Frontiers in Tinnitus Research

“Frontiers in Tinnitus Research” is the motto of the upcoming 4th International TRI Tinnitus Meeting. Exploring frontiers has been a very successful strategy in tinnitus research during the last years. But we should not stay where we are, but rather be aware that the more we explore, the more remains to be explored. It may seem paradoxical at first glance, but increasing knowledge of tinnitus creates new frontiers like the coast line becomes longer, when an island grows. A good example is the stepwise exploration of the important role of the central nervous system in tinnitus pathophysiology. First studies in the 90s demonstrating neuroplastic changes in the central auditory pathways of tinnitus patients moved the focus of research on the central nervous system. As a next step the involvement of non-auditory brain areas has been described and very recent research aims at identifying the way how auditory and non-auditory areas interact in tinnitus patients.

All these advances prompt new therapeutic options and the TRI meeting in Dallas will try to focus on cutting edge developments at these growing frontiers of Tinnitus research.

Another important Frontier in Tinnitus Research is the implementation of recent research findings into clinical practice. An increasing number of publications describe specific forms of tinnitus which can be cured by specific interventions. It is especially pulsatile tinnitus where frequently vascular malformations can be identified as the underlying cause and where curative treatment can be offered (see publications of EC Nam, p 55, K Brantberg, p 59, D de Ridder, p 78, A Bink, p 88 and YZ Wang, p 88, in this issue). However this requires the adequate diagnostic procedures, starting with a detailed case history and a clinical examination. As long as uniform etiologic and pathophysiological mechanisms are assumed and as long as treatment guidelines do not stress the importance of a comprehensive diagnosis, there will be many patients with a potentially treatable tinnitus, who will never be correctly diagnosed or adequately treated. The flowchart for diagnosis and treatment of tinnitus, which has been developed by the TRI clinic workgroup aims to provide a guideline for a stepwise diagnostic approach. Also the “Textbook of Tinnitus” which will be available in September / Oktober 2010, focuses on the diagnosis of the different forms of tinnitus. We hope that these activities will contribute to close the gap between clinical research and clinical practice.

Berthold Langguth
Susanne Staudinger
Orbituary

Carlos Herraiz Puchol † March 2010

Just before Easter we received the terrible news of the tragic death of our friend and colleague Carlos Herraiz Puchol. He lost his life at the end of March in a motorcycle accident.

As one of the leading tinnitus experts in Spain, Carlos aimed to provide the best possible care for his tinnitus patients. At the same time, he always looked for new and innovative treatments of tinnitus. With these ambitions he joined TRI already in 2006.

Within TRI he was always one of the most creative clinicians, motivated to translate knowledge from basic research into a clinically useful application. His research activities were always clinically oriented and encompassed a broad field, including methodologic studies for the assessment of treatment, the benefits of somatosensoric interventions, pharmacologic treatment and auditory training.

He was actively involved in the TRI Tinnitus Clinic Workgroup and contributed many chapters to the book “Tinnitus. Pathophysiology and Treatment” as well as to the new book “Textbook of Tinnitus”. He also represented Spain in the EUTi, the European Federation of Tinnitus Associations.

Carlos was always a very special person, modest, open minded, energetic and friendly. With his optimism he inspired and motivated colleagues around him.

We are grateful and proud that we had the privilege to work with him and to have him as a friend.

We will miss his joyful presence.
Fourth International TRI Tinnitus Conference

Frontiers in Tinnitus Research

Organized by the Tinnitus Research Initiative and The University of Texas at Dallas
and co-sponsored by the American Tinnitus Association

June 8 - 11, 2010

Opening: Tuesday, June 8th, 2010, in the late afternoon

Venue: The Adolphus, 1321 Commerce St, Dallas, TX 75202, USA

Conference Topics will include:

- Clinical Management of Tinnitus
- Basic Neuroscience
- Sound therapy
- Hearing Aids
- Brain Stimulation
- Imaging, Neurofeedback
- Tinnitus Subtyping etc...
- Diagnosis
- Genetics, Pharmacology
- Auditory Training
- Electrical Stimulation of the cochlea
- Somatosensory Modulation
- Nutrition and Diet

Speakers, who have already confirmed their participation:

- Dirk de Ridder, Belgium
- Ana Belén Elgoyhen, Argentina
- Tobias Kleinjung, Germany
- Aage Møller, USA
- Ranulfo Romo, Mexico
- Luca del Bo, Italy
- Paul Fuchs, USA
- Berthold Langguth, Germany
- Larry Roberts, Canada
- Richard Salvi, USA

This meeting is sponsored by
# OVERVIEW SCIENTIFIC PROGRAM

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<th>June 11&lt;sup&gt;th&lt;/sup&gt;</th>
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</table>
| **PLENARY TALK:** Thalamocortical Dysrhythmia and Tinnitus  
Roderico Linhas | **PLENARY TALK:** Synaptic Physiology of Cochlear Hair Cells: Afferent Signaling  
Pavel Fuchs | **PLENARY TALK:** Tinnitus and Neural Plasticity  
Larry Roberts | **PLENARY TALK:** Increase in gain in the auditory system  
Arnaud Navera |
| 09:00 - 09:30 a.m. | 09:30 - 10:00 a.m. | 10:30 a.m. - 12:30 p.m. | **Coffee Break (30 min)** |

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| Pathophysiology of Tinnitus  
A Normán, D de Ridder | Somatosensory Tinnitus  
C. Sanchez | Behavioral Therapy  
M Mazzol | TMS / VNS  
A Londero |
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<td>10:30 a.m. - 12:30 p.m.</td>
<td>12:30 p.m. - 1:30 p.m.</td>
<td><strong>LUNCH</strong></td>
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| Neuroimaging in Tinnitus: Mechanisms and Networks  
F. Hussain | Design of Clinical Trials  
M. Londero, WH Martin | The TRI Flowchart for Patient Management  
B. Languth | Animal Models  
R. Salvi |
|--------------------------|-----------------|-----------------|-----------------|
| 04:00 - 06:00 p.m. | **POSTER SESSION**  
Specific Forms of Tinnitus:  
T. Kleinjung  
Animal Models:  
R. Salvi | Electrical Stimulation to the Brain and to the Ear  
A. Mitter | Perceptual Training  
G. Searchfield |
| **Coffee Break (30 min)** | **Coffee Break (30 min)** | **Coffee Break (30 min)** | **Coffee Break (30 min)** |

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| **OPENING LECTURE:** Richard Salvi  
*Welcome Cocktail*  
MEETING: Is there a need for an international Tinnitus Society  
F. Hussain | **MEETING:** Is there a need for an international Tinnitus Society  
F. Hussain | **BANQUET** | **BANQUET** |
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<td>08:00 - 07:00 p.m.</td>
<td>08:00 - 09:00 p.m.</td>
<td><strong>BANQUET</strong></td>
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### Detailed Scientific Program

**Tuesday, June 9th**

06:00 - 07:00 p.m.  
Opening Lecture: The Role of the Hippocampus in Tinnitus and Hearing  
Richard Salvi  
*Welcome Cocktail*

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**Wednesday, June 9th**

08:00 - 09:00 a.m.  
Plenary Talk: Thalamocortical Dysrhythmia and Tinnitus  
Rodolfo LINHAS

09:00 - 10:00 a.m.  
Plenary Talk: Do Sensory Cortices Process More than One Sensory Modality During Perceptual Judgments?  
Ranulfo Romo

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**Pathophysiology of Tinnitus**  
A. Norena / D. de Ridder  

R. Levine: the brainstem and tinnitus: Adjustments to the dorsal cochlear nucleus tinnitus hypothesis  
D. De Ridder & Elsa van der Loo: The involvement of auditory cortex in tinnitus  
S. Vanneste: A network approach for understanding tinnitus pathophysiology  
B. Langguth: The involvement of nonauditory brain regions in tinnitus

**Neuroscience and Clinical Research on Somatosensory Tinnitus**  
T.G. Sanchez  

R. Bürgers et al: Temporomandibular joint and masticatory muscle disorders in patients with tinnitus  
T.G. Sanchez: Deactivation of myofascial trigger points is effective to control somatosensory tinnitus  
S. Shore: Neural basis of somatosensory influence on tinnitus  
Q. Yang et al: Abnormalities of vergence eye movements in somatic tinnitus  
J. Zhang: Electrical suppression of tinnitus

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**Poster Session**

01:30 - 03:30 p.m.  
Poster Session

**Neuroimaging in Tinnitus: Mechanisms and Networks**  
F. Husain  

E. Diesch: Altered inhibitory processes in Tinnitus: MEG studies  
D. Hall et al: Challenges and rewards of brain imaging in tinnitus  
F. Husain et al: Neural network differences in tinnitus and hearing loss: An fMRI study  
J. Melcher et al: Is the frontal lobe involved in tinnitus? A structural MRI study  
D.J. Strauss et al: Event-Related Potentials as Correlates of Attentional Binding in Tinnitus: Some insight from Neurodynamical Multiscale Modeling

**Design of Clinical Trials**  
P. Davis, S. Ranadell: Meta-Analysis of Current Tinnitus Treatments  
M. Koller et al: Which changes in the THI score are clinically relevant?  
W.H. Martin et al: Fatal experimental design flaws in clinical trials of tinnitus interventions  
B. Schmidt: Bringing a Tinnitus Medication to Market: Challenges for the Pharmaceutical Industry

