to modulate their tinnitus can be used in neuroimaging studies (tinnitus modulated by movements of head and neck) and bilateral tinnitus subjects analyzed by means of PET.

Treatment
Specialized multidisciplinary care and extension of psychological and cognitive behavioral treatment programs are essential in understanding and controlling tinnitus and its associated complaints. They are needed in order to prevent tinnitus not becoming a major problem in our rapidly growing, demanding society. Treatment of subjective tinnitus needs a multidisciplinary approach, in which audiology, psychology and medicine contribute. A majority of tinnitus sufferers can be helped by means of this multidisciplinary approach, based on counseling and controllability of the tinnitus, more or less in combination with hearing aids or masking devices.

We previously mentioned the analogy between tinnitus and other hyperexcitability disorders, all consequences of neural plasticity. Previously developed treatment modalities for other hyperexcitability disorders can create opportunities for development of new treatment modalities for tinnitus. Neuromodulation devices have already been used to treat various chronic pain syndromes, shown to be intractable to other treatment modalities. Moreover, neurostimulation has been performed in neural structures in- and outside the central nervous system, and encompasses various techniques like Transcutaneous Electrical Nerve Stimulation (TENS), Peripheral Nerve Stimulation, Spinal Cord Stimulation, Deep Brain Stimulation and cortical stimulation (28-31). Spinal Cord Stimulation is described to be effective in the treatment of neuropathic pain syndromes like reflex sympathetic dystrophy, peripheral nerve injury, post-amputation pain, spinal cord lesions, and ischemic pain syndromes as seen in angina pectoris and peripheral vascular disease (32;33).

Based on the analogy between tinnitus and other hyperexcitability disorders, new treatment modalities for tinnitus have been developed, also described in this thesis. First, neuromodulation of the central auditory pathways via continuous electrical stimulation of the vestibulocochlear nerve (Chapter 7), was based on scientific principles of spinal cord stimulation for chronic pain (34). Long-term evaluation of this treatment showed promising results. Treatment success was determined by means of calculating effect sizes, according to Cohen effect size ‘d’ (1), and recordings on visual analogue scales. The reported reduction of tinnitus severity could not be objectified using tinnitus-specific audiometric tests. Since tinnitus did not disappear in any of the subjects, the replacement of tinnitus into another, pleasantly-perceived sound explained the treatment success. The results of this study also proved the safety of this treatment since no long-lasting surgical risks
or complications occurred and no side effects were noted during long-term evaluation.

Second, TMS (Chapter 8) is currently widely used in several hypersensitivity or hyperactivity disorders, such as chronic pain, schizophrenia, mania, depression, and movement disorders. Site and depth of stimulation and inter-individual variability are limitations of TMS. A disadvantage of neuromodulation by means of TMS is its transient effect on tinnitus-related neural activity. For more permanent implications on tinnitus perception, more or less continuous neuromodulation of the central nervous system is needed. Continuous neuromodulation can predominantly be achieved by means of implanted devices. Neuromodulation via stimulation of the nervus vestibulocochlearis (Chapter 7) is one option, cochlear implants (35-37) or epidural/cortical devices (9;10) are currently investigated interventions with great potentials.

Overall, we can conclude that current treatment options and lifestyle adjustment can reduce tinnitus to a controllable level in the majority of tinnitus sufferers. However, most frequently tinnitus cannot be completely eradicated and still induces reduced quality of life in almost every subject. Therefore, and especially for those who suffer severely in particular, new medical treatment modalities need to be developed. Besides expanding psychological and cognitive-behavioral therapies and development of new audiological and masking devices, new treatment modalities need to be directed at neuromodulation of the neural plastic brain.
Reference List


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