Dear Colleagues,

Tinnitus Research Initiative is dedicated to find a cure for Tinnitus. In this context, we are delighted to present you this first issue of the TRI NEWSLETTER. We hope that this newsletter, will facilitate collaboration and knowledge sharing between supported institutions and interest new stakeholders in order to develop our common network.

We would like this newsletter to provide relevant new information for TRI related institutions and assure that maximum knowledge is shared in order to provide a common basis. The newsletter is intended to become an inherent part of communication within TRI and we would highly appreciate your cooperation in compiling interesting contents. Contributions can be sent to: newsletter@tinnitusresearch.org or Susanne.Staudinger@tinnitusresearch.org.

This first issue includes three parts. The first two parts - an overview about upcoming Meetings and a selection of recently published Literature will appear regularly. The third part News is dedicated this time to the results of the Consensus workshops at the First Tinnitus Research Initiative Meeting at Regensburg.

We hope that this first issue meets your interest and we will be thankful for all kinds of feedback.

Susanne Staudinger
Berthold Langguth
Upcoming Meetings

April 2007

19th Annual American Academy of Audiology Convention & Expo
When: April 18 – 21, 2007
Where: Denver, Colorado, USA
Detailed information: http://www.audiologynow.org

May 2007

Annual Electric Response Audiometry and Oto-Acoustic Emissions (ERA & OAE) Course
When: May 14 – 18, 2007
Where: Harrogate, UK
Contact: Dr Guy Lightfoot
E-Mail: g.lightfoot@liverpool.ac.uk

June 2007

The International Evoked Response Audiometry Study Group (IERASG) XXth biennial symposium
When: June 10 – 14, 2007
Where: Bled, Slovenia
Contact: Dr. Dušan Butinar
Phone: ++386-1-522-1514
Fax: ++386-1-522-1533
E-Mail: dusan.butinar@kclj.si

Advances in Tinnitus – Assessment, Treatment & Neuroscience Basis
When: June 22 – 24, 2007
Where: Holiday Inn Grand Island Resort and Conference Center
Grand Island, New York, USA
Register online at http://wings.buffalo.edu/faculty/research/chd
Or get a registration form by e-mail calman@buffalo.edu
or by phone +1-716-829-2001
Detailed information: http://wings.buffalo.edu/faculty/research/chd

July 2007

2nd Tinnitus Research Initiative Meeting
Together for a cure of Tinnitus – challenging our basic assumptions
When: July 17 – 21, 2007
Where: Principality of Monaco
Contact: Tinnitus Research Initiative
Phone: +49-941-941-2096
E-Mail: info@tinnitusresearch.org
Detailed information: www.tinnitusresearch.org
2007 Annual Meeting & OTO EXPO
When: September 16 – 29, 2007
Where: Washington D.C., USA
Contact: American Academy of Otolaryngology – Head and Neck Surgery
Phone: +1-703-836-4444
Fax: +1-703-683-5100
E-Mail: OTOEXPO@entnet.org
or meetings@entnet.org
Detailed information: http://www.entlink.net/meetings/meetings/Annual-Prep.cfm

Fifteenth annual Conference on Management of the tinnitus patient
When: September 20 – 22, 2007
Where: University of Iowa, Iowa City
Contact: Richard Tyler PhD
Phone: +1-319-356-2471
E-Mail: rich-tyler@uiowa.edu

IXth International Tinnitus Seminars
When: June, 15 – 18, 2008
Where: Göteborg, Sweden
Contact: Congrex Sweden AB, Ref. Tinnitus 2008
P.O.Box 5078
402 22 Göteborg, Sweden
Phone: +46-31-708-6000
Fax: +46-31-708-6025
E-Mail: tinnitus2008@congrex.com
Detailed information: http://www.congrex.se/ITS2008

The 10th International Workshop on the Mechanism of Hearing
When: July 27 – 31, 2008
Where: Keele University, UK
Contact: Dr. N.P. Cooper
School of Life Sciences
Keele University
Keele, Staffordshire
ST5 5BG
UK
Phone: +44-1782-583056
Fax: +44-1782-583055
E-Mail: secretary@mechanicsofhearing.com
Detailed information: http://www.mechanicsofhearing.com
Recently published literature and results of the latest research
(starting in 2007)

I Pharmacotherapy

Antidepressants for patients with tinnitus.
Centro di Riferimento Oncologico—CRO Aviano (PN) Italy, Hospital Pharmacy, Via Pedemontana Occi-
dentale, 12, Aviano (PN), Friuli-Venezia-Giulia, Italy. pbaldo@cro.it

Background: Tinnitus is described as the perception of sound or noise in the absence of real acoustic
stimulation. It has been compared with chronic pain, and may be associated with depression or depres-
sive symptoms which can affect quality of life and the ability to work. Antidepressant drugs have been
used to treat tinnitus in patients with and without depressive symptoms.

Objectives: To assess the effectiveness of antidepressants in the treatment of tinnitus and to ascertain
whether any benefit was due to a direct tinnitus effect or a secondary effect due to treatment of concomi-
tant depressive states.

Search Strategy: We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register,
the Cochrane Central Register of Controlled Trials (CENTRAL) The Cochrane Library Issue 1, 2006);
MEDLINE (January 1951 to 2006); EMBASE (1974 to 2006), CINAHL (to 2006), PSYCINFO (to 2006),
LILACS (to 2006), and Cambridge Scientific Abstracts. The date of the most recent search was March
2006.

Selection Criteria: Randomised controlled clinical studies of antidepressant drugs versus placebo in
patients with tinnitus.

Data collection and analysis: The studies retrieved were critically appraised and data extracted inde-
pendently by two authors. Where necessary study authors were contacted for further information.

Main results: Five trials involving 525 patients were included. Four of these trials looked at the effect of
tricyclic antidepressants on tinnitus, investigating 405 patients. One trial investigated the effect of a se-
lective serotonin reuptake inhibitor (SSRI) in a group of 120 patients. No trials involving other antidepres-
sant agents met the inclusion criteria. Only the trial using the SSRI drug met the highest quality standard.
None of the other included trials met the highest quality standard, due to use of inadequate outcome
measures, large drop out rates or failure to separate the effects on tinnitus from the effects on symptoms
of anxiety and depression. All the trials assessing tricyclic antidepressants suggested that there was
a slight improvement in tinnitus but these effects may have been attributable to methodological bias.
The trial that investigated the SSRI drug found no overall improvement in any of the validated outcome
measures that were used in the study although there was possible benefit for a subgroup that received
higher doses of the drug. This observation merits further investigation. Reports of side effects including
sedation, sexual dysfunction and dry mouth were common.

Authors’ Conclusion: There is insufficient evidence to say that antidepressant drug therapy improves
tinnitus.
(because of the special interest of this publication it has been included even if it was published in 2006)

Clinical development of SPI-1005, an otoprotectant for noise induced hearing loss.
(Abstract of ARO Meeting Denver, Colorado)
Jonathan Kil, Bret MacPherson, Carol Pierce, Eric Lynch
Sound Pharmaceuticals, Inc.

Ebselen (SPI-1005), an oral small molecule GPx mimic, has been shown to provide significant protection
from TTS and PTS in F344 rats (Lynch et al., 2004, Lynch et al., 2005), Sprague Dawley Rats (Park et
al., ARO Abst. 2006) and Guinea Pigs (Pourbahkt and Yamasoba 2003, Yamasoba et al., 2005) when
dosed in the range of 8-30 mg/kg. Our current efforts are now focused on translating these pre-clinical findings into a therapeutic for the prevention and treatment of noise induced hearing loss in humans. We have completed a phase I study of SPI-1005 capsules in 32 normal healthy volunteers to determine the safety, toxicity, ADME, and PK. Dose escalation was performed in 4 groups ranging from 200 to 1600 mg po. Subjects were followed in house for a period of 72 hours. Multiple EKGs, orthostatic vitals, Chem20, and CBCs were taken during the period of clinical observation. No significant adverse events were noted in 24 drug treated and 8 placebo treated individuals. PK analysis of ebselen and its metabolites was performed using WinNonlin®5.1 from plasma and urine samples analyzed by LC-MS/MS. These results closely matched the PK analysis of total selenium in plasma samples by ICP-MS from the same treated individuals. The plasma PK of ebselen in these human subjects was similar to that in nonhuman primates dosed with SPI-1005 at comparable levels (10mg/kg). Phase II safety and efficacy trials will be performed in military populations exposed to noise during weapons training. Historically, a Significant Threshold Shift (STS) occurs even with the use of hearing protective devices. The Clinical trial design for these phase II studies will be discussed along with primary and secondary endpoints using STS and the Tinnitus Handicap Inventory.

**Effects of Gacyclidine Extracochlear Perfusion on Tinnitus in Humans and Intracochlear Perfusion on ABR Thresholds in Guinea Pigs.**

(Abstract of ARO Meeting Denver, Colorado)

Gentiana I Wenzel¹, Hubert H Lim¹, Timo Stöver¹, Thomas Lobl², John Schloss², Burkard Schwab¹, Thomas Lenarz¹

¹Medizinische Hochschule Hannover, ²NeuroSystec

Gacyclidine is a highly specific NMDA receptor antagonist with neuroprotective properties. In guinea pigs, administration of gacyclidine (adsorbed to Gelfoam) into the round window niche or as a bolus injection into the cochlea suppressed salicylate-induced tinnitus. Thus, we investigated in humans and animals if gacyclidine could provide a safe and effective treatment for tinnitus.

We administered gacyclidine as a compassionate treatment in unilateral deaf patients with tinnitus. These patients experienced temporary relief from tinnitus after constant perfusion of gacyclidine into the round window niche for 40-60 hours. This demonstrated that gacyclidine has the potential to suppress tinnitus. However, controlled and long-term delivery of the drug will be necessary for effective treatment. Since the main candidates for this therapy will be hearing patients, we needed to assess whether chronic administration of this drug would compromise hearing performance. Thus, we measured the effects of chronic intracochlear gacyclidine perfusion on frequency-specific ABR thresholds in guinea pigs.

Guinea pigs were implanted with osmotic pumps that delivered 0.5 μL/h of 0.3 mM gacyclidine for 9 days via a catheter inserted through the round window membrane. The concentration and rate of drug delivery were selected to provide a dose that was substantially higher than is expected for tinnitus control in humans. Frequency-specific ABRs (1-40 kHz, 10-80 dB SPL in 10dB steps) were recorded before implantation and compared with those obtained after drug administration. No significant changes in ABR thresholds were observed suggesting that prolonged administration of gacyclidine for tinnitus treatment should be safe in terms of hearing preservation.

Further studies investigating the toxicological effects of different dosages and durations are under way to ensure the safety of the drug for long-term human use and to warrant clinical trials.

**Intratympanic dexamethasone for sudden sensorineural hearing loss after failure of systemic therapy.**


Objective: Intratympanic steroids are increasingly used in the treatment of inner ear disorders, especially in patients with sudden sensorineural hearing loss (SNHL) who have failed systemic therapy. We reviewed our experience with intratympanic steroids in the treatment of patients with sudden SNHL to determine overall success, morbidity, and prognostic factors.

Hypothesis: Intratympanic steroids have minimal morbidity and the potential to have a positive effect on hearing recovery in patients with sudden SNHL who have failed systemic therapy.

Study design: The authors conducted a retrospective review.

Methods: Patients presenting with sudden SNHL defined as a rapid decline in hearing over 3 days or less affecting 3 or more frequencies by 30 dB or greater who underwent intratympanic steroids therapy (24 mg/mL dexamethasone) were reviewed. Excluded were patients with Meniere disease, retrocochlear disease, autoimmune HL, trauma, fluctuating HL, radiation-induced HL, noise-induced HL, or any other identifiable etiology for sudden HL. Patients who showed signs of fluctuation of hearing after injection were excluded. Pretreatment and posttreatment audiometric evaluations including pure-tone average (PTA) and speech reception threshold (SRT) were analyzed. Patient variables as they related to recovery were studied and included patient age, time to onset of therapy, status of the contralateral ear, presence of diabetes, severity of HL, and presence of associated symptoms (tinnitus, vertigo). A 20-dB gain in PTA or a 20% improvement in SDS was considered significant.

Results: Forty patients fit the criteria for inclusion in the study. The mean age of the patients was 54.8 years with a range from 17 to 84 years of age. Overall, 40% (n = 16) showed any improvement in PTA or SDS. Fourteen (35%) men and 26 (65%) women were included. Using the criteria of 20-dB improvement in PTA or 20% improvement in SDS for success, 27.5% (n = 11) showed improvement. The mean number of days from onset of symptoms to intratympanic therapy was 40 days with a range of 7 days to 310 days. A statistically significant difference was noted in those patients who received earlier injection (P = .0008, rank sum test). No patient receiving intratympanic dexamethasone after 36 days recovered hearing using 20-dB PTA decrease or a 20% increase in discrimination as criteria for recovery. Twelve percent (n = 5) of patients in the study had diabetes with 20% recovering after intratympanic dexamethasone (not significantly different from nondiabetics at 28.6%, Fisher exact test, P = 1.0). Comparison to other studies that used differing steroid type, concentration, dosing schedule, inclusion criteria, and criteria for success revealed, in many instances, a similar overall recovery rate.

Conclusions: Difficulty in proving efficacy of a single modality is present in all studies on SNHL secondary to multiple treatment protocols, variable rates of recovery, and a high rate of spontaneous recovery. Forty percent of patients showed some improvement in SDS or PTA after treatment failure. When criteria of 20-dB PTA or 20% is considered to define improvement, the recovery rate was 27.5%. Modest improvement is seen with the current protocol of a single intratympanic steroid injection of 24 mg/mL dexamethasone in patients who failed systemic therapy. Dramatic hearing recovery in treatment failures was rarely encountered. No patient showed significant benefit from intratympanic steroids after 36 days when using this protocol for idiopathic sudden SNHL. If patients injected after 6 weeks are excluded from the study, the improvement rate increases from 26.9% to 39.3%. Earlier intratympanic injection had a significant impact on hearing recovery, although with any therapeutic intervention for sudden SNHL, early success may be attributed to natural history. If we further exclude seven patients treated with intratympanic steroids within 2 weeks of the onset of symptoms (i.e., study only those patients treated with intratympanic dexamethasone between 2 and 6 weeks after onset of symptoms), still, 26% improved by 20 dB or 20% SDS. The recovery rates after initial systemic failure are higher than would be expected in this treatment failure group given our control group (9.1%) and literature review. These findings indicate a positive effect from steroid perfusion in this patient population.
Modeling drug dispersion in the inner ear fluids: The importance of accurate 3D anatomical studies.
(Abstract of ARO Meeting Denver, Colorado)

Alec N. Salt¹, Timothy A. Holden¹, Ruth M. Gill¹, Stefan K. Plontke²
¹Washington University School of Medicine, ²University of Tubingen

Locally-applied drugs are increasingly being used for the clinical treatment of inner ear disorders such as Meniere’s disease, sudden hearing loss and tinnitus. Knowledge of the dosages achieved and where in the ear the drugs reach is essential to optimize therapies. In animals, experimental studies have shown that drug spread in the inner ear is dominated by diffusion that takes place slowly along the fluid spaces. Quantitative interpretation of experimental measurements and prediction of the likely drug distribution in humans is only possible through quantitative computer models. Whether the model is a simple 1D representation of a scala or a sophisticated 3D representation of the inner ear, the calculations are highly dependent on the dimensions of the compartments that are used. With more sophisticated models, the interactions of each compartment with adjacent structures also need to be incorporated. At present, models are restricted by the limited availability of anatomic descriptions of the ear. Quantitative anatomic studies have become more feasible with the increased availability of 3D reconstruction programs and the increased capabilities of desktop computers. Data sets for analysis can be obtained from serial histological sections, magnetic resonance microscopy (MRM), computed tomography (CT) and orthogonal plane fluorescence optical sectioning (OPFOS). Each of these methods has different capabilities in terms of which tissues can be detected and at what resolution. As the voxel resolution of the methods increases, the effort required to segment structures increases dramatically, limiting the number of specimens that can be analyzed. Other limitations arise from tissue shrinkage and long preparation times. In some applications, combining structures segmented from different data sets, such as bone from a CT scan and soft tissues from an OPFOS scan can aid the analysis. The long-term goal of this work is to develop a 3D model of the ear, through which drug dispersal can be calculated based on the anatomic communications present and incorporating the transport and permeability properties of tissue boundaries (Supported by NIH/NIDCD grants DC01368 (AS) and DC000581 (TH) and BMBF grant 0313844b (SP)).

A pilot clinical trial of the effects of coenzyme Q10 on chronic tinnitus aurium.

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Objective: To determine the short-term effects of coenzyme Q10 (CoQ10) on the antioxidative status and tinnitus expression in patients with chronic tinnitus aurium.

Study Design: A 16-week prospective nonrandomized clinical trial (n = 20). Tinnitus and Short Form-36 Questionnaires (TQ/SF-36) were evaluated together with the plasma concentrations of CoQ10, malondialdehyde, and the total antioxidant status.