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06:00 - 07:00 p.m.  
MEETING: Is there a need of an international Tinnitus Society
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| 08:00 - 09:00 a.m. | Plenary Talk: Synaptic Physiology of Cochlear Hair Cells: Afferent Signaling  
Paul Fuchs |
| 09:00 - 10:00 a.m. | Plenary Talk: Tinnitus and Affective Disorders  
Berthold Langguth |
| Coffee Break (30 min) | Coffee Break (30 min)  
Coffee Break (30 min) |
| 10:30 - 12:30 p.m. | Behavioral Therapy  
M. Mazzioli  
H. Argstetter et al.: The Heidelberg Model Music therapy in chronic tinnitus – treatment outline and neuroscientific evaluation  
M. Mazzioli et al.: Mindfulness based stress reduction (MBSR) intervention in tinnitus therapy  
L. McKenna: A cognitive therapy model of tinnitus distress  
K. Peterson: 10 dilemmas in clinical work with tinnitus sufferers - Why neurophysiology and psychology should join forces in research and clinical practice  
H-P. Zener: Psychophysiological treatment of tinnitus  
TMS / VNS  
A. Londero  
M. Landgrebe et al.: rTMS for the treatment of tinnitus: Results of a large randomized sham controlled trial  
T. Kleinjung et al.: Strategies for enhancement of temporal rTMS in tinnitus patients  
J. F. Piccirillo et al.: Low-frequency rTMS over the left temporoparietal area for bothersome tinnitus  
N. Weiss, I. Lorenz: The Quest for the Magic Bullet against tinnitus: can sound stimulation aid in improving the spatial accuracy of rTMS  
S. Vaneste: Correlation between tDCS, TMS and TENS: are some brains more responsive than others to neuromodulation  
K. Engineer et al.: Reversing Pathological Neural Plasticity to Treat Tinnitus |
| 12:30 - 1:30 p.m. | LUNCH |
| 01:30 - 02:30 p.m. | POSTER SESSION |
| 02:30 - 03:30 p.m. | Specific Forms of Tinnitus  
T. Kleinjung  
F. Bast et al.: Otosclerosis and Tinnitus – Effect of the laser-assisted stapedotomy on preoperatively cases of tinnitus  
M. E. Hoffer et al.: Blast Induced Tinnitus  
D. Roitman: Lightning and tinnitus. Three new cases of tinnitus resulting from lightning  
T. G. Sanchez et al.: Auditory hallucinative phenomenon, tinnitus and hearing loss: truth or myth?  
Animal Models  
R. Salvi  
B. J. Farley, A. Norrena: Auditory cortex voltage-sensitive dye imaging reveals spatiotemporal patterns of spontaneous and evoked neural activity at high resolution  
A. Fryatt et al.: Altered voltage-gated sodium channel expression following moderate sound exposure in rat spiral ganglion neurons  
Th. Imig et al.: Unilateral sound damage causes an increase in single unit spontaneous activity in the inferior colliculus of freely moving rats  
S. Voyerdenko, A. Galazhuk: Sound-triggered suppression of spontaneous firing in central auditory neurons and residual inhibition of tinnitus  
T. Kitahara et al.: Behavioral and molecular combined animal studies for visualization of phantom tinnitus  
S. Hébert, P. Fournier: From rats to humans: Validation of the acoustic gap startle paradigm to objectively tinnitus  
E. Lobarrinas: The effects of Tonabinestat and Cytocinobenzoprie on Noise Induced Tinnitus in rats  
J. G. Turner et al.: Effects of Neramexane in a Mouse Model of Tinnitus  
C. Wu et al.: Screening of Investigational Tinnitus Drugs Using Cultured Auditory Cortex Networks |
| Coffee Break (30 min) | Coffee Break (30 min)  
Coffee Break (30 min) |
| 04:00 - 06:00 p.m. | The TRI Flowchart for Patient Management  
M. Koller: Introduction: Medical Guidelines  
T. Kleinjung: History / Clin exam / Audiol Measurements  
D. De Ridder: Pulsatile Tinnitus  
T. Kleinjung: Tinnitus + Conduct. Hearing Loss  
L. Del Bo: Tinnitus + Sensorineural Hearing Loss  
A. Londero: Tinnitus + Vertigo  
J. M. Lahez: Tinnitus + Headache  
M. Landgrebe: Tinnitus + Psychiatric Comorbidity  
T. Sanchez: Somatosensory Tinnitus  
G. Searchfield: Auditory Stimulation  
B. Langguth: Pharmacotherapy  
M. Landgrebe: Cognitive Behavioral Therapy  
D. De Ridder: Neurostimulation |
| Banquet |

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<th>Time</th>
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| 08:00 - 09:00 a.m. | Plenary Talk: Tinnitus and Neural Plasticity  
Larry Roberts                                           |                                                                                                         |
| 09:00 - 10:00 a.m. | Plenary Talk: Neuroplastic changes induced by auditory stimulation  
Arnaud Norena                                           |                                                                                                         |
| 10:30 - 12:30 p.m. | Sound Stimulation  
G. Searchfield  
M. Berghoelm et al: Internet-based acoustic therapy (IBAT) for tinnitus patients  
G. Searchfield et al: The effect of fractal sounds on tinnitus perception  
P.A. Tass et al: Long-lasting tinnitus relief achieved by acoustic coordinated reset stimulation - Clinical investigation: Phase 1 - Prospective clinical investigation on the acoustic stimulation with the "coordinated reset of neural subpopulations" in the treatment of chronic Tinnitus  
B. Raymond et al: The New Zealand experience with a new sound therapy concept  
L. Del Bo et al: Passive Auditory Stimulation by a prototype of hearing aid that implements the high-pitch auditory stimulation.  
O. Dyrland: High frequency dual sound generator combination instrument for tinnitus sound therapy.  
Pharmacological Treatment of Tinnitus  
A.B. Elgoyhen  
C. Coelho: Cyclobenzaprine to treat chronic tinnitus: results of a 16 weeks prospective open-label trial  
R. Figuereiro et al: Effects of Caffeine in tinnitus: preliminary data  
O. Meeus et al: Administration of the combination Clonazepam – Deannix as a treatment for tinnitus |                                                                                                         |
| 12:30 - 01:30 p.m. | LUNCH                                                                                           | LUNCH                                                                                                   |
| 01:30 - 03:30 p.m. | Electrical Stimulation to the Brain and to the Ear  
A. Molier  
E. Simon et al: Epidural electrical auditory cortex stimulation in the management of chronic unilateral disabling tinnitus: first results of the pilot study "Elec"  
J. Zhang et al: Auditory Cortex Electrical Stimulation to Suppress Tinnitus: An Animal Model  
J.E. Chang et al: Variability in Tinnitus Suppression via Electrical Stimulation  
A. Kleine Punte et al: Electrical primate stimulation to predict tinnitus suppression after cochlear implantation  
A. Kleine Punte et al: Cochlear Implantation as a durable tinnitus treatment in patients with single-sided deafness | Perceptual Training  
G. Searchfield  
D. Hoare et al: The effects of auditory training on tinnitus perception and intrusiveness: a systematic review  
L.E. Roberts, D. Bosnyak: Augmentation of cortical representations for sound in the tinnitus frequency region and its effects on tinnitus  
G. Searchfield, K. Wise: Attention Process Training for Tinnitus  
I. Viald-Delmon et al: Virtual reality protocol for Tinnitus |                                                                                                         |
| 04:00 - 06:00 p.m. | Imaging II  
R. Weisz  
K.L. Hyde et al: A Voxel-Based-Morphometry Study of Structural Brain Differences in Unilateral Tinnitus  
A. Maudoux et al: Resting state auditory network in tinnitus patients: a fMRI study  
A. Dimitrijevic et al: Electrophysiological correlates of tinnitus and tinnitus suppression  
H. Okamoto et al: Detrimental effects of extensive portable music player usage on population-level frequency tuning in human auditory cortex  
H. Stracke et al: Listening to tailor-made notched music reduces tinnitus loudness and tinnitus-related auditory cortex activity | Audiologic Assessment  
R. Roesser  
M. Sera et al: The relationship between tinnitus pitch and audometric variables: A meta analysis  
J. Smurzynski et al: Distortion product otoacoustic emissions in normally hearing patients with unilateral tinnitus  
O. Warusfel et al: Virtual Reality for Tinnitus therapy: Tinnitus recreation method  
X. Zhou et al: Loss of Cochlear compression is predictive of Tinnitus for subjects with mild to moderate hearing loss | New Hypotheses  
J.M. Lainez  
K. Brookler, N. Gilstone: Molecular biology of tinnitus: Cytokine and Endocrine Causes  
D.W. Holmes: The Use of Ultrasound in the Treatment of Tinnitus  
D. de Ridder: Allotasis as a mechanism for tinnitus chronification  
M. Murase: Towards a New Synthesis: Health and Disease |
# Posters

**June 09, 2010**  
1:30 – 2:20 p.m.

## Assessment Questionnaires

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<tr>
<td>R. Görtelmeyer et al</td>
<td>Development and Psychometric Validation of the Attention and Performance Self Assessment Scale (APSA) in tinnitus patients</td>
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<td>DW Holmes</td>
<td>Development of a Tinnitus Evaluation Software Program</td>
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<tr>
<td>US Korbel et al</td>
<td>Intercultural Validation of the Tinnitus Handicap Inventory 12 (THI-12)</td>
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<tr>
<td>O. Maccus et al</td>
<td>Independence of variables in a tinnitus population</td>
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## Audiological Assessment

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<tr>
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<tbody>
<tr>
<td>B. Chaudhury et al</td>
<td>Individual Profiling of Tinnitus Perception by developing Interactive Tinnitus Analyzer Software</td>
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<tr>
<td>P. Nee et al</td>
<td>Comparing an Online Tinnitus Examination to a Tinnitus Exam in a Research Environment</td>
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<tr>
<td>H. J. Shim et al</td>
<td>Hearing abilities at high frequency in patients with tinnitus</td>
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## Clinical Trials

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<tr>
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<tbody>
<tr>
<td>M. Koller et al</td>
<td>THI score changes over the course of therapy and patient’s subjective perception of tinnitus change</td>
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## Epidemiology

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<thead>
<tr>
<th>Authors</th>
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<tbody>
<tr>
<td>R. Figueiredo et al</td>
<td>Incidence of tinnitus in teenagers and young adults mp3 players users</td>
</tr>
<tr>
<td>D. Rollman, A. Aspinwall</td>
<td>Survey Online about Tinnitus and hyperacusis, via our website</td>
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## Health System

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<tr>
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<tbody>
<tr>
<td>D. Hoare et al</td>
<td>A survey of Audiology departments across England: Tinnitus assessment, treatment and outcome measures</td>
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<tr>
<td>J. Lim et al</td>
<td>Experience of a tinnitus counseling clinic in Singapore</td>
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## Pathophysiology

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<tr>
<td>J. Yilokoski et al</td>
<td>Stress reaction in patients with acute noise induced tinnitus</td>
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<td>H. P. Zenner</td>
<td>The sensitization model for acquired centralized tinnitus</td>
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<tr>
<td>N. Catz, A. J. Norena</td>
<td>Changes in the cortical spectro-temporal receptive fields induced by notched stimuli</td>
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<tr>
<td>L. Lagemann et al</td>
<td>Frequency tuning in chronic tinnitus patients</td>
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**June 09, 2010**  
2:30 – 3:30 p.m.