Results: The mean plasma CoQ10 concentration rose under external CoQ10 supply and remained elevated after medication stopped without overall effects on the tinnitus score. However, in a subgroup of 7 patients with low initial plasma CoQ10 concentration and significant increase in the plasma CoQ10 level, a clear decrease in the TQ score was observed.

Conclusion: In patients with a low plasma CoQ10 concentration, CoQ10 supply may decrease the tinnitus expression.

Significance: This is the first study to examine the effect of CoQ10 in chronic tinnitus aurium.
Impaired auditory temporal processing is improved by the drug γ-vinyl-GABA (Sabril) that increases GABA levels in the brain (Gleich et al., 2003, Neureport 14:1877-1880). However, Sabril can reduce the visual field. Thus we began evaluating the anticonvulsant Gabapentin (GP). GP was effective in the treatment of certain forms of tinnitus, where GABA mechanisms have repeatedly been implicated (Bauer and Brozoski, 2001, JARO 2:54-64; 2006, Laryngoscope 116: 675-681).

In each animal threshold for an 800 ms broad band noise pulse was determined. The noise pulse was subsequently used as a carrier for the gap with a level set 30 dB above each individual's threshold. GP was administered in the drinking water at a dose of 350 mg/kg/day. Testing was performed 1-2 hours after GP intake. Gap detection thresholds were determined, before, during and at least two weeks after cessation of GP administration for 5 young (8-13 months) and 10 old (27-37 months) gerbils.

A two way repeated measure ANOVA using age and treatment as factors revealed a significantly higher mean gap detection threshold for old (3.1 ms) as compared to young (2.0 ms) gerbils (p = 0.019). Mean gap detection threshold during GP treatment (2.9 ms) was slightly higher compared to thresholds determined before (2.5 ms) and after GP treatment (2.3 ms), however, these differences were not significant (p = 0.212) and there was no interaction between age and treatment (p = 0.923).

These preliminary data provide no evidence for a beneficial effect of GP on temporal resolution, if anything, the group mean data suggest that performance may deteriorate during GP treatment. In contrast to initial expectations, GP has no effect on GABA receptors, enzymes or transporters (Errington et al., 2005, Curr. Top. Med. Chem. 5, 15-30) and consequently cannot compensate age dependent declines in the GABA system (We thank S. Kopetschek and C. Wögerbauer for help with the behavioral experiments. Supported by the DFG Str275/4-5).

Sulpiride plus hydroxyzine decrease tinnitus perception.
Lopez-Gonzalez MA, Moliner-Peiro F, Alfaro-Garcia J, Esteban-Ortega F
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Objectives: The aim of the study is to confirm the effectiveness of sulpiride and hydroxyzine in tinnitus patients. The administration of sulpiride, a D2 antagonist of dopamine receptors, together with hydroxyzine, a subcortical sedative, covers the areas of tinnitus perception.

Methods: A prospective, randomized, single blinded, placebo-control study was done in general otorhinolaryngology consultations for 2002-2004 in Seville and Zaragoza (Spain). One hundred and fifty patients consulted for subjective tinnitus. They were included randomly in three groups of 50. A group took sulpiride (50 mg/8 h) alone, other the same dose of sulpiride plus hydroxyzine (25 mg/12 h), and the third placebo (lactose), for 1 month. One hundred and twenty-two patients completed the study. Clinical history, tonal audiometry, tympanometry, and tinnitus were done in the beginning and end of the study. Subjective Grading of Tinnitus Perception and visual analogical scale (0-10) were done for result evaluation.

Results: Based on the Subjective Grading of Tinnitus Perception, tinnitus perception diminished by 56% in patients treated with sulpiride and by 81% in patients treated with sulpiride plus hydroxyzine. Based on the visual analogical scale, tinnitus perception diminished from 7.8 to 6.3 in the patients treated with sulpiride, and from 7.8 to 5.1 in those treated with sulpiride plus hydroxyzine.

Conclusions: Sulpiride plus hydroxyzine decreases tinnitus perception. Tinnitus auditory dopaminergic pathway opens wide therapeutical implications.
Treatment of tinnitus with gabapentin: a pilot study.

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Division of Otolaryngology, Head and Neck Surgery, Department of Surgery, Durham, North Carolina, USA. witse001@mc.duke.edu

Objective: To evaluate the effectiveness of gabapentin (Neurontin) improve the disease-specific quality of life in patients with moderate tinnitus.

Study design: Randomized, double blind, placebo-controlled clinical trial.

Setting: Single-center academic outpatient otolaryngology practice.

Intervention: Gabapentin 1800 mg daily versus placebo.

Main outcome measures: The study design is a randomized, double blind placebo controlled single site trial conducted in an academic medical center. Inclusion criteria included patients between ages 18 and 70 with a complaint of nonpulsatile, subjective tinnitus, bilateral or unilateral, greater than 3 months in duration. The primary outcome measure is the Tinnitus Handicap Inventory; secondary measures include the Profile of Mood States (POMS) rating scale, subjective tinnitus severity. The null hypothesis addressed in this study is that the drug would not result in significant alleviation of the symptom of tinnitus.

Results: Seventy-six patients completed the trial; of these 52 received the drug. No significant differences were found between the two groups after 5 weeks of treatment with gabapentin.

Conclusion: There is insufficient evidence to support the effectiveness of gabapentin in the treatment of tinnitus.

Il Auditive stimulation

Cerebral activity in response to a masking sound in patients with intractable tinnitus.
(Abstract of ARO Meeting Denver, Colorado)

Mikio Suzuki¹, Hideaki Kouzaki², Minao Tamaki¹, Ken Uehara¹
¹University of the Ryukyus, ²Shiga University of Medical Science

Functional magnetic resonance imaging was performed in twelve patients with intractable tinnitus and normal subjects to determine the tinnitus-related regions where cerebral activity showed a positive or negative correlation to monaural masking noise stimulus. A blood oxygenation level-dependent (BOLD) signal increase was observed in the exclusive contralateral auditory cortex. There was no significant difference of the BOLD signal increase between normal subjects and patients in the conjunction analysis using random effect model. Cerebral regions that showed a BOLD signal decrease in normal subjects were the cuneus, cingulate gyrus, and paracentral lobule. In the patients group, the cerebral regions that showed a BOLD signal decrease were the postcentral gyrus, bilateral thalamus, and bilateral lingual gyrus. A conjunction analysis using random effect model was performed to compare the decrease in BOLD signals between the tinnitus patients and controls, and revealed that the only significant difference in BOLD decrement was in the bilateral thalamus. Although the relationship between tinnitus and thalamic activity is not fully understood, such thalamic activity is consistent with the findings about other peripheral neural injuries.
Effectiveness of unilateral usage of the sound generator for Tinnitus Retraining Therapy.
(Abstract of ARO Meeting Denver, Colorado)
Nobumichi Maeyama¹, Atsuhiko Uno¹, Miki Okubo¹, Yuko Takai¹, Kazuyasu Baba², Seiji Shibata², Kouhei Kawamoto², Hiromichi Kuriyama², Katsumi Doi³, Masato Nishimura¹
¹Department of Otolaryngology, KKR Otemae Hospital, ²Osaka Kita Japan Post Hospital, ³Osaka University

Tinnitus Retraining Therapy (TRT) developed by Jastreboff and his colleagues, is a world-wide spreading treatment for tinnitus. TRT consists of directive counseling and sound therapy that typically the patient uses a sound (noise) generator to reduce awareness of tinnitus distinguished from the background noise. Generally the sound generator is recommended to use on the bilateral ears. However, because of the reasons such as the cost, appearance and difficulty in daily conversation, we usually begin with the unilateral use, following repeated counseling and explanation of TRT itself.

To assess the effectiveness of the sound therapy using the sound generator on one side, we retrospectively examined the results of 27 patients who underwent TRT at KKR Otemae Hospital and at Osaka Kita Japan Post Hospital from November 2004 to April 2006.

Two kinds of questionnaires including Tinnitus Handicap Inventory and Visual Analogue Scale were used to evaluate the results at 6 and 12 months.

Even for the patients complaining of bilateral tinnitus, TRT with unilateral sound therapy showed significant improvements at 6 months. We think that the sound therapy can begin with one sound generator on the one side, then after 6 months, the results should be evaluated. For the patient who did not show clear improvements, bilateral usage of the sound generator may be suggested.

Intervention for Restricted Dynamic Range and Reduced Sound Tolerance: Clinical Trial Update.
(Abstract of ARO Meeting Denver, Colorado)
Monica Hawley, LaGuinn Sherlock, Susan Gold¹, Allyson Segar, Christine Gmitter, Justine Cannavo, Craig Formby
University of Maryland School of Medicine, Baltimore

Hyperacusis is the intolerance to sound levels that normally are judged acceptable to others. The presence of hyperacusis (diagnosed or undiagnosed) can be an important reason that some persons reject their hearing aids. Tinnitus Retraining Therapy (TRT), originally proposed for the treatment of persons with debilitating tinnitus, offers the significant secondary benefit of increased Loudness Discomfort Levels (LDLs) in many persons. TRT involves both counseling and the daily exposure to soft sound from bilateral noise generator devices (NGs). We implemented a randomized, double-blind, placebo-controlled clinical trial to assess the efficacy of TRT as an intervention for reduced sound tolerance in hearing-aid eligible persons with hyperacusis and/or restricted dynamic ranges. Subjects were assigned to one of four treatment groups: 1) NGs with counseling, 2) placebo NGs with counseling, 3) NGs without counseling, and 4) placebo Ngs without counseling. They were evaluated at least monthly, typically for five months or more, on a variety of audiometric tests, including LDLs, the Contour Test for Loudness for tones and speech, word recognition measured at each session’s comfortable and loud levels, and on electrophysiological measures. Success for the treatment is defined as a tolerance increase by more than 10 dB as measured by either LDLs or Contour Test for Loudness. For the subjects in Group 1 (NGs and counseling), there was a high rate of success (5/6 subjects). A lower success rate was observed for the partial treatment options: Group 2 (placebo NGs with counseling): 1/5 subjects; Group 3 (NGs without counseling): 4/7 subjects; and Group 4 (placebo NGs without counseling): 0/2 subjects. In some subjects who initially had poor word recognition at comfortable levels, the increased tolerance allowed them to increase the level of their comfortable speech allowing a marked improvement in word recognition at comfortable levels. The interim results are very promising and support the hypothesis of this
randomized controlled study that modified TRT appears to offer a new intervention for improving sound tolerance in the general hearing-impaired population, allowing persons with reduced tolerance or limited dynamic ranges to use hearing aids more effectively (Supported by NIH R01 DC04678).

Optimizing Electric Stimulation to Suppress Tinnitus.
(Abstract of ARO Meeting Denver, Colorado)
Fan-Gang Zeng¹, Qing Tang¹, Jeff Carroll¹, Andrew Dimitrijevic¹, Arnold Starr¹, Leonid Litvak², Jan-nine Larky³, Nikolas Blevins³
¹University of California Irvine, ²Advanced Bionics Corporation, ³Stanford University

Here we reported psychophysical, electrophysiological, and clinical results from a unique subject, CINH001, who received a Clarion HiRes90k cochlear implant to control debilitating tinnitus in his right ear. CINH001 had essentially normal hearing in his left ear, so that he could match both tinnitus and electric stimulation in the right ear to acoustic stimulation in the left ear. CINH001 matched his tinnitus to an acoustic stimulus of 4000-8000 Hz and at 70-90 dB SPL. The effect of electric stimulation on tinnitus was evaluated as a function of pulse rate from 25 to 5000 Hz, pulse duration from 10 to 500 μs per phase, electrode position from apex to base, and stimulation configuration from monopolar to bipolar mode. Different from previous studies showing a suppressive effect of high-rate stimulation on tinnitus, only stimuli with low rates (40-100 Hz), short pulse duration, the most apical electrode, and monopolar mode could suppress his tinnitus. Objective measures in both spontaneous and event-related evoked potentials also showed a difference related to the presence and absence of tinnitus. An innovative acoustic waveform employing a Gaussian-enveloped sinusoid and optimized programming of electric parameters allowed CINH001 to use his behind-the-ear processor to suppress tinnitus effectively at home. These results underscore the need to customize electric stimulation for tinnitus suppression and suggest that complementary stimulation, rather than masking, is the brain mechanism underlying the present surprising finding (Supported by NIH RO1 DC002267).

Tinnitus and cochlear implantation in adults - a retrospective study.
(Abstract of ARO Meeting Denver, Colorado)
Esma Idrizbegovic¹, Anders Freijd², Eva Karlorp², Gerhard Andersson³
¹Department of Audiology, Karolinska University Hospital, Stockholm, Sweden, ²Department of ENT, section for Cochlea Implant, Karolinska University Hospital, Huddinge, Sweden, ³Department of Behavioural Sciences, Linköping University, Sweden

Few studies have outlined the temporal association between cochlear implantation and tinnitus onset or changes. The aim of the study was to use validated self-report measures in a consecutive sample of cochlea implant (CI)- patients who reported tinnitus.

Methods: A total of 151 (83% response rate) responded to postal questionnaires, and of these 111 reported that they had tinnitus. Questions regarding tinnitus in relation to CI and the operation were asked. In addition, three established self-report questionnaires were included measuring tinnitus handicap, hearing disability and handicap and finally a measure of anxiety and depression.

Results showed that few patients had permanently worsened tinnitus or got tinnitus following cochlear implantation. However, a fifth did report that their tinnitus was worsened. As many as 25 patients reported that their tinnitus completely disappeared when the processor was turned on and that it returned when the processor was turned off again. Only 4 patients reported that their tinnitus increased when the processor was turned on. A common response (N=31) was that tinnitus was unchanged following the CI operation. Data from established questionnaires showed relatively low levels of tinnitus handicap, moderate levels of hearing disability and handicap, and low scores on the anxiety and depression scales.
**Conclusion:** Significant amount of patients either experience no change in their tinnitus or a decrease. Level of tinnitus handicap overall is not marked in this population. However, tinnitus could be a significant problem in some CI patients.

### III Brain stimulation

**Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation.**

**Plewnia C, Reimold M, Najib A, Brehm B, Reischl G, Plontke SK, Gerloff C**
Department of Psychiatry, Neurophysiology Section, University of Tuebingen, Tuebingen, Germany.

Recent data suggest that chronic tinnitus is a „phantom auditory perception“ caused by maladaptive neuroplasticity and subsequent hyperactivity in an extended neuronal network including the primary auditory cortex, higher-order association areas, and parts of the limbic system. It was suggested that attenuation of this tinnitus-associated hyperactivity may offer a rational option for lasting tinnitus reduction. Here, we tested the hypothesis that tinnitus loudness can be attenuated by low-frequency repetitive transcranial magnetic stimulation (rTMS) individually navigated to cortical areas with excessive tinnitus-related activity as assessed by [(15)O]H(2)O positron-emission tomography (PET). Nine patients with chronic tinnitus underwent this combined functional imaging and rTMS-study. Group analysis of the PET data showed tinnitus-related increases of regional cerebral blood flow in the left middle and inferior temporal as well as right temporoparietal cortex and posterior cingulum. Repetitive TMS was performed at 1 Hz and 120% of the motor threshold for 5, 15, and 30 min, navigated to the individual maximum of tinnitus-related cortical hyperactivity. A noncortical stimulation site with the same distance to the ear served as sham control. Tinnitus loudness was reduced after temporoparietal, PET-guided low-frequency rTMS. This reduction, lasting up to 30 min, was dependent on the number of stimuli applied, differed from sham stimulation, and was negatively correlated with the length of the medical history of tinnitus in our patients. These data show the feasibility and effectiveness of rTMS guided by individual functional imaging to induce a lasting, dose-dependent attenuation of tinnitus. Of note, these effects were related to stimulation of cortical association areas, not primary auditory cortex, emphasizing the crucial role of higher-order sensory processing in the pathophysiology of chronic tinnitus. Hum Brain Mapp, 2007. (c) 2006 Wiley-Liss, Inc.

**Effects of repetitive transcranial magnetic stimulation on chronic tinnitus. A randomised, cross over, double blind, placebo-controlled study.**

**Rossi S, De Capua A, Ulivelli M, Bartalini S, Falzarano V, Filippone G, Passero S**
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**Background:** chronic tinnitus is a disabling, almost untreatable, condition usually accompanied by psychiatric distress. In patients with complex neuropsychiatric diseases as chronic pain, with whom tinnitus shares pathophysiological similarities, placebo effects may be pronounced. Moreover, it may be difficult to distinguish actual rTMS-induced clinical benefits beyond placebo effects in neuropsychiatric patients. **Methods:** 16 patients with chronic tinnitus underwent a randomized, double-blind, cross-over, placebo controlled trial of 1 Hz rTMS (120% of motor threshold; 1200 stimuli/day for 5 days) of the left temporoparietal region. Patients were screened for psychiatric comorbidity; additionally, anxiety and depression were monitored throughout the study. Moreover, an original placebo rTMS procedure produced the same activation of ipsilateral face muscles (a condition which may per se change tinnitus subjective rating) of the real rTMS.
Results: responders were 8 out of 14. Two patients dropped out for transient tinnitus worsening. Active rTMS induced an overall significant, but transient, improvement (35% of the basal score) of subjective tinnitus perception, that was independent either by tinnitus laterality or by mood or anxiety changes. No correlations were found between response to rTMS and tinnitus duration, initial subjective score or patients’ age. When asked after the study was over, 71.4% of patients failed to identify the temporal sequence of the real or sham rTMS interventions.