## Case

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<td>Z. Komacek et al</td>
<td>Unilateral Tinnitus – The Only Symptom of a Large Vestibular Schwannoma</td>
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<tr>
<td>J. J. Song, J. W. Koo</td>
<td>Recording and analysis of pulsatile tinnitus in dural sinus diverticulum</td>
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<tr>
<td>P. Winkler</td>
<td>Early intervention in sudden onset tinnitus</td>
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## Others

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<tbody>
<tr>
<td>G. R. Paul, M. Malusevic</td>
<td>American Tinnitus Association: Our Mission To Cure Tinnitus</td>
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### Somatosensoric Tinnitus

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<td>E. Elesinger et al</td>
<td>Qigong for the treatment of tinnitus. A randomized controlled pilot study</td>
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<tr>
<td>M. Estola</td>
<td>Muscular tension and tinnitus. An experimental Trial of Trigger Point Injections on Tinnitus</td>
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<tr>
<td>R. Levine et al</td>
<td>Continuous auricular electrical stimulation quiets the tinnitus of the somatosensory pulsatile tinnitus syndrome</td>
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<tr>
<td>J. Park</td>
<td>Clinical Characteristics and Therapeutic Responses of Muscle Origin Tinnitus</td>
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<tr>
<td>C. Rocha, T.G. Sanchez</td>
<td>Efficacy of myofascial trigger point deactivation for tinnitus treatment</td>
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<tr>
<td>V. Vielmeier et al</td>
<td>Tinnitus and temporomandibular joint disorders – a special subgroup of tinnitus patients?</td>
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<tr>
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<tr>
<td>G. Baracca et al</td>
<td>Botulinum toxin treatment for objective tinnitus caused by palatal myoclonus</td>
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<tr>
<td>A.C. Binetti et al</td>
<td>Tinnitus in Vestibular Migraine</td>
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<td>P. Gao, J. Jin</td>
<td>New Pathogen and Therapy - In 17 Cases of Chronic Conductive Tinnitus</td>
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<tr>
<td>J-W. Koo</td>
<td>Recording and analysis of pulsatile tinnitus in dural sinus diverticulum</td>
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<tr>
<td>J-H. Lee</td>
<td>Evaluation of Tinnitus in the patients with Meniere’s Disease</td>
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<tr>
<td>S. N. Park</td>
<td>A Case of Palatal Myoclonus Associated with Orofacial Buccal Dystonia</td>
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### June 10, 2010
01:30 – 02:30 p.m.

#### Auditory Stimulation

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<tr>
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<tr>
<td>G. Baracca et al</td>
<td>Customized Sound Therapy for Tinnitus</td>
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<tr>
<td>D. Choy</td>
<td>Sequential phase shift sound cancellation RX predominant tone tinnitus</td>
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<tr>
<td>M. Nakagawa</td>
<td>A Study of Music Therapy using “1/1-fluctuation sounds” for Tinnitus patients</td>
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<tr>
<td>C.W. Newman, S.A. Sandridge</td>
<td>Benefit from and economic value associated with two alternative sound therapy tinnitus management options</td>
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<tr>
<td>M. Pliskocz</td>
<td>Clinical application of a new Tinnitus Sound Generator (TSG) device</td>
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<tr>
<td>VS. Rothholz et al (pres. author: K.M. Reavis)</td>
<td>Tinnitus Suppression by Low-Rate Modulated Sounds</td>
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<tr>
<td>S.A. Sandridge, C.W. Newman</td>
<td>First year findings of three-year study of long-term benefits of neuromonics treatment</td>
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<tr>
<td>M-W. Suh et al</td>
<td>Specific Effects and Prognostic Factors of Hearing Aids on Tinnitus</td>
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#### Brain Stimulation

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<tr>
<td>S.J. Burger</td>
<td>rTMS for the treatment of tinnitus: Are there clinical parameters which predict the therapeutic response and what happens with responders over longer follow-up periods?</td>
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<tr>
<td>K. Ogawa</td>
<td>Repetitive transcranial magnetic stimulation for treatment of chronic tinnitus. -Clinical and experimental study</td>
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<tr>
<td>M. Landgrebe</td>
<td>Clinical improvement after repetitive transcranial magnetic stimulation is accompanied by changes in gray matter detected by voxel-based morphology</td>
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#### Cochlear Implant

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<td>M. Cosgarea et al</td>
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#### Neurofeedback

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<td>B. Richmond et al</td>
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<td>M.A. Lopez-Gonzalez et al</td>
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<td>AK Shukuryan et al</td>
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Poster Format: portrait 90 cm width x 120 cm height (35.5 inch x 47.5 inch).
Dear colleague,

Brazil has been elected to host the next International Tinnitus Seminar during the last 2008 meeting held in Sweden. It is the first time such an event takes place in Latin America.

We are pleased to announce the X International Tinnitus Seminar to be held in March 16 to 19, 2011 at the Resort of Costão do Santinho, situated in the paradisiacal island of Florianopolis, Santa Catarina, Brazil (www.its2011brazil.com.br)

The event will host the world’s health community with a common interest in tinnitus. It will be a great opportunity to share and discuss related topics and a mind-opening experience to new ideas.

Along with an exciting scientific program we are also organising a unique cultural experience of the warm and friendly “Brazilian way”.

Your invaluable presence will help us to make this an unforgettable event full of new knowledge and fun.

We look forward to welcoming you to Brazil in March 2011.

Prof Tanit Ganz Sanchez, MD, PhD  
President of ITS 2011

Claudia Barros Coelho, MD, PhD  
President of the Scientific Committee
News

Iowa Hyperacusis Project

Hyperacusis is difficult to treat, in part because so little is known about it. The University of Iowa Hospital and Clinics have begun a major research effort to understand hyperacusis and develop treatment options.

Please go to the hyperacusis web site and complete the questionnaires. Please ask anyone you know with hyperacusis to complete the questionnaire.

Jennifer Parrish and Rich Tyler
The University of Iowa Hospital and Clinics
Department of Otolaryngology - Head and Neck

Proceedings of Tinnitus Discovery

Grant Searchfield and Ron Goodey edited the Proceedings of „Tinnitus Discovery“: Asia-Pacific Tinnitus Symposium, 11-12 September 2009, in Auckland, New Zealand. For download please see Proceedings
Upcoming Meetings  
Meetings exclusively dedicated to Tinnitus are marked red

ESPO 2010 European Society of Pediatric Otorhinolaryngology
When: June 05 – 08, 2010
Where: Baluarte Conference Centre, Pamplona, Spain
Contact: Secretaria Cientifica, ORL Congresos, S.L.
C/ Fundadores, nº 13
28028 Madrid, Spain
Phone: 0034 91 575 93 93
Fax: 0034 91 431 26 92
E-Mail: orlcongresos@seorl.net
Detailed information: http://www.espopamplona2010.com/

Human Brain Mapping Annual Meeting
When: June 06 – 10, 2010
Where: Barcelona, Spain
Detailed information: www.humanbrainmapping.org

4th International TRI Tinnitus Conference. Frontiers in Tinnitus Research
When: June 9 – 11, 2010
Where: The Adolphus Hotel, Dallas, Texas, USA
E-Mail: dallas2010@tinnitusresearch.org
Detailed Information: http://www.utdallas.edu/research/tri/

4th World Congress of International Federation of Head and Neck Oncologic Societies (IFHNOS)
When: June 15 – 19, 2010
Where: Lotte Hotel, Seoul, Korea
Contact: IFHNOS 2010 Congress Secretariat
c/o Meci International Convention Services, Inc.
Rm. 1906, 19th floor, Daerung Post Tower #1 212-8 Guro-dong, Guro-gu
Seoul 152-790, Korea
Phone: 0082 2 2082 2310
Fax: 0082 2 2082 2314
E-Mail: ifhnos2010@ifhnos2010.org
Detailed information: http://www.ifhnos2010.org/

International Conference on Adult Hearing Screening (AHS) 2010
When: June 10 - 12, 2010
Where: Cernobbio, Italy
E-mail: ahs2010@polimi.it
Detailed Information: http://www.ahs2010.polimi.it/
CI2010 11th International Conference on Cochlear Implants and other Implantable Auditory Technologies
When: June 30 – July 03, 2010
Where: Stockholm International Fairs (Stockholmsmässan), Stockholm, Sweden
Contact: MCI Stockholm
Box 6911
102 39 Stockholm, Sweden
Phone: 0046 8 5465 1500
Fax: 0046 8 5465 1599
E-Mail: ci2010@mci-group.com
Detailed information: http://www.ci2010.com

Conventus Meeting of the Societas ORL Latina
When: September 1 – 4, 2010
Where: Acaya Golf Resort, Lecce, Italy
Contact: M.C.A. Events srl
Via G. Pellizza da Volpedo, 4
20149 Milan, Italy
Phone: 0039 02 34934404
Fax: 0039 02 34934397
E-Mail: info@mcaevents.org
Detailed Information: http://www.conventus2010.org

Eighteenth Annual Conference on Management of the Tinnitus Patient
When: September 16 - 18, 2010
Where: Iowa, IA, USA
Contact: Center for Conferences and Institutes
The University of Iowa
250 CEF
Iowa City, IA, 52242-5000
Phone: 001 800-551-9029
Fax: 001 319-335-4039
Detailed information: uihealthcare.com/depts/med/otolaryngology/conferences

Herbsttagung Arbeitsgemeinschaft Deutschsprachiger Audiologen und Neurootologen (ADANO)
When: September 16 – 19, 2010
Where: Zürich, Switzerland
Detailed information: http://www.hno.org/adano/tagungen.htm

APA 2010 - XV Anniversary Symposium in Audiological Medicine
When: September 19 – 22, 2010
Where: Krakow Poland
Phone: 004842636-35-18
Fax: 004842636-35-18
E-Mail: info@iapa2010.eu
Detailed Information: http://www.iapa2010.eu
International Symposium on Objective Measures in Auditory Implants
When: September 23 – 25, 2010
Where: St. Louis, MO, USA
Detailed information: https://cme.wustl.edu/om2010/

IAPA 2010 - XV International Symposium in Audiological Medicine
When: September 23 – 26, 2010
Where: Krakow Poland
Contact: Professor Mariola Sliwinska-Kowalska
Detailed Information: http://iapa-online.org/symposia/future-symposia/#

American Academy of Otolaryngology, Head and Neck Surgery Annual Meeting
When: September 26 – 29, 2010
Where: Boston, MA, USA
Detailed information: http://www.entnet.org/ConferencesAndEvents/upcomingconferences.cfm

55th International Congress of Hearing Aid Acousticians
When: October 13 – 15, 2010
Where: Messe Hannover, Germany
Detailed information: http://www.euha.org

ASHA 2009 Annual Convention
When: November 18 – 20, 2010
Where: Philadelphia, PA, USA
Detailed information: http://www.asha.org/about/events/convention/
Recently published literature (articles of authors who are funded by TRI are marked in blue)

I Epidemiology

Epidemiological Study of Chronic Tinnitus in Assiut, Egypt.
Neuroepidemiology. 2010 Apr 8;35(1):45-52. [Epub ahead of print]

Khedr EM, Ahmed MA, Shawky OA, Mohamed ES, El Attar GS, Mohammad KA.
Department of Neurology, Assiut University Hospital, Assiut, Egypt.

Background and Aim: Few comprehensive epidemiological studies of the prevalence of tinnitus have been undertaken, and none has been carried out in Egypt. A community-based survey was conducted in the Assiut Governorate to estimate the prevalence of tinnitus, its associations with psychiatric disorders and its effect on the quality of life. Material and Methods: The study involved 8,484 subjects, 5,783 (68.2%) from the rural community and 2,701 (31.8%) from the urban community. Patients were identified from a door-to-door survey and evaluated using a semistructured questionnaire, the Tinnitus Handicap Inventory and the Hamilton Anxiety and Depression Scales. Results: Four hundred and thirty-nine patients with tinnitus were found, giving a prevalence of 5.17 tinnitus cases/100 inhabitants. Males and females were equally affected. The highest age-specific prevalence rate was recorded among subjects above 60 years (17.66%) and was significantly higher among urban than rural inhabitants (6.3 vs. 4.6%) and among illiterate than among educated persons (10.15 vs. 3.07%). A majority of patients (53.3%) had some hearing loss; otitis media was common. Only 15.2% of cases were classified as having severe to catastrophic tinnitus. Nearly two thirds had a degree of depression. There were significant correlations between the severity of tinnitus and the degree of hearing loss, temporomandibular joint pain and the Hamilton depression score. Sleep disturbance was reported by 39.4% of subjects. Life enjoyment was severely affected in 15% of tinnitus patients. Conclusion: Tinnitus is a common problem in our locality, especially in older adults, and is associated with some modifiable risk factors. Copyright © 2010 S. Karger AG, Basel.

Tinnitus in children: an uncommon symptom?
Arch Dis Child. 2010 Apr 6. [Epub ahead of print]

Shetye A, Kennedy V.
St Ann’s Hospital, Haringey Teaching PCT, Tottenham, London, UK.

Tinnitus in children is regarded as an uncommon problem rarely noted by general paediatricians. Its reported prevalence varies from 12% to 36% in children with normal hearing thresholds and up to 66% in children with hearing loss and approximately 3-10% of children have been reported troubled by tinnitus. Some children do not spontaneously complain of it, but may demonstrate behavioural problems at school and home. A careful history, in conjunction with clinical findings, should guide the appropriate management approach. Even very young children are able to provide insights into what troubles them allowing children’s thoughts and fears regarding this symptom to be addressed. We review the available literature on the nature and impact of tinnitus and as guidelines for this do not exist, suggest a pragmatic approach to the management of tinnitus in children. Children with troublesome tinnitus, however, should be referred on to a paediatric audiology department for further investigation and management.
Hearing and vestibular complaints during pregnancy.

Schmidt PM, Flores Fda T, Rossi AG, Silveira AF.
Universidade Federal de Santa Maria, Brazil.

Hormonal dysfunctions in women during pregnancy can cause vestibular and/or cochlear disorders.
AIM: to study hearing and vestibular complaints in pregnant women. MATERIAL AND METHOD: this is a prospective study. 82 pregnant women participated on this study. For hearing and vestibular complaints, a questionnaire proposed by Castagno (1994) was employed. RESULTS: we could observe that tinnitus was the main auditory complaint (33%), although with no differences between the groups. Tinnitus was present among 52.44% of the pregnant women, mainly in the Group 2. According to symptoms related to dizziness, vertigo was the main auditory complaint in first trimester, whereas instability and gait unbalance were more frequent in the second trimester, and instability and tendency to fall in the third trimester. Nausea was the main symptom associated with dizziness in pregnant women, being more frequent in the first trimester of gestation. CONCLUSIONS: women during gestation have auditory and vestibular complaints, mainly dizziness and tinnitus

The impact of gender, age and hearing loss on tinnitus severity.

Pinto PC, Sanchez TG, Tomita S.
Rio de Janeiro Federal University, Brazil.

Tinnitus is a symptom present in approximately 15% of the world population. Most patients are between 40 and 80 years of age; the prevalence above 60 reaches 33%. About 20% have moderate to severe impact in the quality of life but the factors associated with the tinnitus annoyance are not completely known. AIM: The objective of this study is to evaluate the relationship between age, gender and hearing loss on tinnitus annoyance. MATERIALS AND METHODS: 68 patients were evaluated at the tinnitus center at our hospital, from March 2007 to march 2008, with a detailed interview, complete otolaryngological examination, the Portuguese version of the Tinnitus Handicap Inventory and pure tone audiometry. RESULTS: Age varied from 24 to 83 (mean=59); the mean THI value was 39 (females: 36; males: 44). THI grades were: slight: 32.3%; mild: 19.1%; moderate: 20.6%; severe: 13.2% and catastrophic: 14.7%. No significant correlation was found between gender (p=0.30), age (p>0.05 for all averages analyzed) and tinnitus severity. CONCLUSION: Gender, age and hearing loss do not influence tinnitus annoyance, using the THI.

Neurotological symptoms and academic performance of university students.

Marques MM, Ganança MM, Marques CM, Ganança FF, Caovilla HH.
Federal University of São Paulo, Brasil. marcia.mattos@unifesp.br

Objective: To compare the academic performance of university students with or without neurotological symptoms. Method: 100 students enrolled in the Biomedical Sciences Graduate School - Medical Modality of UNIFESP-EPF in 2007 and answered a neurotological screening questionnaire. Results: The symptoms presented once, sometimes, many times or always, in a decreasing order of prevalence, were headache (74.0%), difficulty with concentration (57.0%), lack of memory (45.0%), physical indisposition, nausea /dizziness when in moving vehicle (37.0%), fainting (27.0%), nausea (26.0%), sensation of fullness in the ear (26.0%), hypersensitivity to sounds (26.0%), tinnitus (22.0%), vertigo and other kinds of dizziness (21.0%), imbalance when walking (21.0%), difficulty in hearing (21.0%), imminent sensation of fainting (11.0%) and vomiting (8.0%), alone or in different associations; convulsion was not mentioned. The final academic performance score ranged from 5.1 to 10.0. Conclusion: University students with or without neurotological symptoms have manifested similar academic performance.
Self-assessed auditory symptoms, noise exposure, and measured auditory function among healthy young Swedish men.


Muhr P, Rosenhall U.

The Department of Clinical Neuroscience, Karolinska Institute, and the Department of Audiology, Karolinska University Hospital, Stockholm, Sweden. per.muhr@mil.se

The aim of the study was to estimate the prevalence of the exposure to ototraumatic factors and auditory symptoms, and to analyse the relations between these factors in a group of young healthy men. A total of 839 men, 19-22 years old, were recruited for the study when reporting for primary military service. A questionnaire was distributed and audiometry was performed. The prevalence of tinnitus, sensitivity to noise, and measured hearing impairment in the study group was 23.2%, 15.5%, and 14.5% respectively. Exposure to occupational noise often was reported by 21.4%, and playing loud music often by 16.5%. The young men who had experienced tinnitus after noise exposure had an elevated risk of high frequency hearing impairment, tinnitus, and sensitivity to noise. Those who played loud music had elevated prevalence values of tinnitus but not of hearing impairment. In this young group we observed high prevalence values of ototraumatic factors and auditory symptoms. We also observed significant correlations between tinnitus after noise exposure, self-assessed hearing symptoms, and hearing impairment.

Incidence, Persistence, and Progression of Tinnitus Symptoms in Older Adults: The Blue Mountains Hearing Study.

Ear Hear. 2010 Jan 29. [Epub ahead of print]

Gopinath B, McMahon CM, Rochtchina E, Karpa MJ, Mitchell P.

Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute; Menzies Centre for Health Policy, University of Sydney; and 3Centre for Language Sciences, Department of Linguistics, Macquarie University, Sydney, NSW, Australia.

OBJECTIVE: Temporal population-based data on tinnitus are lacking. We used a representative older population-based cohort to establish 5-yr incidence, persistence, and progression of tinnitus symptoms. DESIGN: Two thousand six participants of the Blue Mountains Hearing Study (1997-1999) had complete tinnitus data, and of these, 1214 participants were followed up at 5-yr examinations in 2002-2004. Presence of prolonged tinnitus was assessed by a positive response to a single question administered by an audiologist. Incident tinnitus was defined in participants who were free of tinnitus symptoms at the baseline study in 1997-1999 but who reported tinnitus symptoms at the 5-yr follow-up in 2002-2004. Progression of tinnitus was defined as the increase in annoyance of tinnitus symptoms from baseline to the 5-yr follow-up study. Persistence of tinnitus symptoms was defined as the presence of tinnitus symptoms at both the baseline and follow-up examinations. Hearing impairment was measured as the pure-tone average (PTA) of audiometric hearing thresholds at 500, 1000, 2000, and 4000 Hz (PTA0.5-4 kHz), defining bilateral hearing loss as PTA0.5-4 kHz >25 dB HL. RESULTS: Five-year incidence of tinnitus was 18.0%. A significant age trend was observed for the 5-yr incidence (p = 0.005), with incident tinnitus decreasing with age. Hearing loss increased the risk of developing incident tinnitus, age-sex adjusted odds ratio 2.13 (95% confidence interval, 1.40 to 3.24). Most (55.5%) incident tinnitus cases reported symptoms that were only mildly annoying. Tinnitus at baseline persisted in 81.6% of participants. Of those reporting mildly annoying tinnitus at baseline, 39.6% progressed to moderately annoying and 5.9% to severely annoying tinnitus. At the follow-up, a higher frequency of participants with persistent tinnitus (old cases) reported their symptoms as very/extremely annoying compared with the new (incident) cases of tinnitus (p = 0.001). A high proportion (85.2%) of subjects receiving tinnitus treatment (mainly medications and hearing aid) at baseline still reported tinnitus at 5-yr examinations. CONCLUSIONS: Incident tinnitus was frequent, with nearly one in five older adults suffering from this condition after 5 yrs. Tinnitus symptoms persisted in more than three-quarters of the cohort, during the 5 yrs. Longitudinal data are an important contribution to the research evidence base to support timely intervention and effective management of this frequent symptom.
Risk factors and impacts of incident tinnitus in older adults.