Conclusions: beneficial effects of rTMS on tinnitus are independent by mood changes. Moreover, they appear in the context of an original placebo stimulation designed to more closely replicate somatic sensation of active stimulation. Due to the limited temporal duration of the clinical benefit, these neuro-modulatory effects could be mediated by transient functional changes taking place in the neural circuits underlying tinnitus processing.

Effect of vagal nerve stimulation on a rat tinnitus model.
(Abstract of ARO Meeting Denver, Colorado)
Joseph Ursick¹, Dianne Durham¹, Hinrich Staecker¹, Philippe Lefebvre², Jean Schoenen³, Martin Scholsem⁴, Thomas Imig⁵
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Vagal nerve stimulation (VNS) has been used to treat a variety of disorders including epilepsy and depression. Recently, VNS has been shown to decrease neuronal spontaneous activity (SA) associated with chronic facial pain in a rat model. Several animal models suggest that tinnitus may be associated with changes in SA in the dorsal cochlear nucleus (DCN), inferior colliculus, and auditory cortex. Using a rat model of noise-induced tinnitus (Durham and Imig, JCN 490:391-413, 2005), we examined the effects of VNS on 2-deoxyglucose (2DG) uptake in the DCN of three groups of Long Evans rats. Rats were anesthetized and exposed to 15-20 kHz band pass noise at 115 dB SPL for one hour. Five days later, the VNS group (n=4) was implanted with a vagal nerve stimulator (Cyberonics, Inc.). On day 6, the stimulators were activated and on day 7, 2DG was injected. A non-VNS group (n=8) received acoustic trauma and 2DG injection after 7 days, but no VNS stimulation. A control group (n=9) received neither noise exposure nor VNS. Animals were placed in a quiet sound attenuated chamber for 45 minutes during 2DG uptake. Rats were sacrificed and brainstem sections were prepared for 2DG film autoradiography. Optical density (OD) measurements were used to determine 2DG uptake in the high frequency (HF) and low frequency (LF) regions of the DCN. These OD values were used to calculate a symmetry ratio (ipsi HF/LF)/(contra HF/LF). In the control group, the symmetry ratio was near one. Noise exposure decreases 2DG uptake in the high frequency region of the ipsilateral DCN. Thus, both noise trauma groups showed a decreased symmetry ratio. However, the VNS group had a symmetry ratio that was intermediate to those in control and non-VNS groups. VNS stimulation may reduce the alteration of SA caused by noise trauma and thus warrants further study as a potential tinnitus therapy (Supported by the Tinnitus Research Consortium and the Dept. of Otolaryngology Head and Neck Surgery, KUMC).

Long-Term Evaluation of Treatment of Chronic, Therapeutically Refractory Tinnitus by Neurostimulation.
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Objective: Long-term evaluation of treatment of chronic, therapeutically refractory tinnitus by means of
chronic electrical stimulation of the vestibulocochlear nerve.

 Patients: Inclusion criteria were severe, chronic, therapeutically refractory, unilateral tinnitus and severe hearing loss at the ipsilateral site. Out of 6 patients, 4 patients were selected for long-term evaluation. Two patients were not evaluated because of premature dropout.

 Material and Methods: A stimulation electrode was placed around the vestibulocochlear nerve through a retrosigmoid approach and connected to a subcutaneously positioned pulse generator via an extension cable. Follow-up was performed 3 months and 42.5 months after implantation. Three measures for treatment outcome were used. First, effect sizes were determined by means of the total Tinnitus Handicap Inventory (THI) score using Cohen's formula. Second, general and tinnitus-specific audiometric tests were performed in on and off conditions of the neurostimulation system. Third, recordings were noted for tinnitus severity and treatment success on a visual analogue scale.

 Results: All 4 patients reported successful treatment with neurostimulation. The effect size after 3 months was 0.7, indicating an average effect, while the effect size measured during long-term follow-up was 1.75, indicating a substantial effect with major clinical implications. No changes in hearing level for both ears were measured. The neurostimulation system did not change the tinnitus pitch in any of the patients, and resulted in a minimal reduction of tinnitus loudness in only 2 patients. In all 4 patients the original tinnitus sound was replaced by another, pleasantly perceived sound. The average VAS score of perceived tinnitus severity was reduced from 8 to 3.25. The average VAS score for treatment success was 7.25. Conclusions: The long-term follow-up of neurostimulation treatment for chronic tinnitus shows promising results. Long-term results were better than those determined after a 3-month follow-up. In all patients the tinnitus was replaced by another sound, which was perceived as pleasant. Further studies are needed before accepting neurostimulation as a treatment modality for chronic, therapeutically refractory tinnitus. Copyright (c) 2007 S. Karger AG, Basel.

 Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study.

 J Neurol Neurosurg Psychiatry. 2007 Feb;78(2):152-156.

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 Background: Tinnitus has been shown to respond to modulations of cortical activity by high-frequency and low-frequency repetitive transcranial magnetic stimulation (rTMS).

 Objective: To determine the tinnitus-attenuating effects of a 2-week daily regimen of rTMS, navigated to the maximum of tinnitus-related increase in regional cerebral blood flow.

 Methods: Six patients with chronic tinnitus were enrolled in this sham-controlled crossover study and treated with 2x2 weeks of suprathreshold 1 Hz rTMS (30 min) applied to the region with maximal tinnitus-related increase in regional cerebral blood flow delineated by functional imaging with [15O]H2O positron emission tomography and a control area. Tinnitus-related distress was assessed before and after each treatment and 2 weeks after the end of the 4-week course of stimulation using a validated tinnitus questionnaire. Additional self-assessment scores of tinnitus change, loudness and annoyance were obtained.

 Results: In five of six patients, rTMS induced greater reduction of the tinnitus questionnaire score than sham stimulation. In two patients, all parameters measured (tinnitus change score, tinnitus loudness, tinnitus annoyance) showed unequivocal improvement. At the group level, the degree of response in the tinnitus questionnaire score was correlated with tinnitus-associated activation of the anterior cingulate cortex. Two weeks after the final stimulation, tinnitus had returned to baseline in all patients but one.

 Conclusion: Tinnitus can be attenuated by low-frequency rTMS navigated to each person's maximum tinnitus-related cortical hyperactivity. The effects are only moderate; interindividual responsiveness varies and the attenuation seems to wear off within 2 weeks after the last stimulation session. Notably, tinnitus-related anterior cingulate cortex activation seems to predict the response to rTMS treatment.
Repetitive Transcranial Magnetic Stimulation for Tinnitus: A Pilot Study.
Laryngoscope. 2007 Mar;117(3):529-534.
Smith JA1, Mennemeier M2, Bartel T1, Chelette KC2, Kimbrell T4, Triggs W5, Dornhoffer JL1, 2
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Objectives/Hypotheses: Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been shown to alleviate tinnitus perception, presumably by inhibiting cortical activity associated with tinnitus. We conducted a pilot study to assess effectiveness of neuronavigated rTMS and its effects on attentional deficits and cortical asymmetry in four patients with chronic tinnitus using objective and subjective measures and employing an optimization technique refined in our laboratory.

Study design: Randomized, placebo-controlled (sham stimulation) crossover study.

Methods: Patients received 5 consecutive days of active, low-frequency rTMS or sham treatment (using a 45-degree coil-tilt method) before crossing over. Subjective tinnitus was assessed at baseline, after each treatment, and 4 weeks later. Positron emission tomography/computed tomography (PET/CT) scans were obtained at baseline and immediately after active treatment to examine change in cortical asymmetry. Attentional vigilance was assessed at baseline and after each treatment using a simple reaction time test.

Results: All patients had a response to active (but not sham) rTMS, as indicated by their best tinnitus ratings; however, tinnitus returned in all patients by 4 weeks after active treatment. All patients had reduced cortical activity visualized on PET immediately after active rTMS. Mean reaction time improved (P < .05) after active but not sham rTMS.

Conclusions: rTMS is a promising treatment modality that can transiently diminish tinnitus in some individuals, but further trials are needed to determine the optimal techniques required to achieve a lasting response. It is unclear whether the improved reaction times were caused by tinnitus reduction or a general effect of rTMS. PET/CT scans immediately after treatment suggest that improvement may be related to reduction of cortical asymmetry associated with tinnitus.

Transcranial magnetic stimulation for the treatment of auditory phantom perceptions (tinnitus) – a randomized placebo controlled study.
(Abstract of ARO Meeting Denver, Colorado)
Tobias Kleinjung1, Berthold Langguth2, Peter Eichhammer2, Michael Landgrebe2, Philipp Sand2, Juergen Strutz1, Goeran Hajak2
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Introduction: Repetitive transcranial magnetic stimulation (rTMS) represents a minimal invasive tool for focal brain stimulation. Patients suffering from auditory phantom perceptions (tinnitus) demonstrated focal brain activation within the auditory cortex. Neuronavigated low frequency transcranial magnetic stimulation of the area of increased activity cortex was able to reduce tinnitus perception in first studies.

Methods: Patients suffering from chronic tinnitus underwent a FDG- PET study (positron emission tomography with [18F]deoxyglucose) to detect areas of increased metabolic activity in the cortex. Fusioning of the individual PET scans with structural MRI-scans (T1, MPRAGE) revealed an increased metabolic activation in the primary auditory cortex as target point for rTMS. The exact position of the figure 8-shaped magnetic coil in relation to the target was monitored with a neuronavigational system. The rTMS (110% motor threshold; 1 Hz; 2000 stimuli/ day over 10 days) was performed in a placebo controlled design.

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For sham stimulation a specific sham-coil system was used. Treatment outcome was assessed over a 3 months period with a tinnitus questionnaire (Goebel and Hiller).

**Results:** Up to now 60 patients have been included in the trial. In a majority of patients we could localize an increased metabolic activation in the upper dorsal part of the left superior temporal gyrus corresponding to areas of the auditory cortex. Preliminary results indicate that active rTMS results in a significant improvement of tinnitus perception compared to sham rTMS. Treatment effects lasted up to 3 months in some patients.

**Conclusion:** Neuronavigated low-frequency rTMS seems to represent a promising strategy for the treatment of chronic tinnitus.

**IV Behavioral therapy**

**Cognitive behavioural therapy for tinnitus.**
Martinez Devesa P, Waddell A, Perera R, Theodoulou M

**Background:** Tinnitus is an auditory perception that can be described as the experience of sound, in the ear or in the head, in the absence of external acoustic stimulation (not usually audible to anyone else). At present no specific therapy for tinnitus is acknowledged to be satisfactory in all patients. Cognitive behavioural therapy (CBT) uses relaxation, cognitive restructuring of the thoughts and exposure to exacerbating situations in order to promote habitation and may benefit tinnitus patients, as may the treatment of associated psychological conditions.

**Objectives:** To assess whether cognitive behavioural therapy is effective in the management of patients suffering from tinnitus.

**Search strategy:** Our search included the Cochrane ENT Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2006), MEDLINE and EMBASE. The last search date was June 2006.

**Selection criteria:** Randomised controlled trials in which patients with unilateral or bilateral tinnitus as main symptom received cognitive behavioural treatment.

**Data collection and analysis:** One review author (PMD) assessed every report identified by the search strategy. The four review authors assessed the methodological quality, applied inclusion/exclusion criteria and extracted data.

**Main results:** Six trials comprising 285 participants were included. 1. Primary outcome: subjective tinnitus loudness

- CBT compared to a waiting list control group: we found no significant difference (Standardised Mean Difference (SMD) 0.06 (95% CI -0.25 to 0.37)).
- CBT compared to another intervention (Yoga, Education, Minimal Contact - Education and Education): we found no significant difference (SMD 0.1 (95% CI -0.22 to 0.42)).

2. Secondary outcomes
   - Depression
     - CBT compared to a waiting list control group: we found no significant difference in either group (SMD 0.29 (95%CI -0.04 to 0.63)).
     - CBT compared to another intervention (Yoga, Education and Minimal Contact - Education): we found no significant difference (SMD 0.01 (95% CI -0.43 to 0.45)).
   - Quality of life
     - CBT compared to a waiting list control group: we found a significant difference in favour of CBT versus the waiting list group (SMD 0.7 (95% CI 0.33 to 1.08)).
     - CBT compared to another intervention (Education, Minimal Contact - Education and Education): we also found a significant difference between CBT and the other intervention control group (SMD 0.64 (95% CI 0.29 to 1.00)).

There were no adverse/side effects reported in any trial.

**Authors’ conclusions:** We did not find a significant difference in the subjective loudness of tinnitus, or in the associated depression. However we found a significant improvement in the quality of life (decrease of global tinnitus severity) of the participants, thus suggesting that cognitive behavioural therapy has an effect on the qualitative aspects of tinnitus and contributes positively to the management of tinnitus.
Ericksonian hypnosis in tinnitus therapy: effects of a 28-day inpatient multimodal treatment concept measured by Tinnitus-Questionnaire and Health Survey SF-36.

Eur Arch Otorhinolaryngol. 2007 Jan 6.
Ross UH, Lange O, Unterrainer J, Laszig R
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For the first time, the therapeutic effects on subacute and chronic tinnitus of an inpatient multimodal treatment concept based on principles of Ericksonian hypnosis (EH) were examined by standardized criteria of the Tinnitus Questionnaire (TQ) and Health Survey (SF-36) within a controlled prospective, longitudinal study. A total of 393 patients were treated within an inpatient closed-group 28-day-setting based on a resource-oriented, hypnotherapeutic concept. The severity of tinnitus was assessed by TQ at times of admission, discharge and also at a 6- and 12-month follow-up. Health-related quality of life was evaluated before and after therapy using the SF-36. After therapy, a decrease in TQ score was seen in 90.5% of the patients with subacute tinnitus and in 88.3% of those with chronic tinnitus. Assessment of the TQ score at the end of therapy revealed highly significant improvements of 15.9/14.1 points in mean. Effect sizes in the treatment groups (0.94/0.80) were superior to those in the waiting-list controls (0.14/0.23). The TQ score remained stable in the follow-up controls. Significant improvement in health-related quality of life has been observed within the treatment groups depending on initial level of tinnitus severity I-IV according to TQ. Using a multimodal treatment concept with emphasis on resource-activating approaches of EH the annoyance of tinnitus can be significantly reduced while health-related quality of life is enhanced within a comparatively short treatment period of 28 days.

V Diagnostics

Acoustic shock.
J Laryngol Otol. 2007 Feb 19;:1-5.
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Acoustic shock is a recently recognised clinical entity: following an abrupt, intense and unanticipated acoustic stimulus, usually delivered by a telephone handset or headset, some individuals report a symptom cluster that includes otalgia, altered hearing, aural fullness, imbalance, tinnitus, dislike or even fear of loud noises, and anxiety and/or depression. Symptoms start shortly after the triggering acoustic incident and can be short-lived or can last for a considerable time. If persistent, the condition can lead to significant disability. Proposed mechanisms include involvement of the tensor tympani muscle, hyperexcitability of central auditory pathways, and a precursive state of raised anxiety or arousal. A formal treatment programme has not yet been proposed, but the potential utility of modern therapeutic techniques for tinnitus and hyperacusis are considered. Given the large number of UK residents working in telephone call centres, this condition is of considerable clinical importance.

Anxiety and Depressive Symptoms in Tinnitus Patients.
(Abstract of ARO Meeting Denver, Colorado)
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1Fondazione Ascolta e Vivi, 2Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena

Our clinical knowledge of tinnitus is based on treatment of over 1500 tinnitus patients. We have observed
a correlation between tinnitus and symptoms of anxiety and depression which often affect daily life. Patients report that an increasing level of anxiety also exacerbates tinnitus symptoms. This can be explained neurophysiologically by the effect of the limbic system, cortex and peripheral neuropathways in tinnitus. The aim of this study is to investigate any correlation between tinnitus and anxiety and depressive symptoms.

**Materials and methods:** The assessment is composed of: Visual Analogical Scales (VAS) for the evaluation of tinnitus induced problems; Tinnitus Handicap Inventory (THI); State and Trait Anxiety Inventory-Y (STAI S-T); Beck Depression Inventory (BDI). These instruments were chosen based on their psychometric properties, time of administration and validity in many languages; the sample consists of 67 patients.