Gopinath B, McMahon CM, Rochtchina E, Karpa MJ, Mitchell P.

Centre for Vision Research, Dept of Ophthalmology, Westmead Millennium Institute, University of Sydney, Australia.

PURPOSE: We used a representative older population-based cohort to establish the predictors and impacts of tinnitus. METHODS: A total of 1,214 participants of the Blue Mountains Hearing Study were followed for 5 years (1997-1999 to 2002-2004). The presence of tinnitus was assessed by an audiologist-administered questionnaire. Hearing impairment was defined as the pure tone average (PTA)(0.5-4KHz)>25 dB HL, in the better ear. Quality of life was measured by use of the Short Form 36-item Health Survey (SF-36). Depression was assessed using either the SF-36 (Mental Health Index, subscale) and the Center for Epidemiologic Studies Depression Scale. RESULTS: Symptomatic dizziness and hearing loss were significant risk factors for incident tinnitus, multivariable-adjusted odds ratio, 2.41 (95% confidence interval, 1.62-3.58) and odds ratio 2.31 (95% confidence interval, 1.46-3.66), respectively. Incident tinnitus cases demonstrated significantly lower mean SF-36 scores compared with subjects without tinnitus and were more likely to be depressed as assessed by both the Mental Health Index and Center for Epidemiologic Studies Depression Scale. CONCLUSIONS: Incident tinnitus was predicted by two otological risk factors, dizziness and hearing loss. Temporal data documented diminished quality of life and psychological well-being in those subjects experiencing tinnitus. This finding highlights the importance of effective intervention strategies to prevent potentially debilitating morbidity associated with tinnitus. 2010 Elsevier Inc. All rights reserved.

Tinnitus in children without hearing impairment.

Savastano M, Marioni G, de Filippis C.

Department of Medical-Surgical Specialities, University of Padua, Italy. marina.savastano@unipd.it

OBJECTIVE: Tinnitus is not an uncommon symptom in the pediatric population and, despite its incidence, is still an unrecognized problem, particularly in normal hearing children. As tinnitus is frequently described by adults without evidence of ear disease, reports of tinnitus can be obtained also from a group of children without otological pathology. The present review has been performed in order to emphasize the great importance to try to identify children suffering from tinnitus and to recognize the difference between the tinnitus characteristics in children with ear pathology and those one without otological problems. METHODS: A review of the literature regarding the nature of pediatric tinnitus and the practical diagnostic approach to this symptom has been carried out. RESULTS: Children rarely complain spontaneously of tinnitus but are able to describe it when questioned. In our experience the total percentage of children with tinnitus rises from 6.5% (tinnitus reported spontaneously), to 34% when children are specifically questioned. Most children, more than 50%, have normal hearing; in those with hearing impairment, no particular type or severity of hearing loss has been found. An important point that must be considered much more seriously is tinnitus sequela following head injuries to which children are particularly exposed during their daily activities. Due to the serious consequences that may be caused by tinnitus, it is of great importance to identify and analyze it, so as to minimize its damage, utilizing a protocol of study of pediatric tinnitus which allows to collect interesting informations about tinnitus characteristics. CONCLUSIONS: In considering that tinnitus in children exists and may provoke serious consequences, even in absence of ear pathology, it is necessary to investigate and understand more about this symptom in children. From this viewpoint, it is very important to recognize the value of a global evaluation of a child suffering from tinnitus. There is no reason why such an important symptom well reported in adults should not be investigated in the pediatric population in which it seems to be as frequent as in the adult one. It is reasonable to believe that also in children tinnitus may have significant implications for medical and rehabilitative management. Copyright 2009 Elsevier Ireland Ltd. All rights reserved.
II Pathophysiology

Experience with a medicolegal decision-making system for occupational hearing loss-related tinnitus.

Dejonckere PH, Coryn C, Lebacq J.

Federal Institute of Occupational Diseases, Brussels, Belgium. Ph.DeJonckere@umcutrecht.nl

Owing to an increasing number of requests for compensation, a medicolegal decision-making system for tinnitus related to noise-induced hearing loss (NIHL) has been elaborated at the Federal Belgian Institute of Occupational Diseases. Experience with 113 patients, all of them claiming compensation for NIHL and tinnitus, is now available. The patients underwent an exhaustive audiological investigation, and their professional career and noise exposure were carefully and objectively documented. We reviewed the group of 35 “accepted” cases (i.e., with chronic tinnitus recognized as related to NIHL and financially compensated as an occupational disease) and analyzed the medicolegal arguments for acceptance or rejection. In these patients, tinnitus was mostly bilateral, was perceived on average at a frequency of 4 KHz and with a supraliminal intensity of 7.2 dB, and lasted on average for 7.3 years. To gain better insight into the relationship between cochlear damage and chronic tinnitus, we compared our group to a control group of 35 patients with similar hearing thresholds at 3 and 4 KHz but free of tinnitus. The main difference is a significantly steeper slope of the audiometric curve between 2 and 3 KHz in the tinnitus group. Furthermore, a notch in the distortion product-gram is noticed in 60% of the ears affected by tinnitus versus 9% of the ears in the control group. This abrupt discontinuity in the activity along the tonotopic axis of the auditory system—the main characteristic of NIHL—could be a factor eliciting tinnitus, as a correspondence between the audiometric notch and tinnitus frequency appears to exist.


Shulman A, Strashun AM.

Department of Otolaryngology, Health Science Center at Brooklyn, State University of New York, Downstate Medical Center, Brooklyn, USA. metrc@inch.com

It is hypothesized that in all traumatic brain injury (TBI) patients with a clinical history of closed or penetrating head injury, the initial head trauma is associated with a vibratory sensation and noise exposure, with resultant alteration in vascular supply to the structures and contents of the fluid compartments of brain and ear (i.e., the fluid dynamics vascular theory of brain-inner-ear function [FDVTBE]). The primary etiology—head trauma—results in an initial fluctuation, interference, or interaction in the normal fluid dynamics between brain and labyrinth of the inner ear, with a resultant clinical diversity of complaints varying in time of onset and severity. Normal function of the brain and ear is a reflection of a normal state of homeostasis between the fluid compartments in the brain of cerebrospinal fluid and perilymph-endolymph in the labyrinth of the ear. The normal homeostasis in the structures and contents between the two fluid compartment systems—intracerebral and intralabyrinthine—is controlled by mechanisms involved in the maintenance of normal pressures, water and electrolyte content, and neurotransmitter activities. The initial pathophysiology (a reflection of an alteration in the vascular supply to the brain-ear) is hypothesized to be an initial acute inflammatory response, persistence of which results in ischemia and an irreversible alteration in the involved neural substrates of brain-ear. Clinically, a chronic multisymptom complex becomes manifest. The multisymptom complex, individual for each TBI patient regardless of the diagnostic TBI category (i.e., mild, moderate, or severe), initially reflects processes of inflammation and ischemia which, in brain, result in brain volume loss identified as neurodegeneration and hydrocephalus ex vacuo or an alteration in cerebrospinal fluid production (i.e., pseudotumor cerebri) and, in ear, secondary endolymphatic hydrops with associated cochleovestibular complaints of hearing loss, tinnitus, vertigo, ear blockage, and hyperacusis.
The FDVTBE integrates and translates a neurovascular hypothesis for Alzheimer’s disease to TBI. This study presents an FDVTBE hypothesis of TBI to explain the clinical association of head trauma (TBI) and central nervous system neurodegeneration with multisensory complaints, highlighted by and focusing on cochleovestibular complaints. A clinical case report, previously published for demonstration of the cerebrovascular medical significance of a particular type of tinnitus, and evidence-based basic science and clinical medicine are cited to provide objective evidence in support and demonstration of the FDVTBE.

An Examination of KCNE1 Mutations and Common Variants in Chronic Tinnitus
Genes 2010, 1(1), 23-37;
Sand PG¹, Luettich A², Kleinjung T³, Hajak G¹, Langguth B¹

¹Dept of Psychiatry, Univ, of Regensburg, ²Experimental and Clinical Neurosciences Graduate Program, Univ, of Regensburg, ³Dept of Otorhinolaryngology, Univ, of Regensburg, Germany; goeran.hajak@medbo.de

Chronic tinnitus is a highly prevalent and often incapacitating condition frequently associated with sensorineural hearing loss. While its etiology remains incompletely understood there is a growing awareness of genetic factors that predispose to, or aggravate chronic tinnitus. Candidate genes for the disorder include KCNE1, a potassium channel subunit gene that has been implicated in maturation defects of central vestibular neurons, in Menière’s disease, and in noise-induced hearing loss. 201 Caucasian outpatients with a diagnosis of chronic tinnitus were systematically screened for mutations in the KCNE1 open reading frame and in the adjacent sequence by direct sequencing. Allele frequencies were determined for 46 known variants, plus two novel KCNE1 mutations. These comprised one missense substitution (V47I) in the highly conserved region encoding the KCNE1 transmembrane domain, and one rare variant in the gene’s 3’UTR. When genotypes were grouped assuming dominance of the minor alleles, no significant genotype or compound genotype effects were observed on tinnitus severity. The newly identified V47I substitution argues in favor of an enlarged spectrum of mutations in hearing disorders. However, with regard to allele frequencies in healthy control populations from earlier studies, more common KCNE1 variants are unlikely to play a major role in chronic tinnitus. Further investigations are invited to address variation in additional channel subunits as possible risk factors in tinnitus.

Keywords: tinnitus; KCNE1; missense mutation; hearing disorder

Too much of a good thing: Long-term treatment with salicylate strengthens outer hair cell function but impairs auditory neural activity.
Hear Res. 2010 Mar 6. [Epub ahead of print]

Chen GD, Kermany MH, D’Elia A, Ralli M, Tanaka C, Bielefeld EC, Ding D, Henderson D, Salvi R.

Center for Hearing and Deafness, SUNY at Buffalo, Buffalo, NY, USA.

Aspirin has been extensively used in clinical settings. Its side effects on auditory function, including hearing loss and tinnitus, are considered as temporary. A recent promising finding is that chronic treatment with high-dose salicylate (the active ingredient of aspirin) for several weeks enhances expression of the outer hair cell (OHC) motor protein (prestin), resulting in strengthened OHC electromotility and enhanced distortion product otoacoustic emissions (DPOAE). To follow up on these observations, we carried out two studies, one planned study of age-related hearing loss restoration and a second unrelated study of salicylate-induced tinnitus. Rats of different strains and ages were injected with salicylate at a dose of 200mg/kg/day for 5days per week for 3weeks or at higher dose levels (250-350mg/kg/day) for 4days per week for 2weeks. Unexpectedly, while an enhanced or sustained DPOAE was seen, permanent reductions in the amplitude of the cochlear compound action potential (CAP) and the auditory brainstem response (ABR) were often observed after the chronic salicylate treatment. The mechanisms underlying these unexpected, permanent salicylate-induced reductions in neural activity are discussed. Copyright © 2010 Elsevier B.V. All rights reserved.
The relationship between various psychosocial factors and physical symptoms reported during primary-care health examinations.

Dorner TE, Stronegger WJ, Rebhandl E, Rieder A, Freidl W.

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OBJECTIVES: The aim of the study was to determine indicators for psychosocial factors and to investigate the associations between them and physical complaints, as well as to examine possible gender-dependent differences. METHODS: This was an observational (cross-sectional) study in primary care (health examinations in several Austrian regions); participants were 312 men and 374 women aged 19-60 years. The impact of psychosocial factors on ten physical symptoms (cardiac complaints, dyspnea, gastric complaints, headaches, joint or muscle pain, dry skin, hearing impairment, tinnitus, decrease of strength and endurance, and insomnia) was analyzed using logistic regression analyses and multiple linear regression models. RESULTS: People with psychosocial stress or dissatisfaction exhibited a higher probability of reporting at least one physical symptom. Age-adjusted odds ratios (95% CI) were as follows: pressure at work 1.72 (1.08-2.73) in men and 2.53 (1.46-4.39) in women, social stress in the workplace 3.37 (1.41-8.05) in men and 3.09 (1.01-9.43) in women, sexual dissatisfaction 4.48 (1.47-13.62) in men and 1.77 (0.80-3.96) in women, discomfort in family/partnership 4.71 (1.34-16.57) in men and 1.76 (0.66-4.67) in women. Among men, the psychosocial parameter most strongly related to the number of physical symptoms was discomfort in family/partnership, followed by social stress in the workplace, sexual dissatisfaction, and pressure at work with means of 2.00, 1.27, 0.92 and 0.33 symptoms respectively (linear regression model, adjusted for age). Among women the strongest association found was also with discomfort in family/partnership, followed by sexual dissatisfaction, pressure at work and social stress in the workplace with means of 1.32, 1.20, 0.58 and 0.50 symptoms respectively. CONCLUSIONS: The reporting of physical symptoms is often associated with psychosocial factors and these should be taken into account during primary care and, where appropriate, should be further clarified. There are unexpected, gender-related patterns in the association of different psychosocial factors with physical symptoms that warrant further investigation.

Cigarette smoking as a risk factor for auditory problems.

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Smoking is a public health concern and we are still unsure of its relation with auditory problems. AIM: To study the effects of cigarette smoking in auditory thresholds, in otoacoustic emissions and in their inhibition by the efferent olivocochlear medial system. MATERIALS AND METHODS: 144 adults from both genders, between 20 and 31 years of age, smoking and non-smoking individuals were submitted to conventional and high-frequency audiometry, transient stimuli otoacoustic emissions and suppression effect investigation. RESULTS: smokers presented worse auditory thresholds in the frequencies of 12,500Hz in the right ear and 14,000 kHz in both ears. Regarding the otoacoustic emissions, smokers group presented a lower response level in the frequencies of 1,000Hz in both ears and 4,000Hz in the left ear. Among smokers there were more cases of cochlear dysfunction and tinnitus. CONCLUSION: Our results suggest that cigarette smoking has an adverse effect on the auditory system.
Noise trauma impairs neurogenesis in the rat hippocampus.
Neuroscience. 2010 Mar 3. [Epub ahead of print]

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The hippocampus, a major site of neurogenesis in the adult brain, plays an important role in memory. Based on earlier observations where exposure to high-intensity noise not only caused hearing loss but also impaired memory function, it is conceivable that noise exposure may suppress hippocampal neurogenesis. To evaluate this possibility, nine rats were unilaterally exposed for 2 h to a high-intensity, narrow band of noise centered at 12 kHz at 126 dB SPL. The rats were also screened for noise-induced tinnitus, a potential stressor which may suppress neurogenesis. Five rats developed persistent tinnitus-like behavior while the other four rats showed no signs of tinnitus. Age-matched sham controls showed no signs of hearing loss or tinnitus. The inner ear and hippocampus were evaluated for sensory hair cell loss and neurogenesis 10 weeks post-exposure. All noise exposed rats showed severe loss of sensory hair cells in the noise-exposed ear, but essentially no damage in the unexposed ear. Frontal sections from the hippocampus were immunolabeled for doublecortin to identify neuronal precursor cells, or Ki67 to label proliferating cells. Noise-exposed rats showed a significant reduction of neuronal precursors and fewer dividing cells as compared to sham controls. However, we could not detect any difference between rats with behavioral evidence of tinnitus versus rats without tinnitus. These results show for the first time that high intensity noise exposure not only damages the cochlea but also causes a significant and persistent decrease in hippocampal neurogenesis that may contribute to functional deficits in memory. Copyright © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Self-assessed auditory symptoms, noise exposure, and measured auditory function among healthy young Swedish men.

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The aim of the study was to estimate the prevalence of the exposure to ototraumatic factors and auditory symptoms, and to analyse the relations between these factors in a group of young healthy men. A total of 839 men, 19-22 years old, were recruited for the study when reporting for primary military service. A questionnaire was distributed and audiometry was performed. The prevalence of tinnitus, sensitivity to noise, and measured hearing impairment in the study group was 23.2%, 15.5%, and 14.5% respectively. Exposure to occupational noise often was reported by 21.4%, and playing loud music often by 16.5%. The young men who had experienced tinnitus after noise exposure had an elevated risk of high frequency hearing impairment, tinnitus, and sensitivity to noise. Those who played loud music had elevated prevalence values of tinnitus but not of hearing impairment. In this young group we observed high prevalence values of ototraumatic factors and auditory symptoms. We also observed significant correlations between tinnitus after noise exposure, self-assessed hearing symptoms, and hearing impairment.
Associations between duration of illicit drug use and health conditions: results from the 2005-2007 national surveys on drug use and health.

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PURPOSE: To estimate and compare prevalence rates of lifetime health conditions by inferred duration of illicit drug use among the general U.S. adult population and to investigate associations between duration of use of each specific illicit drug (marijuana, cocaine, heroin, hallucinogens, or inhalant) and each lifetime health condition after controlling for potential confounding factors. METHODS: Data from respondents aged 35 to 49 (N = 29,195) from the 2005-2007 National Surveys on Drug Use and Health (NSDUH) were analyzed. RESULTS: The prevalence rates of a broad range of health conditions by duration of use of specific illicit drug among persons 35 to 49 years of age in the United States were estimated and compared. After adjustment for potential confounding factors, the results of 20 multivariate logistic regression models indicated positive associations between duration of marijuana use and anxiety, depression, sexually transmitted disease (STD), bronchitis, and lung cancer; between duration of cocaine use and anxiety and pancreatitis; between duration of heroin use and anxiety, hepatitis, and tuberculosis; between duration of hallucinogen use and tinnitus and STD; and between duration of inhalant use and anxiety, depression, HIV/AIDS, STD, tuberculosis, bronchitis, asthma, sinusitis, and tinnitus. CONCLUSIONS: This study provides initial analyses on the relationships between illicit drug use and health conditions based on a large nationally representative sample. These results can help prepare for treating health problems among former and continuing illicit drug users. Published by Elsevier Inc.

Low heritability of tinnitus: results from the second Nord-Trøndelag health study.

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OBJECTIVE: To estimate the heritability of tinnitus. DESIGN: Self-report questionnaire data collected from August 1, 1995, through June 30, 1997, from individuals in the Nord-Trøndelag Hearing Loss Study (an integrated part of the Nord-Trøndelag Health Study) were used. The study also included information on first-degree family relationships, and age-corrected polychoric correlations of relatives’ tinnitus status were calculated. A structural equation model was fit to the data, and the relative contributions of genes and unique environmental effects were estimated. Models that included sex-specific effects were also tested. SETTING: Nord-Trøndelag County, Norway. PATIENTS: A population-based sample of 12 940 spouses, 27 607 parent-offspring, and 11 498 siblings was used. A total of 28 066 respondents were tested twice, yielding a test-retest correlation of 0.65 for the report of tinnitus. MAIN OUTCOME MEASURE: Heritability of tinnitus. RESULTS: Correlations for parent-offspring ranged from 0.01 to 0.07 for the various sex combinations, sibling correlation ranged from 0.06 to 0.14, and the spouse correlation was 0.04. This family correlation pattern implies an upper limit for heritability of 0.11 with no sex differences in the heritability estimates. CONCLUSIONS: This is the first large population-based family study, to our knowledge, to report on the heritability of tinnitus. In contrast to previous speculations in the literature, this low heritability indicates that additive genetic effects explain only a small proportion of the variance of tinnitus in the population.
Salicylate causes a moderate hearing loss and tinnitus in humans at high dose levels. Salicylate induced hearing loss has been attributed to impaired sound amplification by outer hair cells (OHCs) through its direct action on the OHC motility sensor and/or motor. However, there is a disparity of salicylate concentrations between the clinical and animal studies, i.e. extremely high extracellular concentrations of salicylate (from 1 to 10 mM) is required to produce a significant reduction of electromotility in animal studies. Such concentrations are above the clinical/physiological range for humans. Here, we demonstrated that clinical/physiological concentration range of salicylate caused concentration-dependent and reversible reductions in IK,n (KCNQ4) and subsequent depolarization of OHCs. Salicylate reduced the maximal tail current of the activation curve of IK,n without altering the voltage-sensitivity (Vhalf). The salicylate-induced reduction of IK,n was almost completely blocked by linopirdine (0.1 mM) and BaCl2 (10 mM). Consistent with the finding in OHCs, salicylate significantly reduced KCNQ4-mediated current expressed in CHO cells by comparable amplitude to OHCs without significantly shifting Vhalf. Non-stationary fluctuation analysis shows that salicylate significantly reduced the estimated single-channel current amplitude and numbers. Intracellular Ca(2+) elevation resulting from cytoplasmic acidosis also contributes to the current reduction of IK,n (KCNQ4) of OHCs. These results indicate a different model for the salicylate-induced hearing loss through the reduction of KCNQ4 and subsequent depolarization of OHCs, which reduces the driving force for transduction current and electromotility. The major mechanism underlying the reduction of IK,n (KCNQ4) is the direct blocking action of salicylate on KCNQ4.