**Results:** Correlation between anxiety symptoms and THI score is significant (p<0,01); the same significance was found between depressive symptoms and THI as well as between STAI and BDI. Significant correlation was also found between these questionnaires and the intensity of tinnitus, annoyance and effect on life evaluated by the VAS scale. 23% of the sample had severe tinnitus. Mean anxiety was around the 65th percentile; 35% having an anxiety disorder. 12% of the total sample shows a depressive pathology. 11% of the sample have both anxiety and depression. An inverse correlation between STAI and BDI scores and the duration of tinnitus was observed.

**Conclusions:** Although about 1/3 of patients are suspected of suffering from anxiety, a pathological level of anxiety and depression was found in only about 10% of the sample. The THI questionnaire is a good predictor for patients with higher levels of depression and anxiety.

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**Cholesterol granuloma surrounding the endolymphatic sac.**


**Kanzaki S, Araki Y, Okamoto Y, Kurita A, Ogawa K**

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We report a unique case of cholesterol granuloma (CG) surrounding the endolymphatic sac (ES). A 49-year-old man presented with the left side of sensorineural hearing loss, tinnitus, and vertigo. Magnetic resonance and computed tomography imaging revealed a CG surrounding the left ES. The patient initially underwent left transmastoid surgical resection of the tumor. At the time of surgery, brown fluid was aspirated from the tumor, but no other tumors were found. Histopathological examination revealed that the tumor contained cholesterol crystals, confirming the diagnosis of CG. At his 12-month postoperative follow-up, there was no evidence of recurrence. We discuss the radiology, pathology, and surgical removal of CGs surrounding ES.

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**Clinical characterization and genetic analysis of a large Brazilian family with Familial Migrainous Vertigo.**

(Abstract of ARO Meeting Denver, Colorado)

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**Introduction:** Since 1995, we have been studying a large Brazilian family whose members are affected with migrainous vertigo syndrome.

**Objectives:** The aim of this study is to describe clinical features and the natural history of this symptom
complex. We also wish to characterize the genetic basis for this condition in the family.

Methods: A six generation Caucasian family originating from the center of Brazil was followed over ten years and data was collected from 146 members. Clinical data collected has included detailed case histories, otolaryngological and neurological examinations, audiometric evaluation, vestibular testing and imaging studies. Serial clinic and audiometric evaluations were done. We have also undertaken a genome wide linkage analysis in 64 family members and subsequent fine mapping using microsatellite markers.

Results: Our study reveals an autosomal dominant pattern of transmission with incomplete penetrance of the gene and variable expression. Of the 146 members, 32 suffer from migraine with aura. Of these 32 individuals, 10 also suffer from episodic vertigo, tinnitus and/or aural fullness. Audiometric evaluation did not show classic low tone fluctuating sensorineural hearing loss (SNHL). Imaging studies were normal. In this family, migraine preceded the neuro-otological symptoms by 15-20 years on average. Overall, migraine symptoms decreased with time, while the vertigo symptoms had a tendency to get worse. Genetic analysis revealed an area with high lod scores in chromosome 5. Therefore, the genetic locus for this symptom complex in this family appears to be on chromosome 5. Studies are ongoing to investigate candidate genes in this locus.

A clinical study of the efferent auditory system in patients with normal hearing who have acute tinnitus.


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Objective: Etiological diagnosis and treatment of tinnitus still remain challenging in clinical practice. The aim of this study was to determine the potential contribution of a defective cochlear efferent innervation to the onset of tinnitus in patients with normal hearing.

Study design: Prospective randomized controlled study.

Setting: Otorhinolaryngology department of a general hospital.

Patients: The patient group consisted of 18 normal-hearing adults (7 men, 11 women) with acute tinnitus (bilateral in 3 patients).

Interventions: Tympanogram, stapedial muscle reflex, pure tone audiometry, tinnitus pitch matching, spontaneous otoacoustic emissions, and distortion product otoacoustic emissions (DPOAEs) in the absence and presence of contralateral suppression by white noise.

Main outcome measure: DPOAEs suppression amplitudes recorded from tinnitus and nontinnitus ears of the patients’ group were compared with each other and with a control group. RESULTS: The contralateral application of white noise induced the enhancement of DPOAE amplitudes in some patients. The suppression of DPOAE amplitudes by contralateral white noise did not reach statistically significant levels in either ear (with or without tinnitus). On the contrary, under the same conditions, our control group demonstrated statistically significant reduction of DPOAE amplitudes at all frequencies.

Conclusion: Patients with normal hearing acuity who have acute tinnitus seem to have a less effective functioning of the cochlear efferent system because the application of contralateral noise enhanced the DPOAEs or suppressed them less intensely than it did in a control group. Further studies may establish the clinical applications for the diagnosis of changes in efferent function, in the subjective evaluation, patient etiological grouping, treatment, or prognosis of tinnitus.
The Epidemiology of Meniere's Disease and the Problems of Diagnosis.
(Abstract of ARO Meeting Denver, Colorado)
George Gates
University of Washington

MD is a common disorder of unknown etiology that causes episodic vertigo with hearing loss, tinnitus, and ear fullness. Stress is a commonly cited co-factor in the pathogenesis of MD. MD affects both genders equally and is most common in 40-55 year olds. Some women have symptoms in relation to their menstrual cycle; whether this is hormonal or a reflection of stress is unclear. The overall prevalence of MD is estimated from 17/100,000 population in the U.S. To 46/100,000 in Sweden. The clinical course is variable and unpredictable. About 70% of patients respond to conservative treatment, such as low salt diet, diuretics and symptom suppressants, however 30% get progressively worse and often require surgical therapy. Although the long-term treatment results are acceptable, selection of cases for medical and surgical therapy varies widely.

Imaging of pulsatile tinnitus: a review of 74 patients.
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Department of Radiology, GATA Haydarpasa Teaching Hospital, Istanbul, Turkey.

Objective: Our aim was to assess the effectiveness of imaging modalities in detecting the underlying pathologies in patients with pulsatile tinnitus.

Materials and methods: Seventy-four patients with pulsatile tinnitus were radiologically evaluated. All patients except two are evaluated on a thin-section bone algorithm computed tomography scan covering the temporal bone and skull base, 14 patients with or without contrast-enhanced brain computed tomography, 7 patients with magnetic resonance imaging and magnetic resonance angiography, 5 patients with digital subtraction angiography, and 12 patients with Doppler ultrasonography.

Results: The underlying pathology of tinnitus was detected in 50 patients (67.6%), and 24 patients were normal with radiologic studies. The most common cause was high jugular bulb (21%) followed by atherosclerosis, dehiscent jugular bulb, aneurysm of internal carotid artery, dural arteriovenous fistula, aberrant internal carotid artery, jugular diverticulum, and glomus tumor.

Conclusion: It was concluded that radiologic imaging methods are effective in detecting the underlying pathology of pulsatile tinnitus.

Post-traumatic pulsatile tinnitus: the hallmark of a direct carotico-cavernous fistula.
Department of Otolaryngology, Az St Jan Hospital, Bruges, Belgium.

Following trauma to her right frontal region, a 68-year-old woman suffered bilateral, benign, paroxysmal, positional vertigo and a left-sided, longitudinal petrosal bone fracture, with secondary facial palsy and ossicular luxation. From the onset, the patient complained of pulsatile, left-sided tinnitus. After eight weeks, she developed left-sided ocular symptoms, progressing from conjunctival hyperaemia and orbital oedema to an abducens nerve palsy, and ultimately to heart failure. The case and the final diagnosis of carotico-cavernous fistula are discussed. Guidelines are proposed for a diagnostic approach to pulsatile tinnitus and for the optimal management of patients presenting with pulsatile tinnitus associated with ocular symptoms.
Perceptual Components of Tinnitus Severity
(Abstract of ARO Meeting Denver, Colorado)
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Most existing questionnaires for assessing the severity and negative impact of tinnitus tend to emphasize functional or emotional effects of tinnitus. While such measures are important for diagnostic purposes and as outcome measures, they require time periods of several days to several weeks or longer for observation of meaningful changes following treatment. More rapid evaluation of treatment outcomes can be obtained using patients’ reports of the perceptual characteristics of tinnitus such as its loudness, salience, unpleasantness, intrusiveness, and the percentage of time the tinnitus sensations are perceived. However, the extent to which such perceptual attributes of tinnitus are appropriate indicators of the clinical severity of tinnitus has received relatively little systematic attention. To maximize measurement sensitivity, we designed a 43-item questionnaire to quantify patients’ responses concerning functional, emotional and perceptual aspects of tinnitus, using a 0-10 point response scale for each question. A total of 327 subjects with varying levels of tinnitus, recruited from a diverse group of patients attending clinics in three locations (Oregon, Ohio, Florida), responded to the questionnaires before and after receiving treatment. As expected, the perceptual attributes listed above were positively related to global measures of tinnitus distress, including (1) a Visual Analog Scale and (2) the question “How much of a problem is your tinnitus?” (response levels: 0=Not a problem; 1=Small problem; 2=Moderate problem; 3=Big problem; 4=Very big problem). Effect sizes for the perceptual measures (computed for subjects reporting treatment benefit) ranged from 0.49- 1.50. Additional data will be presented concerning the ability of perceptual measures to serve as reliable, sensitive outcome measures for studies that require rapid evaluation of tinnitus treatments having immediate effects, such as stimulation with electrical, magnetic, or acoustic stimuli.

Relationships among speech perception, self-rated tinnitus loudness and disability in tinnitus patients with normal pure-tone thresholds of hearing.
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Exactly how speech perception and tinnitus perception are related remains unclear. This study investigated how tinnitus alone affects speech perception and the relationship between speech perception, tinnitus loudness, and tinnitus disability. The Mandarin Speech Perception in Noise Test (MSPIN), Tinnitus Loudness Scaling (TLS), and Tinnitus Handicap Inventory (THI) were utilized to assess 20 tinnitus patients with normal hearing. The tinnitus group had a significantly lower MSPIN score than the control group (p < 0.01). TLS and THI scores were strongly correlated (r(2): 0.534 approximately 0.627, p < 0.05). Correlations between MSPIN and TLS or THI scores were not significant. Tinnitus loudness correlated well with tinnitus-related disability. Neither tinnitus loudness nor disability was strongly correlated with speech perception. In noisy environments, tinnitus sufferers had significantly poorer ability to recognize speech than control subjects. Copyright (c) 2007 S. Karger AG, Basel

Sofia profile plot: a new graphical approach to present the changes of hearing thresholds with time.
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After pure-tone audiometry, we have several sequences of threshold values. Usually, a multiple-line plot is used to present and compare data between measurements by overlaying them in a single graph. Calculation of air-bone gap and pure-tone average is widely accepted as an approach to simplify statistical handling of these data. The aim of this report was to introduce the Sofi profile plot using as examples different otosclerotic cases. This plot provides a simple way to visually present several pre- and postoperative hearing thresholds. Individual data points (pure-tone average and some other thresholds) are presented by marks in two-dimensional space. The vertical axis represents the time line and starts with the first threshold evaluation. The horizontal scale is used to mark hearing levels in decibels -- the right ear on the left of the vertical axis and the left ear on the right. The Sofi profile plot was developed especially for otosclerotic patients and permits the unambiguous marking of the onset of any individual unilateral or bilateral event (e.g. operation, revision, tinnitus) and thus to visually inspect its impact on hearing levels.

**Susceptibility to Tinnitus Revealed at 2 kHz Range by Bilateral Lower DPOAEs in Normal Hearing Subjects with Noise Exposure.**


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Centre de Recherches du Service de Sante des Armees (CRSSA), La Tronche, France.

We investigated potential markers of susceptibility to tinnitus in a group of normal hearing young pilots aged 25-35 years and with 8 +/- 5 years of aircraft noise exposure. 316 pilots were interviewed about their tinnitus status and were tested for hearing thresholds (audiograms) and distortion products otoacoustic emissions (DPOAE-grams). There was no subject with permanent tinnitus. 23% reported having occasionally perceived tinnitus after flight missions and 77% reported never having experienced tinnitus after flight missions. General discomfort in the ears to noise was higher in the occasional tinnitus group (15 vs. 6%). The major finding was that difference of susceptibility to tinnitus in normal hearing subjects exposed to noise on a daily basis seemed to be clearly related to lower DPOAEs, bilaterally, in the 1500- to 2800-kHz range. However, no difference could be observed between groups on audiograms at the 2-kHz frequency range. This study provided evidence of outer hair cell dysfunctions in normal hearing subjects exposed to noise and susceptible to tinnitus. Hypersensitivity to noise and decreased DPOAEs in a non-noise-specific frequency range support the idea of another alteration mechanism than noise itself. This point was discussed in the light of recent publications. Copyright (c) 2007 S. Karger AG, Basel.

**[Validation of the German-Version Tinnitus Handicap Inventory (THI).]**

*Psychiatr Prax.* 2007 Jan;34(S1):140-142. [Article in German].


Klinik für Hals-Nasen-Ohren-Heilkunde der Universität Regensburg

**Objective:** Tinnitus counts among the most debilitating auditory handicaps and is often complicated by insomnia, concentration difficulties, depression, frustration and irritability. To facilitate the grading of symptoms, we validated a German-version Tinnitus Handicap Inventory (THI) in 74 subjects suffering from chronic tinnitus.

**Methods:** Outcome validity was assessed using the Tinnitus Questionnaire (TQ, German adaptation by Goebel u. Hiller [1998]). Construct validity was assessed using the Beck Depression Inventory (BDI).

**Results:** The German THI featured excellent internal consistency (total score Cronbach’s alpha = 0.93). Factor analysis disclosed three THI subscales as proposed earlier by Newman et al. [1996]. Intercorrelations were strong both between the THI and the TQ ( R = 0.70), and between the THI and the BDI ( R = 0.64).

**Conclusions:** The German-version THI qualifies as a rapid and statistically robust tool for grading the impact of tinnitus on daily living. With regard to depressive symptomatology, sensitivity of the THI was comparable to that of the TQ.
Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation.
Hum Brain Mapp. 2007 Mar;28(3):238-246.
Plewnia C, Reimold M, Najib A, Brehm B, Reischl G, Plontke SK, Gerloff C
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Recent data suggest that chronic tinnitus is a „phantom auditory perception“ caused by maladaptive neuroplasticity and subsequent hyperactivity in an extended neuronal network including the primary auditory cortex, higher-order association areas, and parts of the limbic system. It was suggested that attenuation of this tinnitus-associated hyperactivity may offer a rational option for lasting tinnitus reduction. Here, we tested the hypothesis that tinnitus loudness can be attenuated by low-frequency repetitive transcranial magnetic stimulation (rTMS) individually navigated to cortical areas with excessive tinnitus-related activity as assessed by [(15)O]H(2)O positron-emission tomography (PET). Nine patients with chronic tinnitus underwent this combined functional imaging and rTMS-study. Group analysis of the PET data showed tinnitus-related increases of regional cerebral blood flow in the left middle and inferior temporal as well as right temporoparietal cortex and posterior cingulum. Repetitive TMS was performed at 1 Hz and 120% of the motor threshold for 5, 15, and 30 min, navigated to the individual maximum of tinnitus-related cortical hyperactivity. A noncortical stimulation site with the same distance to the ear served as sham control. Tinnitus loudness was reduced after temporoparietal, PET-guided low-frequency rTMS. This reduction, lasting up to 30 min, was dependent on the number of stimuli applied, differed from sham stimulation, and was negatively correlated with the length of the medical history of tinnitus in our patients. These data show the feasibility and effectiveness of rTMS guided by individual functional imaging to induce a lasting, dose-dependent attenuation of tinnitus. Of note, these effects were related to stimulation of cortical association areas, not primary auditory cortex, emphasizing the crucial role of higher-order sensory processing in the pathophysiology of chronic tinnitus. Hum Brain Mapp, 2007. (c) 2006 Wiley-Liss, Inc.

Effects of tinnitus laterality on brain activity – a positron emission tomography study.
(Abstract of ARO Meeting Denver, Colorado)
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Modern brain imaging methods including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) afford unprecedented opportunities for the in vivo study of central auditory system function. With the advent of these mapping techniques new insights into the etiology of chronic tinnitus could be gained. Particularly, PET studies have contributed to a paradigm shift, demonstrating that the actual generator of chronic tinnitus is central in most cases. In detail, using [18F] deoxyglucose (FDG) as a radiotracer our group could replicate and confirm previous findings pointing to a significantly increased metabolic activity in the left primary auditory cortex (PAC, Brodmann area 41) in patients suffering from permanent tinnitus complaints. These imaging results have also build the rationale basis to use low-frequency PET-guided repetitive transcranial magnetic stimulation as a causally orientated treatment option for tinnitus.

This finding of unilaterally increased metabolic activity in the left auditory cortex independently of tinnitus laterality contrasts with findings in animal models of tinnitus where increased activity has been detected in the auditory cortex contralateral to the tinnitus side.

To further investigate the effect of tinnitus laterality on brain activation patterns we compared FDG PET data from patients with different tinnitus laterality (unilateral left, unilateral right, bilateral predominantly...
right, bilateral). Results have shown that differences in tinnitus laterality are reflected by different metabolic activity patterns in distinct nonauditory cortical regions. These results may help to develop new treatment targets for chronic tinnitus and to further individualize treatment strategies.

Metabolic activation of auditory cortex and inferior colliculi during salicylate-induced tinnitus in rats: A microPET imaging study.
(Abstract of ARO Meeting Denver, Colorado)
Asit Paul, Edward Lobarinas, John Luisi, Richard Simmons, Hani Nabi, Richard Salvi
University at Buffalo

The purpose of this study is to investigate the metabolic activities in central auditory structures in vivo during salicylate-induced tinnitus in rats. The behavioral paradigm, schedule induced polydipsia-avoidance conditioning (SIPAC), was first used to determine if tinnitus was present in rats treated with a high dose of salicylate. Following verification of salicylate induced tinnitus, a dedicated, high resolution animal positron emission tomography system (microPET Focus 120) was used to image the changes in brain metabolic activities associated with a high-dose of salicylate (250 mg/kg, i.p). In both the baseline and salicylate condition, rats were placed in a sound attenuating cubicle for 60 min after the injection of a radiolabeled glucose analog, F-18 labeled fluorodeoxyglucose (FDG, ~74 MBq, i.p). Thereafter, microPET scans of the rat brains were performed for 60 min in the prone position under isoflurane gas anesthesia. The frontal pole was considered as reference (control) area; FDG counts in frontal pole were expressed as a fraction of injected FDG dose per unit volume. Counts ratio between central auditory structures (auditory cortices, thalami and inferior colliculi) and frontal pole was used to compare between baseline and post-salicylate metabolic activity. The results show that the frontal pole FDG activity did not change between baseline and the post-salicylate condition, suggesting it as a metabolically inert area during tinnitus. During salicylate induced tinnitus, inferior colliculi (P=0.03) and auditory cortices (P=0.003) showed significant increase in FDG activities, whereas there was no significant difference in thalamic activity (P=0.07) from the pre-salicylate, baseline state. Our study shows increased metabolic activity consistent with neuronal activation in inferior colliculi and auditory cortices during salicylate-induced tinnitus in rats (Supported by Tinnitus Research Consortium).

The neural code of auditory phantom perception.
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Tinnitus is defined by an auditory perception in the absence of an external source of sound. This condition provides the distinctive possibility of extracting neural coding of perceptual representation. Previously, we had established that tinnitus is characterized by enhanced magnetic slow-wave activity (approximately 4 Hz) in perisylvian or putatively auditory regions. Because of works linking high-frequency oscillations to conscious sensory perception and positive symptoms in a variety of disorders, we examined gamma band activity during brief periods of marked enhancement of slow-wave activity. These periods were extracted from 5 min of resting spontaneous magnetoencephalography activity in 26 tinnitus and 21 control subjects. Results revealed the following, particularly within a frequency range of 50-60 Hz: (1) Both groups showed significant increases in gamma band activity after onset of slow waves. (2) Gamma is more prominent in tinnitus subjects than in controls. (3) Activity at approximately 55 Hz determines the laterality of the tinnitus perception. Based on present and previous results, we have concluded that cochlear damage, or similar types of deafferentation from peripheral input, triggers reorganization in the central auditory system. This produces permanent alterations in the ongoing oscillatory dynamics at the
higher layers of the auditory hierarchical stream. The change results in enhanced slow-wave activity reflecting altered corticothalamic and corticolimbic interplay. Such enhancement facilitates and sustains gamma activity as a neural code of phantom perception, in this case auditory.

VII Pathophysiology

Acoustic Trauma Induces Long-Term Temporal Correlations in DCN.
(Abstract of ARO Meeting Denver, Colorado)

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Changes to the functional properties of the dorsal cochlear nucleus (DCN) that follow acoustic trauma are not well understood. Past studies (e.g. Kaltenbach et al.) have reported an increase in mean spontaneous firing rates following acoustic trauma. However, recent work from our lab in DCN principal cells has found no change in mean spontaneous firing rate. This finding has led us to study temporal patterns in DCN spontaneous activity that may change independent of the mean rate. One pattern of specific interest is long-range dependence (LRD). LRD is an effect of fractal rate fluctuations, where rate fluctuations have weak correlations on the scale of minutes.

Cats were acoustically traumatized by exposure to 10kHz noise at 107dB SPL for four hours. Compound action potentials showed a >60dB threshold shift at and above 10kHz. Ten minutes of spontaneous activity were recorded from isolated single DCN units in these deaf cats as well as a group of normal hearing cats. LRD can be quantified by computing the Fano factor for a range of counting times. The Fano factor has a power-law dependence on counting time, and the exponent of the power-law is called the fractal dimension. This dimension is a measure of the spike count variance and LRD. The average fractal dimension of the 10kHz-exposed DCN units is significantly higher than that of normal DCN units.

Surprisingly, there is no correlation between higher fractal dimension and the degree of threshold shift (or spontaneous activity). The increased fractal dimension implies that neurons in exposed cats have more long-term correlations and higher spike count variance. Increased spike count variance could contribute to tinnitus by providing a fluctuating rate signal that would be interpreted as resulting from a fluctuating sound. (Supported by NIH grant DC00109 and the Tinnitus Consortium).

Alterations In Spontaneous Discharge Rates Of Single Units In The Dorsal Cochlear Nucleus Induced By Intense Sound Exposure.
(Abstract of ARO Meeting Denver, Colorado)

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Wayne State University

Hyperactivity in the dorsal cochlear nucleus (DCN), characterized by increases in spontaneous activity, has been implicated as a possible factor contributing to tinnitus following noise exposure. Evidence for the phenomenon of noise induced hyperactivity in the DCN has been obtained mostly using methods that examine activity of neural clusters (multiunit recordings) or populations of neurons (c-fos, 2-deoxyglucose), an exception being a study by Brozoski et al., 2002, demonstrating noise-induced increases in single unit spontaneous discharge rates in the chinchilla DCN. Evidence for noise-induced hyperactivity from our laboratory has been based almost entirely on multiunit recordings, raising the question of whether these increases reflect increased discharge rates at the single unit level, or instead, might be due to some other change. Increased multiunit activity could result from increases in extracellular voltages caused by increases in single unit spike amplitude, increased synchronous discharges, increases
in the number of active units, or breakdown in intercellular insulation (demyelination). The present study was undertaken to determine whether intense sound exposure causes increases in the discharge rates of single units in the DCN. We performed three separate experiments, each comparing spontaneous discharge rates of single units in the DCNs of tone-exposed and control hamsters. In each experiment, a different combination of electrode impedance, electrolyte solutions, exposure conditions and recovery times were used. Animals were exposed to an intense (115-127 dB SPL) 10 kHz tone for 4 hours, either while anesthetized or while awake and freely mobile. Post-exposure recovery times were varied from 5 to 30 days. Recordings were obtained from more than 200 units at varying depths below the DCN surface. The results from all three experiments revealed considerable overlap in the range of spontaneous rates recorded in the two animal groups. Despite this overlap, the mean single unit discharge rates from exposed animals were consistently higher than those from control animals and were statistically significant. These results make it likely that multiunit hyperactivity reflects, at least in part, increases in single unit discharge rate. The possibility that one or more other factors might also contribute to multiunit hyperactivity cannot be ruled out. (Supported by NIH grant DC003258).

**Correlated neural activity as the driving force for functional changes in auditory cortex.**

Hear Res. 2007 Jan 16.

Eggermont JJ

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The functional role of neural synchrony is reflected in cortical tonotopic map reorganization and in the emergence of pathological phenomena such as tinnitus. First of all experimenter-centered and subject-centered views of neural activity will be contrasted; this argues against the use of stimulus-correction procedures and favors the use of a correction procedure based on neural activity without reference to stimulus timing. Within a cortical column neurons fired synchronously with on average about 6% of their spikes in a 1ms bin and occasionally showing 30% or more of such coincident spikes. For electrode separations exceeding 200mum the average peak correlation strength only occasionally reached 3%. The experimental evidence for coincidence of neural activity, neural correlation and neural synchrony shows that horizontal fibers activity can induce strong neural correlations. Cortico-cortical connections for a large part connect cell groups with characteristic frequencies differing by more than one octave. Such neurons have generally non-overlapping receptive fields but still can have sizeable peak cross-correlations. Correlated neural activity and heterotopic neural interconnections are presented as the substrates for cortical reorganization; increased neural synchrony and tonotopic map reorganization go hand in hand. This links cortical reorganization with hypersynchrony that can be considered as an important driving force underlying tinnitus.

**Cortical and subcortical fMRI of unilateral tinnitus.**

(Abstract of ARO Meeting Denver, Colorado)

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The current understanding of possible mechanisms of tinnitus generation is still poor. Our goal is to find a possible neural correlate of tinnitus, using fMRI.

In this work we used 10 patients (5 male) with unilateral tinnitus (5 left sided, 5 right sided) and 9 healthy subjects (4 male). Subjects had no or minor hearing deficits in both ears (max. 30 dB HL). Experiments were performed on a 3T Philips Intera scanner. 41 coronal slices (2 mm) were acquired using a matrix of 128x128 voxels (1.75 x 1.75 mm2) using sparse sampling (TR=10 s). Stimuli consisted of right and left
stimulation with levels of 40 and 70 dB (SPL) of rippled noise. Data were realigned and normalized to a custom made template using SPM5. First level analysis was performed using multiple regression and regions of interest (ROI) of the auditory pathway were defined (cortex, MGB, IC, SOC and CN). Percent signal changes were obtained for each condition for each region and symmetry indices were obtained. A second level analysis was performed using an ANOVA design to assess group differences and group-by-level interactions. Results from the ROI analysis indicate that for the control group the cortex and inferior colliculus responded strongest to contralateral stimuli. A difference was observed between the two tinnitus patient groups. The left sided tinnitus group showed a predominant response towards ipsilateral stimuli at the cortex while the right sided tinnitus group responded more like the control group. A general trend of higher activation in the inferior colliculus as response to stimuli was observed in tinnitus patients compared to controls. Our data suggest that there are differences in activation on cortex level and inferior colliculus level between the control group and the patient groups. Analysis of other nuclei will be performed.

**Differential Expression of HCN Channels in the Cochlear Nucleus.**
(Abstract of ARO Meeting Denver, Colorado)

**Ana Caban Cardona, Rebecca Eernisse, Paul Popper, David Friedland**
Medical College of Wisconsin

Hyperpolarization-activated currents (Ih) have been identified in many auditory brainstem neurons including octopus and bushy cells. The channels responsible for these currents are hyperpolarization-activated cyclic nucleotide-gated potassium channels of which four isoforms are known (i.e., HCN1-4). These channels influence resting membrane potentials, regulate neuronal excitability and likely play important roles in auditory signal processing. We used real-time RT-PCR and immunohistochemistry to investigate differential expression of all four HCN channels among the subdivisions of the cochlear nucleus. Higher levels of HCN2 and HCN4 mRNA were detected in the ventral subdivisions of the cochlear nucleus than in the DCN, although this did not reach statistical significance. Real-time RT-PCR results for HCN1 and HCN3, in contrast, showed no differential expression. We found immunostaining for HCN2 and HCN4 in the DCN but no staining in this region for the other two channels. Our HCN2 labeling was predominantly found in cartwheel cells although previous reports have also shown HCN2 in fusiform cells. We found HCN4 to be most highly expressed in the fusiform cells. HCN4 was also noted among large neurons within the auditory nerve root. We found no neuronal staining for HCN3 in any subdivision and all HCN3 staining appeared localized to fibers in the peri-neuronal spaces. Similar to other studies, we found strong HCN1 staining on octopus cells of the PVCN but in contrast to other studies we did not identify significant staining in bushy cell regions. This study adds to the increasing evidence for differential expression among auditory neurons of the various hyperpolarization-activating potassium channels. The particular expression of HCN2 and HCN4, which are strongly regulated by cAMP, in the DCN may underlie some forms of neuronal plasticity such as that associated with noise-induced DCN hyperactivity and the generation of tinnitus (Supported by NIH/NIDCD K08DC006227).

**Differential gene expression profiles in salicylate ototoxicity of the mouse.**
(Abstract of ARO Meeting Denver, Colorado)

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**Conclusion:** This study demonstrated differential gene expression profiles in salicylate ototoxicity with
oligonucleotidemicroarray. This study may also provide basic information to candidate genes associated with hearing loss and/or tinnitus or recovery after salicylate-induced cochlear dysfunction. Objectives: Salicylate ototoxicity is accompanied by temporary hearing loss and tinnitus. The purpose of the present study is to evaluate the gene expression profiles in the mouse cochlea with salicylate ototoxicity using DNA microarray.

Materials and Methods: The subject mice were injected intraperitoneally with 400 mg/kg of sodium salicylate, and an approximate 30 dB threshold shift that was observed by auditory brainstem response was achieved 3 hours after an injection of sodium salicylate and the hearing threshold returned to within normal range at 3 days. Differential gene expression profiles at 3 hours after salicylate injection in comparison to the normal cochlea were analyzed with DNA microarray technology.

Results: The analysis of the ontogenic distribution was performed in up-regulated or down-regulated genes with the Gene Ontology Database system and GFINDer. Microarray revealed that 87 genes were up-regulated two-fold or more in the mouse cochlea with salicylate ototoxicity in comparison to the normal cochlea. Among these genes, increased expression levels of 30 functional genes were confirmed by semi-quantitative RT-PCR.

The dorsal cochlear nucleus as a contributor to auditory and non-auditory components of tinnitus.
(abstract of ARO Meeting Denver, Colorado)
James Kaltenbach
Waynes State University

The dorsal cochlear nucleus (DCN) has been modeled in numerous studies as a possible source of tinnitus-generating signals. This hypothesis was originally developed on the basis of evidence that the DCN becomes hyperactive following exposure to intense noise. Since these early observations, evidence that the DCN is an important contributor to tinnitus has grown considerably. In this paper, the available evidence to date will be summarized. In addition, the DCN hypothesis of tinnitus can now be expanded to include possible involvement in other, non-auditory components of tinnitus. It will be shown by way of literature review that the DCN has direct connections with non-auditory brainstem structures, such as the locus coeruleus, reticular formation and raphe nuclei, that are implicated in the control of attention and emotional responses. The hypothesis will be presented that attentional and emotional disorders, such as anxiety and depression, which are commonly associated with tinnitus, may result from an interplay between these non-auditory brainstem structures and the DCN. Implicit in this hypothesis is that attempts to develop effective anti-tinnitus therapies are likely to benefit from a greater understanding of how the levels of activity in the DCN are influenced by different states of activation of these non-auditory brainstem structures and vice versa.

Effects of salicylate on spontaneous activity in brain slices of different central auditory structures.
(Abstract of ARO Meeting Denver, Colorado)
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Salicylate is well known to produce tinnitus in humans and animals as well. It has been shown that systemic application of salicylate primarily changes outer hair cell electromotility and can influence neuronal activity in several parts of the auditory system. A direct action of salicylate on neurons of the inferior colliculus has been shown earlier in brain slice preparations. However, such an effect cannot be excluded for other parts of the central auditory pathway. The present study therefore investigated the in-vitro-effect
of salicylate application on the single unit spontaneous activity in brain slices of the cochlear nucleus, medial geniculate body and primary auditory cortex. Single unit responses were extracellularly recorded in 200 μm thick slices of the related deafferentiated brain area. During the measurement of spontaneous activity, 1.4 mM sodium salicylate (corresponding to tinnitus related serum levels in rats (Cazals, 2000, Prog. Neurobiol. 62, 583-631)) were added by superfusion. Sixty seven percent of the neurons in the cochlear nucleus, 76 percent of the neurons in the medial geniculate body and 64 percent of the neurons in the primary auditory cortex responded with a significant and reversible change in firing rate during superfusion with salicylate. The mean value of absolute changes in neuronal firing rate was significantly lower in the cochlear nucleus and primary auditory cortex than in the medial geniculate body. The response of neurons within the medial geniculate body was not significantly different to those obtained earlier from the inferior colliculus. The present data suggest that the auditory midbrain and thalamus plays a key role in the salicylate-induced tinnitus generation (Supported by the Sonnenfeld Foundation, Berlin, Germany).

Effects of Sodium Salicylate Induced Tinnitus on Auditory Cortex Local Field Potentials in Awake Rats.