Sensitization to masked tones following notched-noise correlates with estimates of cochlear function using distortion product otoacoustic emissions.

Zhou X, Henin S, Thompson SE, Long GR, Parra LC.

Neuronal gain adaptation has been proposed as the underlying mechanism leading to the perception of phantom sounds such as Zwicker tones and tinnitus. In this gain-adaptation theory, cochlear compression plays a significant role with weaker compression leading to stronger phantom percepts. The specific aim of this study was to find a link between the strength of neuronal gain adaptation and cochlear compression. Compression was assessed using distortion product otoacoustic emissions (DPOAEs). Gain adaptation is hypothesized to manifest itself in the sensitization observed for the detection of masked tones when preceded by notched noise. Perceptual thresholds for pure tones in notched noise were measured at multiple frequencies following various priming signals. The observed sensitization was larger than expected from the combined effect of the various maskers. However, there was no link between sensitization and compression. Instead, across subjects, stronger sensitization correlated with stronger DPOAEs evoked by low-level primaries. In addition, growth of DPOAEs correlated reliably with perceptual thresholds across frequencies within subjects. Together, the data suggest that short-term dynamic adaptation leading to perceptual sensitization is the result of an active process mediated by the outer hair cells, which are thought to modulate the gain of the cochlear amplifier via efferent feedback.
Non-explosive blast injury of the tympanic membrane in Umuahia, Nigeria.

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BACKGROUND: To examine the clinical features and causes of non-explosive blast injury to the ear, as well as the frequency of the State police involvement. METHOD: Prospective clinical study of consecutive patients with traumatic tympanic membrane perforations resulting from non-explosive blast trauma to the ear without history of previous middle ear disease who attended ENT clinic of Federal Medical Center Umuahia. Clinical features and causes of non-explosive blast injury to ear; healing outcome at 2, 4, 8, and 12 weeks; perforation size versus healing outcome and cause of injury were the main outcomes measured. RESULTS: Five hundred and ninety three new patients with aural disease were analysed. Sixty-one patients, (38 males and 23 females), aged 10-56 years had tympanic membrane perforation from non-explosive blast injury to the ear. The commonest symptoms were hearing loss (64%), tinnitus (61%), and ear ache (57%). The causes of injury were: slap against the ear by State police (31%), spouse (28%), armed bandits (18%), school teachers (8%), parents (5%), and blow against the ear during street fight (10%). Ninety two percent of the perforations healed spontaneously. Healing was associated with significant closure of air bone gap (t = 15.08; p < 0.01). Non-healing of perforation was significantly associated with the large perforations occupying estimated 50% or more of the entire tympanic membrane area (chi2 = 8.67; p = 0.003). CONCLUSION: The ear is very susceptible to injury from non-explosive blast trauma. There was a high spontaneous healing rate of the resulting tympanic membrane perforation, favoring conservative management in most of the case. Non-healing was associated with large-sized perforations. Abusive slap by the State police men was the commonest cause of non-explosive blast injury to the tympanic membrane. Our results are hoped to stimulate a change in the attitude of the culprits and lead to a reduction in the incidence of avoidable TM perforations from slap assaults.

The distressed (Type D) personality is independently associated with tinnitus: a case-control study.

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BACKGROUND: Tinnitus is a common and disturbing condition, reported by 10% to 20% of the general population. OBJECTIVE: The authors sought to determine personality characteristics associated with tinnitus patients versus a control group of ear-nose-throat (ENT) patients without tinnitus. METHOD: Adult chronic tinnitus sufferers (N=265) and ENT patients without tinnitus (N=265) participated in a cross-sectional study. The authors evaluated personality characteristics with tests for distressed personality (Type D), neuroticism, extraversion, and emotional stability. RESULTS: As compared with control subjects, tinnitus patients had statistically significant and clinically relevant higher levels of neuroticism, negative affectivity, and social inhibition, on one hand, and lower levels of extraversion and emotional stability on the other hand. Also, tinnitus patients were more likely to have a type D personality. CONCLUSIONS: Neuroticism, reduced extraversion, and reduced emotional stability were associated with tinnitus, but the level of prediction of the model improved with the addition of type D personality to the single traits. This might indicate that personality characteristics, and type D personality, in particular, are associated with having tinnitus and might contribute to its perceived severity.
The relationship between tinnitus pitch and the edge frequency of the audiogram in individuals with hearing impairment and tonal tinnitus.

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Some theories of mechanisms of tinnitus generation lead to the prediction that the pitch associated with tonal tinnitus should be related to the „edge frequency“ of the audiogram, f(e), the frequency at which hearing loss worsens relatively abruptly. However, previous studies testing this prediction have provided little or no support for it. Here, we reexamined the relationship between tinnitus pitch and f(e), using 11 subjects selected to have mild-to-moderate hearing loss and tonal tinnitus. Subjects were asked to compare the pitch of their tinnitus to that of a sinusoidal tone whose frequency and level were adjusted by the experimenter. Prior to testing in the main experiment, subjects were given specific training to help them to avoid octave errors in their pitch matches. Pitch matches made after this training were generally lower in frequency than matches made before such training, often by one or two octaves. The matches following training were highly reproducible. A clear relationship was found between the values of f(e) and the mean pitch matches following training; the correlation was 0.94. Generally, the pitch matches were close in value to the values of f(e). 2010 Elsevier B.V. All rights reserved.

Neural changes in the auditory cortex of awake guinea pigs after two tinnitus inducers: salicylate and acoustic trauma.

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Tinnitus, also called phantom auditory perception, is a major health problem in western countries. As such, a significant amount of effort has been devoted to understanding its mechanisms, including studies in animals wherein a supposed „tinnitus state“ can be induced. Here, we studied on the same awake animals the effects of a high-dose of salicylate and of an acoustic trauma both at levels known to induce tinnitus. Recordings of cortical activity (local field potentials) from chronically implanted electrodes in the same animals under each condition allowed direct comparison of the effects of salicylate and trauma (noise trauma was carried out several days after full recovery from salicylate administration). Salicylate induced a systematic and reversible increase in amplitude of cortical responses evoked by tone bursts over a wide range of frequencies and intensities. The effects of noise trauma, though much more variable than those of salicylate, resulted in both increases and decreases in the amplitude of cortical responses. These alterations of cortical response amplitudes likely reflect associated hypoacusis and hyperacusis. The effects of salicylate administration and noise trauma on spontaneous activity were also studied. Fourier analysis did not reveal any increase in power within any given frequency band; rather, both treatments induced a decrease of power spectrum over a relatively broad frequency band (approximately 10-30 Hz). Entropy rate of spontaneous activity, a measure of complexity (temporal correlations), was found to decrease after salicylate but not after acoustic trauma. The present data on evoked potentials confirm salicylate effects at the cortical level and partially extend such effects to acoustic trauma. While the present study showed that both salicylate and noise trauma induced some changes of spontaneous activity in auditory cortex, none of these changes are interpretable in terms of potential neural correlate of tinnitus. Copyright 2010 IBRO. Published by Elsevier Ltd. All rights reserved.
Behavioral assessment and identification of a molecular marker in a salicylate-induced tinnitus in rats.

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Tinnitus is a non-observable phantom sensation. As such, it is a difficult condition to investigate and, to date, no effective treatment has been developed. To approach this phantom sensation, we aimed to develop a rat behavioral model of tinnitus using salicylate, an active component of aspirin known to induce tinnitus. We also aimed to establish a molecular marker of tinnitus by assessing the expression of transient receptor potential cation channel superfamily V-1 (TRPV1) in the rat auditory pathway during salicylate-induced tinnitus. Animals were trained to perform an active avoidance task: animals were conditioned by electrical footshock to move to the other side of the conditioning box when hearing a sound. Animals received a single injection of saline or salicylate (400 mg/kg i.p.) and false positive responses were measured 2 h after injection as the number of movements during a silent period. The number of responses in salicylate-treated animals was highest when the conditioned stimulus was 60 dB sound pressure level (SPL) and 16 kHz. This indicates that animals could feel tinnitus 2 h after salicylate injection, equivalent to that induced by 60 dB SPL and 16 kHz. By means of real-time PCR and western blot analysis, TRPV1 expression was significantly upregulated in spiral ganglion cells 2 h after salicylate injection and this upregulation together with the increase in the number of false positive responses was significantly suppressed by capsazepine (10 mg/kg i.p.), a specific antagonist of TRPV1. This suggests that salicylate could induce tinnitus through activation of TRPV1 in the rat auditory pathway.

[The significance of stress: its role in the auditory system and the pathogenesis of tinnitus]
[Article in German]

Mazurek B, Stöver T, Haupt H, Klapp BF, Adli M, Gross J, Szcepek AJ.