(Abstract of ARO Meeting Denver, Colorado)

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Effects of Sodium Salicylate Induced Tinnitus on Auditory Cortex Local Field Potentials in Awake Rats

Sodium salicylate (aspirin), a well known inducer of tinnitus in both humans and animals, has been used extensively to investigate the neurophysiological correlates of tinnitus in animal models. Despite the fact that tinnitus is only perceived when subjects are conscious, nearly all of the neurophysiological studies of tinnitus carried out to date have been carried out under anesthetics which disrupt or alter the neural process that give rise to this phantom auditory sensation. To avoid the confounding effects of anesthetics, we carried out a series of experiments in which we measured the tone-burst evoked, local field potential from the auditory cortex (AC) of conscious rats before and after administering a high dose (250 mg/kg, i.p.) of salicylate known to produce behavioral signs of tinnitus around 16 kHz. A chronic, electrode implanted on the AC was used to record the cortical evoked potential in response to tone bursts presented at 4, 8, 12, 16, 24 and 32 kHz. Sound level was increased from the animal's threshold up to 90 dB SPL. Preliminary recordings showed that salicylate caused an increase in the peak-to-peak amplitude of the AC evoked response at 2 h and 6 h post-treatment. The largest amplitude increase, on the order of 80%, occurred at 16 kHz around 90 dB SPL (p<0.05). The salicylate-induced amplitude enhancement was noticeably less at frequencies below 16 kHz (45-55%, 4-12 kHz) and above 16 kHz (35-55%, 24-32 kHz). The AC amplitude enhancement was greatest at 2 h post-salicylate and decreased slightly at 6 h post-treatment, except at 16 kHz where there was a slight amplitude increases (Supported in part by grant from the Tinnitus Research Consortium).

Effects of somatosensory electrical stimulation on neural activity of the dorsal cochlear nucleus of hamsters.

(Abstract of ARO Meeting Denver, Colorado)

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It has been shown that sound exposure induces hyperactivity in the dorsal cochlear nucleus (DCN) in
hamsters, rats and chinchillas. This hyperactivity has been demonstrated to be correlated with the behavioral evidence for tinnitus. It is conceivable that suppression of hyperactivity in the DCN would suppress tinnitus. Somatosensory electrical stimulation (SES) has been used clinically to suppress tinnitus. However, due to a lack of understanding of the mechanisms of tinnitus suppression through SES, this approach has not been developed as an effective and reliable means for treating tinnitus. The current study was to test the effects of SES by delivering electrical current to the basal part of the pinna on DCN activity of both control and tone-exposed animals. Experiments were carried out in 26 adult hamsters, among which 13 were exposed to an intense tone under anesthesia (10 kHz tone, 125-130 dB SPL, 4 hrs) and another 13 age-matched control animals were similarly anesthetized but not exposed to a sound. One to three weeks after sound exposure and control treatment, multiunit activity was recorded at the surface of the left DCN before, during and after electrical stimulation of the left pinna. Electrical stimuli were single biphasic pulses of 200 us duration, delivered at 100-900 uA and 100pps. The results from both control and exposed groups revealed four response types: S-S, referring to suppression during and after stimulation; E-S, manifesting excitation during stimulation but suppression after stimulation; S-E, showing suppression during stimulation but excitation after stimulation; E-E, representing excitation during and after stimulation.

We found that there were more incidences of suppression than excitation during and after stimulation in both control and exposed groups. At higher levels of current, there was a significantly higher degree of suppression after stimulation than during stimulation for both groups, and there was also higher degree of suppression during and after stimulation in exposed animals than in controls. Our results are in line with previous clinical findings and support the view that DCN hyperactivity may be the direct neural correlate of tinnitus and suppression of DCN hyperactivity through SES may be one important approach in tinnitus suppression. (Supported by ATA).

GABAA Receptor Subunit Changes in a Noise-Exposure Model of Tinnitus: Rat Medial Geniculate Body.
(Abstract of ARO Meeting Denver, Colorado)
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The medial geniculate body (MGB) is the major auditory thalamic nucleus. MGB receives segregated ascending inputs from the inferior colliculus and descending cortical inputs from auditory cortex and nonauditory cortices. Previous studies have reported noise-induced evidence of tinnitus in the central auditory system. The present study examined selective GABAA receptor subunit changes three months following a 16kHz octave-band, 115dB noise-exposure, thought to induce tinnitus in rats. Two non “wild-type” GABAA receptor subunits, the α4 and δ subunits appear to be concentrated in synaptic and extra-synaptic constructs in MGB. Subunit message levels were quantified using in situ hybridization and subunit proteins were visualized using fluorescent immunocytochemistry in young and aged noise-exposed rats compared to young and aged unexposed controls. Young noise-exposed rats showed significant upregulation of the α4 subunit in both ipsi- and contralateral MGB (>50% increase), while aged rats showed α4 subunit upregulation in the contralateral MGB (>100% increase). Young and aged noise-exposed rats showed significant δ subunit upregulation in the MGB (dorsal, young>48%; aged>103%; ventral, young>84%; aged>170%) contralateral to the noise exposure.

It has been proposed (Sur et al., 1999) that upregulation of a α4δ GABAA receptor construct may be a compensatory plastic change to offset hyperactive neuronal networks. The present GABAA receptor subunit changes suggest that noise exposure related changes in MGB may, in part, subserve the per
cept of tinnitus. Age-related differences in subunit plasticity associated with noise-exposure might provide insights into the increased incidence of tinnitus in the elderly (Supported in part by American Tinnitus Association, NIH DC00151, and Merck Inc.).

**Hypoxic changes of central nervous system in noise-exposed mouse.**

(Abstract of ARO Meeting Denver, Colorado)

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**Background and objectives:** When noise-induced hearing loss occurs, hypoxia is detected in inner ear tissues. In previous study noise-induced inner ear hypoxia was proved by the increase of HIF-1a, which is expressed in the nucleus under hypoxic condition. Another hypoxic marker, pimonidazole is also widely used to see the hypoxic area by injection from outside. Existence of tinnitus or hyperacusis with noise-induced hearing change may suggest the change of central nervous system, but no exact site or timing of change is alleged until now. The study is designed to investigate the sitespecific hypoxic change in central auditory pathway during noise induced threshold shift.

**Materials and Methods:** Fifty six BALB/c hybrid mice with normal hearing were exposed to 120 dB SPL broad band noise for 3 hours. Immediately after noise and 7 days after noise exposure, the brains of mice were extracted. They were cryosectioned by 15 (m thickness and examined by immunofluorescence using monoclonal antibody of HIF-1a and pimonidazole HCL (hypoxyprobe(-1).

**Result:** After noise, the hearing thresholds of mice decreased to 49.5 (8.0 dB HL and the hearing were recovered to 27.9 (4.3 dB HL in 7 days. In the coronal section of brain, HIF-1a was detected immediately after noise in the auditory cortex, hippocampus and inferior colliculus. At least for 7 days, these signals persisted although without additional noise exposure. When the same slides were double stained by hypoxyprobe(-1, auditory cortex, hippocampus and inferior colliculus showed more localized hypoxic signals. The uptake of pimonidazole increased after 7 days.

**Conclusion:** In noise-induced transient threshold shift, hypoxia occurred in central nervous system and it persisted until 7 days, even though hearing was recovered. These changes were sensitive in auditory cortex and hippocampus.

**Key words:** Noise-induced hearing loss, Central nervous system, Hypoxia, Hypoxia-inducible factor 1a, Pimonidazole

**Molecular Correlates of Noise-Induced Tinnitus: Alterations in Gene Expression Influencing Inhibition in the Dorsal Cochlear Nucleus.**

(Abstract of ARO Meeting Denver, Colorado)

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Noise-induced tinnitus can be a debilitating condition that decreases quality of life. A hallmark of noise-induced central tinnitus is thought to be a change in the balance between inhibition and excitation with sustained increases in spontaneous neuronal activity that begin in the dorsal cochlear nucleus (DCN). To explore mechanisms involved in this imbalance we screened nine genes influencing inhibitory neurotransmission in the DCN for changes in expression at different times following noise exposure. Animals were divided into ten groups: half were exposed to an intense (125-130 dB SPL) 10 kHz tone for 4 hours, and half were age matched unexposed controls. Exposed animals were assessed at each of 5 different post-exposure recovery times: 0d, 2d, 5d, 14d and 29 days. The expression of nine genes, four glycine receptor genes (glyR1a, glyR2a, glyR3a, glyRb), four muscarinic receptors (muscR2, muscR3, muscR4, muscR5), and ChaT were assessed across groups. Each experimental group consisted of 3 RNA pools for each time-point, comprised of the DCN from three rats. Real time RT-PCR indicates that the DCN has...
some normal level of expression for each gene examined. In exposed animals, most glycine receptor subunits showed a trend towards an initial increase in expression followed by a decline in gene expression; however only glyR2a showed statistically significant increases in expression at the 0 (p ≤ 0.035) and 5 (p ≤ 0.020) day time points with a return to normal expression levels by 29 days. A similar trend was seen among muscarinic receptors with increased expression immediately after exposure, followed by decreased expression at later time points. Again, only one of the receptors showed a statistically significant change in expression with muscR4 having decreased levels two (p ≤ 0.025) and five (p ≤ 0.033) days after exposure. Compared with agematched controls, ChAT expression after noise exposure showed a different temporal pattern from those of glycine and muscarinic receptors, with no change in gene expression at the 0 day time point, a sustained increase in expression that was statistically significant by the 14 day time point (p ≤ 0.038) and a 65% decrease in expression at the 29 day time point (p ≤ 0.084). These results suggest that alterations in the expression of neurotransmitter receptors influencing inhibition are among the changes occurring in the DCN that are thought to underlie noise-induced tinnitus (Supported by R01 DC003258 to JAK).

The neural code of auditory phantom perception.
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Tinnitus is defined by an auditory perception in the absence of an external source of sound. This condition provides the distinctive possibility of extracting neural coding of perceptual representation. Previously, we had established that tinnitus is characterized by enhanced magnetic slow-wave activity (approximately 4 Hz) in perisylvian or putatively auditory regions. Because of works linking high-frequency oscillations to conscious sensory perception and positive symptoms in a variety of disorders, we examined gamma band activity during brief periods of marked enhancement of slow-wave activity. These periods were extracted from 5 min of resting spontaneous magnetoencephalography activity in 26 tinnitus and 21 control subjects. Results revealed the following, particularly within a frequency range of 50-60 Hz: (1) Both groups showed significant increases in gamma band activity after onset of slow waves. (2) Gamma is more prominent in tinnitus subjects than in controls. (3) Activity at approximately 55 Hz determines the laterality of the tinnitus perception. Based on present and previous results, we have concluded that cochlear damage, or similar types of deafferentation from peripheral input, triggers reorganization in the central auditory system. This produces permanent alterations in the ongoing oscillatory dynamics at the higher layers of the auditory hierarchical stream. The change results in enhanced slow-wave activity reflecting altered corticothalamic and corticolimbic interplay. Such enhancement facilitates and sustains gamma activity as a neural code of phantom perception, in this case auditory.

Piezoelectricity increases outer hair cell high frequency response.
(Abstract of ARO Meeting Denver, Colorado)
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Outer hair cell (OHC) electromotility is a cochlear amplifier and can actively boost the basilar membrane vibration to enhance auditory sensitivity and frequency selectivity. OHC electromotility is membrane-potential dependent and driven by cross-membrane voltage. Although the conformation of prestin motor proteins can be rapidly changed up to 100 kHz, its driving force (cross-membrane voltage) would be dramatically attenuated at high frequency by membrane capacitance, which forms a low-pass filter with cut-frequency less than 1 kHz. Outer hair cells also have remarkable piezoelectricity. Mechanically elongating and compressing OHC can produce electric currents. Here, we report that
OHC piezoelectricity can overcome membrane capacitance damping to improve OHC high frequency responses. The OHC piezoelectric response showed a high-pass property and was increased as the stimulus frequency was increased. The cut-frequency was 70-90 kHz, mainly limited by the recording system. Simultaneous administrations of electronic and mechanical (piezoelectric) stimulation to the OHC, which mimics the OHC suffered electronic (receptor current through transduction channels) and mechanical (the vibration of the basilar membrane) stimulations in vivo, generated the flat response up to 80 kHz. Abolishment of piezoelectricity eliminated this high frequency enhancement. Like a regular cell, the sole electronic frequency response of the OHC was low-pass; the cut-frequency was ~1 kHz. Finally, as computer modeling expected, the resonant peaks were also visible in the responses to electronic-mechanical stimulation. Our results indicate that OHC electromotility can perform at high frequency effectively to contribute active cochlear mechanics in whole mammalian auditory frequency range (Supported by NIH DC05989 and the Research Foundation of American Tinnitus Association).

Pre- and Postsynaptic Changes Underlying the Maturation of Inner Hair Cell Ribbon Synapses Do Not Depend on the Onset of Hearing.
(Abstract of ARO Meeting Denver, Colorado)
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Inner hair cell (IHC) synapses play a key role in the auditory physiology as they ensure transmission of sound stimuli to first auditory neurons. Glutamate is the neurotransmitter responsible for this fast synaptic transmission which essentially involves AMPA receptors. The glutamate release is dependent on L-type Ca2+ channels with Cav1.3 subunit and occurs at synapses equipped with a dense ribbon thought to mediate the continuous and rapid recruitment of its attached vesicles to the release sites. Despite the importance of the IHC synapse, the cellular and molecular machineries underlying its function are still largely unknown despite their elucidation is of prime importance to gain insight into the occurrence of tinnitus and most forms of deafness.

Using immunocytochemistry, we have studied the expression of a selected set of presynaptic proteins (SNAP25, cysteine-string protein, Rab3 and synaptogyrin) during the postnatal maturation of the rodent cochlea and found that, with the exception of Rab3, they were only detected starting postnatal days 10 and 12, when the first, immature, cochlear potentials can be recorded. During the same postnatal period, we also found that the composition and pharmacological properties of the postsynaptic AMPA receptors changed. GluR2 replaced GluR1 at postnatal day 10, switching the potential composition of AMPA receptors from GluR1/3/4 to GluR2/3/4 and their pharmacology to calcium impermeability.

Finally, we have checked the expression of GluR2 and the 4 presynaptic proteins in the cochlea of the deaf Cav1.3 knock out mice and found that they were all expressed at adult IHC synapses suggesting that their expression was not dependent of the first sound stimuli transduced by IHCs.

Quinine Induced Tinnitus-like Behavior Using a Startled Reflex Paradigm.
(Abstract of ARO Meeting Denver, Colorado)
Edward Lobarinas, Wei Sun, Lei Wei, Richard Salvi
University at Buffalo

The anti-malarial drug, quinine, has been reported to induce tinnitus when administered at high doses and has been used to investigate the neural and biochemical mechanisms underlying tinnitus. Previously, schedule induced polydipsia avoidance conditioning (SIP-AC) was used to evaluate the presence of tinnitus in rats treated with high doses of both salicylate and quinine. Recently, the effects of quinine on tinnitus-like behavior were evaluated using a high-throughput behavioral assay, gap pre-pulse inhibition of acoustic startling (GPIAS), which can be used to estimate tinnitus pitch. GPIAS was used to measure
the onset and pitch of quinine-induced tinnitus in rats treated with different doses of quinine. A 50 ms silent gap (gap pre-pulse) in a continuous background noise was used to inhibit the startle reflex elicited by a high level noise burst. The gap was embedded in narrow band noises (NBN) with center frequencies at 6, 12, 16 or 24 kHz.

Noise burst pre-pulse inhibition of acoustic startle (NBIAS) was also evaluated to monitor potential changes in hearing following quinine. GPIAS results showed evidence of tinnitus like behavior at frequencies above 6 kHz with no changes in hearing threshold at doses of quinine up to 150 mg/kg. Tinnitus-like behaviors with GPIAS were consistent with previous SIP-AC data, strengthening the use of GPIAS as an animal model of tinnitus (Supported in part by Tinnitus Research Consortium).

Salicylate-induced tinnitus: effects of salicylate on neurons in dorsal cochlear nucleus.

(Abstract of ARO Meeting Denver, Colorado)

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University at Buffalo

The neural mechanisms for tinnitus are not well understood, but one hypothesis is that it originates from high rates of spontaneous activity in the dorsal cochlear nucleus (DCN). Support for this hypothesis has come from studies showing elevated spontaneous rates in the DCN following noise and cisplatin-induced hearing loss. High doses of sodium salicylate reliably induce tinnitus, but it is unclear what effects salicylate has on spontaneous activity in the DCN. To test this hypothesis, we prepared brain slices of the DCN from p13-20 rats and recorded the spontaneous firing rate of individual neurons before, during and after treatment with 1.4 mM salicylate. This concentration of salicylate in CSF has been shown to induce behavioral manifestations of tinnitus in rats. Recordings were obtained from three cell types, fusiform, cartwheel and giant cells, with identifications based on their morphological and/or physiological characteristics.

The spontaneous spike rate of cartwheel and giant cells remained unchanged or increased slightly after salicylate perfusion. In contrast, the spontaneous spike rate of most fusiform cells decreased significantly after salicylate treatment.

The results indicate that the effects of salicylate are specific to fusiform cells. Spontaneous spike rate partially recovered following brief (3-5 min) salicylate perfusion and wash-out. The recovery of spontaneous spike rate in fusiform cells was inversely related to perfusion duration and salicylate concentration. To determine if the decrease in spontaneous rate was induced by changes in synaptic activity, we recorded spontaneous post-synaptic currents in voltage clamp. No significant change was seen after salicylate treatment. These results suggest that the salicylate-induced decrease in spontaneous rate in fusiform cells is unlikely to be due a change in synaptic input, but may involve changes in the cell’s intrinsic properties (Supported in part by Tinnitus Research Consortium).

The sound of stress: blunted cortisol reactivity to psychosocial stress in tinnitus sufferers.


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Clinical observations suggest that tinnitus is modulated by stress. However, there is little empirical data to support the link between stress and tinnitus. In this study, we measured the stress hormone cortisol to examine the reactivity of the hypothalamic-pituitary-adrenal (HPA) axis in tinnitus participants as well as in healthy controls without tinnitus. Eighteen participants with tinnitus and 18 controls without tinnitus were exposed to the Trier Social Stress Task and cortisol sampling and subjective ratings were obtained.
at regular intervals. Tinnitus participants displayed a blunted cortisol response to psychosocial stress, in comparison with healthy controls who had a typical cortisol release about 30 min after the beginning of the experiment. The blunted cortisol response displayed by the tinnitus participants suggests that they have an anomaly along the HPA axis. Their cortisol response is similar to that found in other bodily stress-related diseases and thus suggests that tinnitus is related to stress. However, tinnitus intensity might not be modulated by stress in a concurrent manner.

**Suppression of verbal hallucinations and changes in regional cerebral blood flow after intravenous lidocaine: a case report.**


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Simple and complex auditory phantom-perceptions such as tinnitus and musical hallucinations occur predominantly in elderly subjects and are often associated with hearing impairment. Isolated verbal hallucinations without other psychotic features are rare. It has been shown that an intravenous (i.v.) injection of lidocaine can transiently suppress tinnitus. Here we present the case of a 74 year old left-handed women with severely distressing, continuous verbal auditory hallucinations without other psychotic features. I.v. injections of 100 mg lidocaine but not saline resulted in substantial transient suppressions of the hallucinations for several hours. Using \[\text{[\textsuperscript{15}O]}\text{H}\text{[\textsuperscript{2}}O\text{ positron-emission tomography (PET) decreased regional cerebral blood flow associated with reduced perception of voices was found in the right angular and supramarginal gyrus, right inferior frontal gyrus, orbitofronal cortex and in major parts of the cingulate cortex. These data suggest to further investigate the clinical relevance of i.v. lidocaine in patients with therapy-resistant verbal hallucinations, support the notion of common pathophysiological mechanisms in different forms of auditory phantom-perception and demonstrate the feasibility of a new strategy for imaging studies on auditory hallucinations.**

**Time course of recovery of spontaneous activity (SA) in the rat inferior colliculus (IC) following unilateral acoustic trauma**

(Abstract of ARO Meeting Denver, Colorado)

**Thomas Imig\textsuperscript{1}, Henry Heffner\textsuperscript{2}, Gim Koay\textsuperscript{2}, Dianne Durham\textsuperscript{1}**

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SA in the IC of rats was measured following unilateral acoustic trauma (isoflurane anesthesia, continuous 16 kHz tone for 60', 115 – 120 dB SPL). At various times following sound exposure, unanesthetized rats were injected with C14 labeled 2 deoxyglucose (2DG) and placed in a quiet sound isolation chamber during uptake. Groups of 4 rats each received 2DG at different times following exposure (4 hour, 1, 2, 4, 8, 16 day, and control). Optical density (OD) measures were obtained from autoradiographs at 10 equally spaced segments that crossed the tonotopic axis of the central nucleus (ICc) and the external nucleus (ICx). OD for corresponding segments of ipsi and contra IC were compared and showed the following results: 1. OD was bilaterally symmetrical in controls. In exposed rats the contra IC showed a decrement in OD with respect to the ipsi IC at each survival time. Acoustic trauma did not cause an increase in OD at any survival time. 2. SA in contra IC showed partial recovery over time. The greatest decrement in OD was seen at 4 hours with lesser decrements at longer times. 3. Recovery of SA followed different time courses in the ICx and ICc. The decrement in OD extended throughout both the ICc and ICx at four hours. By 2 days, ICx showed full recovery (bilaterally symmetrical OD) but recovery in the contra ICc continued over an 8 day period. 4. Recovery of SA in the ICc showed a low (LF) to high frequency (HF) progression. In 4 h and 1 day groups, SA was decreased throughout the ICc with the greatest decrement...
in the HF half of the ICc. By 8 days SA recovered to normal levels in LF ICc. The HF half of the ICc showed a decrement in SA, although less so than at earlier times. There was no further change in SA at 16 days (Supported by the Tinnitus Research Consortium and MRRC Center Grant HD02528).

**Tinnitus and neural plasticity of the brain.**
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**Objective:** To describe the current ideas about the manifestations of neural plasticity in generating tinnitus.

**Data sources:** Recently published source articles were identified using MEDLINE, PubMed, and Cochrane Library according to the key words mentioned below.

**Study selection:** Review articles and controlled trials were particularly selected.

**Data extraction:** Data were selected systematically, scaled on validity and comparability.

**Conclusion:** An altered afferent input to the auditory pathway may be the initiator of a complex sequence of events, finally resulting in the generation of tinnitus at the central level of the auditory nervous system. The effects of neural plasticity can generally be divided into early modifications and modifications with a later onset. The unmasking of dormant synapses, diminishing of (surround) inhibition and initiation of generation of new connections through axonal sprouting are early manifestations of neural plasticity, resulting in lateral spread of neural activity and development of hyperexcitability regions in the central nervous system. The remodeling process of tonotopic receptive fields within auditory pathway structures (dorsal cochlear nucleus, inferior colliculus, and the auditory cortex) are late manifestations of neural plasticity. The modulation of tinnitus by stimulating somatosensory or visual systems in some people with tinnitus might be explained via the generation of tinnitus following the nonclassical pathway. The similarities between the pathophysiological processes of phantom pain sensations and tinnitus have stimulated the theory that chronic tinnitus is an auditory phantom perception.

**Tinnitus behavior and hearing function correlate with the reciprocal expression patterns of BDNF and Arg3.1/arc in auditory neurons following acoustic trauma.**
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The molecular changes following sensory trauma and the subsequent response of the CNS are poorly understood. We focused on finding a molecular tool for monitoring the features of excitability which occur following acoustic trauma to the auditory system. Of particular interest are genes that alter their expression pattern during activity-induced changes in synaptic efficacy and plasticity. The expression of brain-derived neurotrophic factor (BDNF), the activity-dependent cytoskeletal protein (Arg3.1/arc), and the immediate early gene c-Fos were monitored in the peripheral and central auditory system hours and days following a traumatic acoustic stimulus that induced not only hearing loss but also phantom auditory perception (tinnitus), as shown in rodent animal behavior models. A reciprocal responsiveness of activity-dependent genes became evident between the periphery and the primary auditory cortex (AI): as c-Fos and BDNF exon IV expression was increased in spiral ganglion neurons, Arg3.1/arc and (later on) BDNF exon IV expression was reduced in AI. In line with studies indicating increased spontaneous spike activity at the level of the inferior colliculus (IC), an increase in BDNF and GABA-positive neurons was seen in...
the IC. The data clearly indicate the usefulness of Arg3.1/arc and BDNF for monitoring trauma-induced activity changes and the associated putative plasticity responses in the auditory system.

**VIII Somatic tinnitus**

**Somatic modulation of tinnitus: test reliability and results after repetitive muscle contraction training.**
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**Objectives:** We sought to study the reliability of tinnitus modulation by muscle contractions and to observe the effect of their prolonged repetition.

**Methods:** Thirty-eight patients with tinnitus underwent 9 maneuvers of muscle contractions in test and retest situations. After a 2-month training period of repeating the maneuvers, tinnitus modulation and daily perception were evaluated.

**Results:** There was no difference between the occurrence of tinnitus modulation in test (57.9%) and retest (63.2%) situations. After 2 months, the occurrence of modulation during the maneuvers was similar (55.3%), but a new pattern showed an increase in tinnitus improvement and a decrease in tinnitus worsening. The daily perception of tinnitus was unchanged.

**Conclusions:** Maneuvers of head and neck muscle contractions evoked tinnitus modulation in a frequent and reliable manner. Also, the repetition of such maneuvers for 2 months altered the pattern of modulation.

**Tensor tympani muscle: strange chewing muscle.**
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This work seeks to alert medical and odontological staff to understanding and using interdisciplinary handling for detecting different pathologies common otic symptoms. It offers better tools for this shared symptomatology during therapy’s conservative phase. Tensor tympani muscle physiology and function in the middle ear have been veiled, even when their dysfunction and anatomical relationships may explain a group of confused otic symptoms during conventional clinical evaluation. Middle ear muscles share a common embryological and functional origin with chewing and facial muscles. This article emphasizes that these muscles share a functional neurological and anatomical dimension with the stomatognathic system; these muscles increased tonicity ceases to be a phenomenon having no logical connections. It offers functionality and importance in understanding referred otic symptoms in common with other extra-otic symptom pathologies. Tinnitus, vertigo, otic fullness sensation, hyperacusia, hypoacusia and otalgia are not only primary hearing organ symptoms. They should be redefined and related to the neighboring pathologies which can produce them. There is a need to understand temporomandibular disorders and craniofacial referred symptomatology from neurophysiologic and muscle-skeletal angles contained in the stomatognathic system. Common symptomatology is frequently observed in otic symptoms and temporomandibular disorders during daily practice; this should be understood by each discipline from a broad, anatomical and clinical perspective.
Combined petrosal approaches in the management of temporal bone meningiomas.
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Objectives: To evaluate the indications and outcomes of the combined petrosal approaches in the surgical management of temporal bone meningiomas.
Study design: Retrospective chart review.
Setting: University teaching hospital.
Patients: Adults with temporal bone meningiomas.
Intervention(s): Meningioma removal using a combined petrosal approach.
Main outcome measure(s): Cranial nerve outcomes, complications, completeness of resection, and recurrence rates.

Results: Forty-nine patients underwent surgical excision of a temporal bone meningioma between 1996 and 2004 at our institution. Nineteen of these patients required a combined petrosal approach for excision. The most common presenting complaints were balance disturbance, 11 (58%); hearing loss, 10 (53%); headache, 10 (53%); and tinnitus, 9 (47%). The most common tumor origin was of the petrous ridge (14; 74%). Average tumor size was 3.1 cm. Complete resection was possible in 17 (89%) patients. Upper cranial nerve (III-VI) function was improved in two (11%) patients and worsened in three (16%) patients. Lower cranial nerve (IX-XII) function improved in one (5%) patient and was worsened in one (5%) patient. Postoperative facial nerve function was Grades I to II in 16 (84%) patients and Grades III to IV in 1 (5%) patient at last follow-up. Hearing data were available in 14 patients. Of those patients, 11 (85%) had serviceable hearing after surgery. The most common surgical complication was a cerebrospinal fluid leak, with three (16%) incidences. There were no reported incidents of stroke, death, or meningitis in the cohort.

Conclusion: The use of the combined petrosal approach for temporal bone meningioma resection results in favorable outcomes for the patient. The incidence of complications is acceptably low, and cure rates are high.

How does stapes surgery influence severe disabling tinnitus in otosclerosis patients?
Adv Otorhinolaryngol. 2007;65:343-347.
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Tinnitus is a common symptom in otosclerosis patients. Many papers have been written about tinnitus outcome after stapes surgery. However, none has attempted to quantify the intensity of the symptom pre- and postoperatively in order to evaluate the influence of surgery on the degree of annoyance caused by tinnitus. Severe disabling tinnitus (SDT) is defined by Shulman as a symptom severe enough to disrupt the patient’s routine and to prevent him from performing his daily tasks. We have studied 48 consecutive otosclerosis patients by means of a visual analogue scale measuring tinnitus intensity before and after stapes surgery. We have accepted tinnitus as severe and disabling when the symptom score was 7 or above in a visual analogue scale from 1 to 10. Of 19 patients with preoperative SDT, 10 reported complete remission and 7 reported significant improvement. Two patients had no change and none reported worsening of tinnitus after stapes surgery. We conclude that stapes surgery can improve SDT significantly in 90% of otosclerosis patients and is very unlikely to make the symptom worse.
Sigmoid sinus diverticulum: a new surgical approach to the correction of pulsatile tinnitus.
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Objective: Tinnitus represents a bothersome symptom not infrequently encountered in an otology practice. Tinnitus can be the harbinger of identifiable middle or inner ear abnormality; but more frequently, tinnitus stands alone as a subjective symptom with no easy treatment. When a patient complains of tinnitus that is pulsatile in nature, a thorough workup is indicated to rule out vascular abnormality. We report of a new diagnostic finding and method of surgical correction for select patients with pulsatile tinnitus.

Study design: Retrospective case series.
Setting: Tertiary care, academic referral center.
Patients: Among patients seen for complaints of unilateral or bilateral pulsatile tinnitus, five were identified with diverticula of the sigmoid sinus. All patients had normal in-office otoscopic, tympanometric, and audiometric evaluations. Patients with paragangliomas or benign intracranial hypertension were excluded. Auscultation of the pinna or mastoid revealed an audible bruit in most patients. All patients underwent computed tomographic angiography of the temporal bone. In all cases, this finding was on the side coincident with the tinnitus.

Intervention: Three of five patients underwent transmastoid reconstruction of the sigmoid sinus.

Main outcome measure: Patients were evaluated clinically for presence or absence of pulsatile tinnitus after reconstructive surgery.

Results: All patients electing surgical reconstruction had immediate and lasting resolution of the tinnitus.

Conclusion: Surgical reconstruction can provide lasting symptom relief for patients with pulsatile tinnitus and computed tomographic evidence of a sigmoid sinus diverticulum.

X Epidemiology

The extent and levels of tinnitus in children of central Ankara.
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Objective: The objective of this study is to determine the presence and prevalence of tinnitus among primary school and junior high school students in central Ankara.

Methods: In the first stage of the study, all students were tested for the presence of tinnitus by answering a comprehensive questionnaire. The students who had previous ear operations were excluded from the rest of the study. The initial survey/tests yielded presence of tinnitus, frequency of occurrence, characteristics, associated symptoms and the age groups.

Results: 15.1% of the children reported to have tinnitus. No significant difference was found between gender (female 45.5%, male 54.4%) and ears (right 25.3%, left 25.5%). The age group that suffered most from tinnitus is 14 years old (20.8%), 25 children had positive family history (16.2%), 44 children had headaches as the most common accompanying symptom (28.6%), 64 of them had tiredness as the predisposing factor (41.6%) and 52 of them have defined worsening of tinnitus during mornings (33.8%). The characteristics of tinnitus were identified as high pitch (n=125, 81.2%), soft loudness (n=124, 80.5%) and ringing (n=61, 39.6%).

Conclusions: The study produced much needed data to shed light onto understanding levels and characteristics of tinnitus in school children in Turkey. The data obtained was carefully analyzed and found to be comparative to international studies.
The natural history and prevalence of tinnitus is still not clear. As both aging and hearing loss are the most important factors for the tinnitus, the prevalence of the tinnitus with aging may provide useful information to clarify the natural history of tinnitus.

We tried to assess the clinical characteristics of tinnitus in healthy population. The subjects were the clients who visited Health Promotion Center of Daegu Fatima Hospital from January 2004 to September 2005 and voluntarily completed hearing questionnaire. We excluded subjects (1) who had past history of ear drainage, usage of known ototoxic drug, such as chemotherapeutic agent, parenteral antibiotics for serious illness such as tuberculosis, and parenteral diuretics, head injury, working in noise environment, attending military service, (2) who tested twice during the period, (3) who aged less than 20 year-old, and (4) who showed asymmetric hearing loss in the pure tone averages (more than 16 dB average difference of 0.5, 1, and 2 kHz). Finally, 1150 subjects were included. They were 219 men (20 to 78.3 year-old, mean age 48) and 913 women (20 to 83.9 year-old, mean age 46.3). Multivariate logistic analysis was used to evaluate the difference between male and female and the effect of aging and hearing loss.

There was no significant difference in gender. Even though the prevalence of tinnitus increased with age, it was not statistically significant. Only the hearing threshold was the factor to affect the presence of tinnitus. The prevalence was increased with hearing threshold, 9.5%, 11.3%, 19.2%, and 40.6% for less than 20dB, 30dB, 40dB and 50 dB by pure tone average of 0.5, 1, 2, and 4 kHz, respectively. Bilateral tinnitus was most common as 62.7%. Remains complained unilateral tinnitus, 22.5 and 14.8% for the right and the left, respectively. According to population based subjects without any significant causes of sensorineural hearing loss, roughly 10% of normal hearing subjects complained tinnitus and it was bilateral in most.

XI Review

Tinnitus.

J Laryngol Otol. 2007 Mar;121(3):201-208.
McFerran DJ, Phillips JS
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Chronic idiopathic subjective tinnitus is a common condition affecting around one in ten of the population at any given time. For the majority of people it is an annoyance rather than a major health issue but for approximately 0.5 per cent of the population tinnitus interferes with their ability to pursue a normal life. Modern theories of the pathogenesis of the condition concentrate on the central auditory system although the peripheral auditory system can be a trigger or ignition site for tinnitus. Although a cure remains elusive there are several good treatment strategies based on psychological and neurophysiological models of tinnitus that promote habituation to the symptom.

XII Holistic
According to the provisions of private accident insurance, mental or psychic reactions are excluded from compensation. Until now, tinnitus was taken as fully psychic and therefore excluded. In two recently published judgments of the Federal Supreme Court in Germany the assessment of tinnitus in private accident insurance and particularly the exclusion clause section sign 2 Abs. 4 AUB 88 has been newly defined. According to this actual jurisdiction the compensation of tinnitus could be possible, when as physical underlying reason a proved harm in the inner ear or the auditory pathway (hearing loss), which can be traced back to the accident according to the rules of causality. This leads to the question how Tinnitus could be compensated without modification of the general terms and conditions of the private accident insurance. A compensating table is proposed, which recognizes the somatic (physical) part of tinnitus and is based on medical and scientific findings of the relation between hearing loss and tinnitus.

Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus.
Bennett M, Kertesz T, Yeung P

Background: Idiopathic sudden sensorineural hearing loss (ISSHL) with or without tinnitus is common and presents a health problem with significant effect on quality of life. Hyperbaric oxygen therapy (HBOT) may improve oxygen supply to the inner ear and, it is postulated, may result in an improvement in hearing and/or a reduction in the intensity of tinnitus.

Objectives: To assess the benefits and harms of HBOT for treating ISSHL and/or tinnitus.

Search strategy: We initially searched in June 2004 and repeated the search in June 2006. Our search included the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2 2006), MEDLINE (1951 to 2006), EMBASE (1974 to 2006), CINAHL, Database of Randomised Trials in Hyperbaric Medicine (DORC-THIM), AMED, LILACS, KOREAMED, INMDMED, National Research Register (NRR), CSA, ISI PROCEEDINGS and ZETOC.

Selection criteria: Randomised studies comparing the effect on ISSHL and/or tinnitus of therapeutic regimens which include HBOT with those that exclude HBOT.

Data collection and analysis: Three authors independently evaluated the quality of the relevant trials using the validated Oxford-Scale (Jadad 1996) and extracted the data from the included trials.

Main results: Six trials contributed to this review (308 subjects). Pooled data from two trials involving 114 patients did not show any significant improvement in the chance of a 50% increase in hearing threshold on Pure Tone Average (PTA) when HBOT was used (relative risk [RR] with HBOT 1.53, 95% CI 0.85 to 2.78, P = 0.16), but did show a significantly increased chance of a 25% increase in PTA (RR 1.39, 95% CI 1.05 to 1.84, P = 0.02). There was a 22% greater chance of improvement with HBOT, and the number needed to treat (NNT) to achieve one extra good outcome was five (95% CI 3 to 20). A single trial involving 50 subjects also suggested significantly more improvement in the mean PTA threshold with HBOT, expressed as a percentage of baseline (WMD 37%, 95% CI 22% to 53%, P < 0.001). The significance of any improvement following HBOT in a subjective rating of tinnitus could not be assessed due to poor reporting. There were no significant improvements in hearing or tinnitus reported in the single study to examine chronic presentation (six months) of ISSHL and/or tinnitus.

Authors’ conclusion: For people with early presentation of ISSHL, the application of HBOT significantly improved hearing loss, but the clinical significance of the level of improvement is not clear. We could not
assess the effect of HBOT on tinnitus by pooled data analysis. The routine application of HBOT to these patients cannot be justified from this review. In view of the modest number of patients, methodological shortcomings and poor reporting, this result should be interpreted cautiously, and an appropriately powered trial of high methodological rigour is justified to define those patients (if any) who can be expected to derive most benefit from HBOT. There is no evidence of a beneficial effect of HBOT on chronic presentation of ISSHL and/or tinnitus and we do not recommend use of HBOT for this purpose based on the single study available.

**Hyperbaric oxygen in tinnitus: influence of psychological factors on treatment results?**


Division of Thoracic Surgery and Hyperbaric Medicine, University of Medicine, Graz, Austria. christian.porubsky@klinikum-graz.at

**Introduction:** The standard treatment of subjective tinnitus hardly reaches the level of placebo controls. Though the effectiveness of hyperbaric oxygenation (HBO) for subjective tinnitus has never been objectified, it is still advocated by some institutions. We analyzed the effectiveness of hyperbaric oxygen treatment in the context of accompanying factors.

**Patients and methods:** We randomized 360 patients suffering from tinnitus into 2 HBO treatment protocols (group A: 2.2 bar for 60 min bottom time and group B: 2.5 bar for 60 min bottom time once a day for 15 days). All patients were asked to fill in a questionnaire (social and medical history, tinnitus characteristics, pre-HBO duration of tinnitus, prior therapy, pretreatment expectation, accompanying symptoms). A subjective assessment of the therapeutic effect was obtained.

**Results:** Twelve patients (3.3%) experienced complete remission of tinnitus, in 122 (33.9%) the intensity lessened, and 44 (12.2%) had a subjectively agreeable change of noise characteristics. No change was found in 157 cases (43.6%) and 25 (6.9%) experienced deterioration. There was no statistically significant difference between groups A and B (p > 0.05). Out of 68 patients with a positive expectation of HBO effects, 60.3% stated that the tinnitus had improved whereas only 47.2% and 19%, respectively, out of patients who underwent therapy with an indifferent (n = 271) or negative expectation (n = 21) reported an improvement. The influence of subjective expectation on the outcome was statistically significant (p < 0.05).

**Conclusion:** The therapeutic effects of HBO on subjective tinnitus may be substantially influenced by psychological mechanisms.
News

Consensus of the TRI Workshop at the 1st Meeting of TRI in Regensburg (2006)

At the first Tinnitus Research Initiative meeting in Regensburg in July 2006 we attempted to gain a consensus both for patient assessments and for outcome measurements. By achieving greater comparability between studies we hope that this will contribute towards more effective cooperation between research centres in seeking and evaluating treatments for tinnitus.

The consensus identified minimum requirements. Items were prioritized in order to facilitate implementation. Items assessed as level A were considered essential, items assessed as level B highly recommended and items assessed as level C desirable in some contexts.

The consensus document consists of three components:

1. The main component is the “Consensus for Patient Assessment and Treatment Outcome Measurement”
2. The second component (“Items list” for tinnitus case history questionnaire) lists 35 items which are most frequently assessed as part of the case history in other questionnaires.
3. The “Tinnitus Sample Case History Questionnaire (TSCHQ)” is attached as a sample of how the 35 items might be asked.

Translations into German and Flemish have already been performed and are available upon request. A French translation is underway. We encourage translation into further languages.

Berthold Langguth Ron Goodey
TRI - CONSENSUS FOR PATIENT ASSESSMENT AND OUTCOME MEASUREMENTS

In each category recommendations are ordered according to their level of significance:
A: Essential      B: highly recommended      C: might be of interest

PATIENT ASSESSMENT

Physical examination
A: Otologic examination by a specialist
A: Examination of the neck (range of motion, tenderness, muscle tension…)
B: Examination of the temporomandibular function

Audiologic Assessment
A: Audiometry (pure tone threshold; up to 8 kHz)
B: Immitance Audiometry
B: High Frequency Audiometry (at least up to 12 kHz)
B: Otoacoustic Emissions
B: Loudness Discomfort Level
C: Auditory Evoked Potentials

Psychophysic Measures of Tinnitus
B: Loudness match
B: Pitch match
B: Maskability (MML)
B: Residual Inhibition

Case History
A majority of participants preferred a questionnaire to be filled in by the patient (with access to someone for clarification) rather than at a structured interview. This was not a consensus. It was agreed that as a first step towards consensus a list of those items common to most existing questionnaires should be made. A first attempt to extract such a list is attached.

Questionnaires
A: Validated questionnaire for the assessment of tinnitus severity, which at present can be THI, THQ, TRQ or TQ (it was agreed that in the future a better and more widely validated questionnaire was required)
B: Assessment of tinnitus severity by additional questionnaires, and especially by the THI because it is believed that THI is validated in most languages
C: Assessment of depressive symptoms (e.g. BDI)
C: Assessment of anxiety (e.g. STAI)
C: Assessment of quality of life (e.g. WHODAS II)
C: Assessment of Insomnia (e.g. PSQI)
OUTCOME MEASUREMENTS

A: Validated questionnaire for the assessment of tinnitus severity, which at present can be THI, THQ, TRQ or TQ (it was agreed that in the future a better and more widely validated questionnaire was required)

B: Assessment of tinnitus severity by additional questionnaires, and especially by the THI because it is believed that THI is validated in most languages

C: Assessment of depressive symptoms (e.g. BDI)

C: Assessment of anxiety (e.g. STAI)

C: Assessment of quality of life (e.g. WHODAS II)

C: Assessment of Insomnia (e.g. PSQI)

C: Tinnitus loudness match

C: Maskability (MML)

C: Objective measurements of brain function (functional imaging, electrophysiology)

ABBREVIATIONS

kHz  kilohertz

dB  decibel

SL  sensation level

MML  minimal masking level

THI  Tinnitus Handicap Inventory (Newman et al, 1998)

THQ  Tinnitus Handicap Questionnaire (Kuk et al, 1990)

TRQ  Tinnitus Reaction Questionnaire (Wilson et al, 1991)

TQ  Tinnitus Questionnaire (Hallam et al. 1988)

BDI  Beck Depression Inventory (Beck and Steer, 1984)

STAI  State-Trait-Anxiety-Inventory (Spielberger et al, 1970)

WHODAS  WHO Disability Assessment Schedule (McArdle et al, 2005)

PSQI  Pittsburgh Sleep Quality Index (Buysse et al, 1989)
“Items list” for tinnitus case history questionnaires.

Items are ordered according to their level of significance:

Category “A” (= essential) in bold type.

Background

1. Age.
2. Gender.
3. Handedness.

Tinnitus history

5. Initial onset. Time?
6. Initial onset. Mode? Gradual or abrupt?
7. Initial onset. Associated events? Hearing change, Acoustic trauma, Otitis media, Head trauma, Whiplash, Dental Treatment, Stress, Other.
9. Site. Right ear? Left ear? Both ears? (symmetrical?) Inside head?
10. Intermittent or constant?
11. fluctuant or non-fluctuant?
12. Loudness. Scale 1-100. At worst & at best?
13. Quality. Own words / Give a list of choices.
14. Pure tone or Noise? Uncertain / polyphonic?
16. Percentage of awake time aware of tinnitus?
17. Percentage of awake time annoyed by tinnitus?
18. Previous tinnitus treatments (no, some, many)?

Modifying influences

19. Natural masking? Music, everyday sounds, other sounds?
20. Aggravated by loud noise?
21. Altered by head and neck movement or touching of head or upper limbs (specification of the respective movements)?
23. Effect of nocturnal sleep on daytime tinnitus?
24. Effect of stress?
25. Effect of medications? Which?

Related conditions

26. Hearing impairment?
27. Hearing aids (No, left ear, right ear, both ears; effect on tinnitus)?
28. Noise annoyance or intolerance?
29. Noise induced pain?
30. Headaches?
31. Vertigo/dizziness?
32. Temporomandibular disorder?
33. Neck pain?
34. Other pain syndromes?
35. Under treatment for psychiatric problems?

As an example of how the above items can be expressed for patients to complete see the TINNITUS SAMPLE CASE HISTORY QUESTIONNAIRE (TSCHQ)
### Tinnitus Sample Case History Questionnaire (TSCHQ)

<table>
<thead>
<tr>
<th>NAME:</th>
<th>DATE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE OF BIRTH:</td>
<td></td>
</tr>
</tbody>
</table>

1. **Age:**

2. **Gender:**
   - [ ] Male
   - [ ] Female

3. **Handedness**
   - [ ] Right
   - [ ] Left
   - [ ] Both Sides

4. **Family history of tinnitus complaints**
   - [ ] YES
   - if YES: [ ] parents
   - [ ] siblings
   - [ ] children
   - [ ] NO

5. **Initial onset:** When did you first experience your tinnitus? ________________

6. **How did you perceive the beginning?**
   - [ ] Gradual
   - [ ] Abrupt

7. **Was the initial onset of your tinnitus related to:**
   - [ ] loud blast of sound
   - [ ] whiplash
   - [ ] change in hearing
   - [ ] stress
   - [ ] head trauma
   - [ ] others

8. **Does your tinnitus seem to PULSATE?**
   - [ ] YES with heart beat
   - [ ] YES, different from heart beat
   - [ ] NO
9. Where do you perceive your tinnitus
   - [ ] right ear
   - [ ] left ear
   - [ ] both ears, worse in left
   - [ ] both ears, worse in right
   - [ ] both ears, equally
   - [ ] inside the head
   - [ ] elsewhere

10. How does your tinnitus manifest itself over time?
   - [ ] intermittent
   - [ ] constant

11. Does the **LOUDNESS** of the tinnitus vary from day to day?
    - [ ] YES
    - [ ] NO

12. Describe the **LOUDNESS** of your tinnitus using a scale from 1-100.
    
    (1 = VERY FAINT; 100 = VERY LOUD)
    
    ___________ (1 – 100)

13. Please describe in your own words what your tinnitus usually sounds like:

    ___________________________

    The following list gives examples of some possible sensations, feel free to use other terms as well: hissing, ringing, pulsing, buzzing, clicking, cracking, tonal (like a dial tone or other kinds of tones), humming, popping, roaring, rushing, typewriter, whistling, whooshing.

14. Does your tinnitus more sound like a tone or more like noise:
    - [ ] tone
    - [ ] noise
    - [ ] crickets
    - [ ] other
15. Please describe the PITCH of your tinnitus:
   - [ ] very high frequency
   - [ ] high frequency
   - [ ] medium frequency
   - [ ] low frequency

16. What percent of your total awake time, over the last month, have you been aware of your tinnitus?
   For example, 100% would indicate that you were aware of your tinnitus all the time, and 25% would indicate that you were aware of your tinnitus ¼ of the time
   __________ % (Please write in a single number between 1 and 100.)

17. What percent of your total awake time, over the last month, have you been annoyed, distressed, or irritated by your tinnitus?
   __________ % (Please write in a single number between 1 and 100.)

18. How many different treatments have you undergone because of your tinnitus?
   - [ ] none
   - [ ] one
   - [ ] several
   - [ ] many

19. Is your tinnitus reduced by music or by certain types of environmental sounds such as the noise of a waterfall or the noise of running water when you are standing in the shower?
   - [ ] YES
   - [ ] NO
   - [ ] I don’t know

20. Does the presence of loud noise make your tinnitus worse?
   - [ ] YES
   - [ ] NO
   - [ ] I don’t know

21. Does any head and neck movement (e.g. moving the jaw forward or clenching the teeth), or having your arms/hands or head touched, affect your tinnitus?
   - [ ] YES
   - [ ] NO
22. Does taking a nap during the day affect your tinnitus?

☐ worsens my tinnitus  ☐ reduces my tinnitus  ☐ has no effect

23. Is there any relationship between sleep at night and your tinnitus during the day?

☐ YES  ☐ NO  ☐ I don’t know

24. Does stress influence your tinnitus?

☐ worsens my tinnitus  ☐ reduces my tinnitus  ☐ has no effect

25. Does medication have an effect on your tinnitus?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect / Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

26. Do you think you have a hearing problem?

☐ YES  ☐ NO

27. Do you wear hearing aids?

☐ Right  ☐ Left  ☐ Both  ☐ None

28. Do you have a problem tolerating sounds because they often seem much too loud? That is, do you often find too loud or hurtful sounds which other people around you find quite comfortable?

☐ Never  ☐ Rarely  ☐ Sometimes  ☐ Usually  ☐ Always
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>29. Do sounds cause you pain or physical discomfort?</td>
<td>□ YES □ NO □ I don’t know</td>
</tr>
<tr>
<td>30. Do you suffer from headache?</td>
<td>□ YES □ NO</td>
</tr>
<tr>
<td>31. Do you suffer from vertigo or dizziness?</td>
<td>□ YES □ NO</td>
</tr>
<tr>
<td>32. Do you suffer from temporomandibular disorder?</td>
<td>□ YES □ NO</td>
</tr>
<tr>
<td>33. Do you suffer from neck pain</td>
<td>□ YES □ NO</td>
</tr>
<tr>
<td>34. Do you suffer from other pain syndromes?</td>
<td>□ YES □ NO</td>
</tr>
<tr>
<td>35. Are you currently under treatment for psychiatric problems?</td>
<td>□ YES □ NO</td>
</tr>
</tbody>
</table>