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Emotional stress is often associated with auditory phenomena such as hyperacusis, tinnitus, Ménière’s disease and vertigo. Stress develops as a result of a person’s attempts to come to terms with the increased or unexpected demands of his or her environment. Stress serves to protect one from physical danger and to temporarily increase one’s performance in order to increase the probability of survival. Sleep and appetite are particularly reduced, while anxiety increases. The mental changes induced by stress may contribute to the onset or exacerbation of tinnitus. The following links exist between the auditory and stress systems: the limbic system, which regulates instinctive behavior and emotions, is linked to the auditory system via the medial geniculate body (amygdala). The hypothalamus, which is the integrative center of the endocrine and autonomic systems, is linked to the auditory system via the inferior colliculus. The reticular system, which is focused on the behavior pattern of attention and excitement, projects serotonergic fibers to all pathways of the auditory system, ranging from the cochlea to the auditory cortex.
Salicylate-induced degeneration of cochlea spiral ganglion neurons-apoptosis signaling.
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Aspirin, whose active ingredient is sodium salicylate, is the most widely used drug worldwide, but it is not recommended for children because it may cause Reye's syndrome. High doses of salicylate also induce temporary hearing loss and tinnitus; while these disorders are believed to disappear when treatment is discontinued some data suggest that prolonged treatment may be neurotoxic. To investigate its ototoxicity, immature, postnatal day 3 rat cochlear organotypic cultures were treated with salicylate. Salicylate did not damage the sensory hair cells, but instead damaged the spiral ganglion neurons (SGN) and their peripheral fibers in a dose-dependent manner. The cross-sectional area of SGN decreased from 205 mum(2) in controls to 143, 116, and 91 mum(2) in cultures treated with 1, 3, or 5 mM salicylate, respectively. Morphological changes and caspase upregulation were indicative of caspase-mediated apoptosis. A quantitative RT-PCR apoptosis array identified a subset of genes up- or down regulated by salicylate. Eight genes showed a biologically relevant change (P<0.05, >/=2 fold change) after 3 h treatment with salicylate; seven genes (Tp53, Birc3, Tnfrsf5, Casp7, Nfkb1, Fas, Lta, Tnfsf10) were upregulated and one gene (Pycard) was downregulated. After 6 h treatment, only one gene (No13) was upregulated and two genes were downregulated (Cideb and Lhx4) while after 12 h treatment, two genes (Il10, Gadd45a) were upregulated and 4 (Prok2, Card10, Lbr, Dapk1) were downregulated. High doses of salicylate in a physiologically relevant range can induce caspase-mediated cell death in immature SGN; changes in the expression of apoptotic genes particularly among members of the tumor necrosis factor (TNF) family appear to play an important role in the degeneration. Copyright © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Altered GAP Coding and Glycinergic Neurotransmission in the DCN of an Animal Model of Tinnitus: Pathologic Plasticity
ARO-abstract

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Tinnitus affects 15–35% of individuals in the United States and up to 10% of these individuals report severe and disabling symptoms. Sound-exposure animal models of tinnitus can be used to assess functional and neurochemical tinnitus-related plastic changes. The dorsal cochlear nucleus (DCN) displays changes consistent with altered pre- and postsynaptic glycinergic inhibition in animals with behavioral evidence of tinnitus. Tinnitus was induced in adult rats using a unilateral, one-hour, 17 kHz-centered octave-band noise (116 dB SPL) and assessed using a gap-startle protocol. Three months following sound exposure, the rats showed no significant ABR threshold elevation, and a subpopulation of animals displayed impaired gap coding, indicative of tinnitus. There was a significant down-regulation of the α1 glycine receptor (GlyR) subunit protein in fusiform cells located in the middle and high frequency regions of the DCN in rats with behavioral evidence of tinnitus. The anchoring/trafficking protein, gephyrin, displayed tinnitus-related increased protein levels across DCN frequency regions. Consistent with decreased α1 subunit protein levels, strychnine binding showed significant tinnitus-related decreases in the number of GlyR binding sites in the fusiform cell area. Single unit studies found that DCN fusiform cells from sound-exposed rats displayed significantly increased spontaneous activity and altered gap coding, especially near the frequency limits of the units excitatory response area. These findings establish that loud sound-exposure produces tinnitus in an animal model that is associated with significant functional and glycinergic pathologic plasticity in the DCN. Supported by Merck Corporation, American Tinnitus Association and NIH DC008532.
Investigating Inner Ear-Derived Neural Progenitors for Hearing Regeneration
ARO-abstract

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There are two critical unsolved issues in stem cell-based replacement therapy for the inner ear. Firstly, the appropriate donor cell type has not been determined. Secondly, the survival and differentiation of implanted stem cells have not been thoroughly explored. Compared to embryonic stem cell and neural stem cell (NSC) derived from the other tissue, inner ear-derived stem cell might be more ready to adopt an inner ear cell fate. To regenerate degenerated spiral ganglion neurons, we recently identify NSCs from the inner ear of mice. These inner ear-derived NSCs (ieNSCs) could proliferate and differentiate into cells expressing not only universal neuronal protein such as class III beta tubulin and neurofilament 200 but also glutamatergic neuronal proteins. We identified the neurotrophin that could stimulate the survival and glutamatergic differentiation of ieNSCs. In implantation of ieNSCs into the adult mammalian inner ear, we found 10-fold more stem cells survived in the neurotrophin-supplied inner ears. This will significantly enhance inner ear regenerative ability and provide clues for the stem cell-based biological and translational research that would explore strategies for treating hearing loss, tinnitus, balance disorder and other neurodegenerative diseases.

Expression and Regulation of NMDA Receptors at Inner Hair Cell-Auditory Nerve Ribbon Synapses
ARO-abstract

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Sound stimulations induce glutamate release at inner hair cell (IHC) ribbon synapses with the dendrites of primary auditory neurons. While these synapses predominantly use AMPA receptors, they also bear NMDA receptors (NMDARs). NMDARs are tetramers formed by NR1 and NR2A-D subunits. These receptors are calcium-permeable cation channels with a strong voltage-dependent magnesium block. Their activity in the cochlea is only unmasked in pathophysiological conditions (e.g. salicylate-induced tinnitus and in neuronal reconnexions after excitotoxicity).

In this study, we demonstrate the expression in cochlear homogenates of several NR1 splice variants (N1, C1, C2 and C2’) and of NR2B and 2D, not that of NR2A and 2C. When using a biotinylation technique, we found that all the expressed subunits were present at the plasma membrane. We have then studied their up- and down-regulation, phosphorylation and glycosylation under pathophysiological conditions, i.e. sound-induced excitotoxicity and salicylate-induced tinnitus. We have also studied the influence of the activation and blockade of NMDARs by dopamine, which negatively regulates the IHC activity, on these post-translational modifications.

BLEV-1: A Transgenic Mouse Model for BDNF Live Exon Viewing
ARO-abstract

Wibke Singer, Rama Panford-Walsh, Hyun-Soon Geisler, Eleonora Passeri, Marlies Knipper

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In various studies we showed an altered brain-derived neurotrophic factor (BDNF) expression in spiral ganglion neurons in aging animals (Rüttiger et al. Knipper, 2007), after acoustic trauma (Tan et al. Knipper, 2007) and after salicylate application (Panford-Walsh et al. Knipper, 2008; Singer et al. Knipper, 2008). BDNF plays a crucial role for activity-dependent plasticity, alteration of synaptic efficacy and the balance of inhibition and excitation. Deletion of the receptor of BDNF leads to progressive hearing loss (Schimmang et al. Knipper, 2003) after salicylate treatment.
The activity dependent usage of BDNF is due to its characteristic gene structure. The BDNF gene consists of a common protein-encoding exon (IX), which can be spliced to any of the eight non-coding upstream exons (I-VIII), resulting in different BDNF transcripts but only in one protein (Timmusk et al., 1993; Aid et al., 2007). Each of the eight upstream exons has a putative promoter on its 5'-flanking region, the activation of which is controlled by activity-dependent molecular components of calcium-dependent signaling cascades. The different exons are not, however, expressed ubiquitously. In the cochlea only BDNF exon IV, VI and IX are expressed.

To get a better insight into the mechanism of a trauma induced differential usage of BDNF exon IV and VI in the auditory system; we generated a transgenic mouse model, which was designed to label the activity-dependent differential usage of BDNF exon IV and VI in vivo by different fluorescence proteins. Supported by the Tinnitus Research Initiative, the Marie Curie Research Training Network CavNET MRTN-CT-2006-035367, the Deutsche Forschungsgemeinschaft, grant DFG-Kni-316-4-1.

Altered Expression of Synaptophysin and CD45 in the Cochlea and Cochlear Nucleus After Antioxidant Treatment in Acute Acoustic Trauma

ARO-abstract

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Acute acoustic trauma (AAT) can cause hearing loss and tinnitus. Excessive noise exposure promotes reactive oxygen species and reactive nitrogen species formation in the inner ear, which can induce cell death and hearing loss. However, up to date, there is very little information about the mechanisms of noise-induced tinnitus. It is believed that tinnitus is generated in the CNS but triggered by cochlear injury. We have previously demonstrated that an antioxidant treatment (4-hydroxy phenyl N-tert-butylnitrone, N-acetyl-L-cysteine, Acetyl-L-carnitine) could significantly reduce hearing threshold shift, as well as 4-HNE and NT formation in the cochlea. In the present study, we have used an indirect synaptic activity marker, synaptophysin, to examine effects of noise exposure and antioxidant treatment on synapses in the central and peripheral auditory systems 10 days after noise exposure (centered at 4 KHz, 105 dB SPL for 6 hours). Densities of positive stained fusiform cells in the dorsal cochlear nucleus (DCN) and of positive stained efferent nerve fibers at the basal turn of the cochleae were calculated and statistically analyzed. Compared with normal controls, significantly down-regulated synaptophysin expression was found in the fusiform cell layer of the DCN, and in the efferent nerve fibers in the cochleae of noise exposed chinchilla. There were no significant changes of total number of neurons in DCN (stained by anti-NeuN antibody) between groups. In the DCN, cartwheel cells deliver strong inhibition to fusiform cells through the synapses. Loss of inhibitory synapses in the DCN may be involved in noise-induced tinnitus. However, the significance of loss of efferent fibers in the cochlea is unclear. Antioxidant treatment significantly reduced the down-regulation of synaptophysin in those locations, suggesting that the antioxidant treatment may not only treat the noise-induced hearing loss but also noise-induced tinnitus. We also used an inflammation marker, CD45, to study the role of inflammation in AAT. Increased numbers of CD45+cells were found in the stria vascularis of noise exposed chinchilla. Antioxidant treatment reduced the number of CD45+ cells, suggesting that antioxidant treatment can reduce inflammatory responses in the inner ear.

Supported by the Office of Naval Research and INTEGRIS Health
Spontaneous Calcium Signals in the Dorsal Cochlear Nucleus After Noise Exposure in Mice

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A noise-induced increase in the spontaneous firing rate of neurons in the dorsal cochlear nucleus (DCN) has been associated with the development of tinnitus in animals. However, the underlying network activity is unknown. In this study, we used calcium imaging to map the spontaneous activity of populations of neurons from brain slices of the DCN. CBA/CAJ mice were exposed to an 8-16 kHz noise at 110 dB SPL for 2 hours in a paradigm established to produce tinnitus. Two weeks later, auditory brainstem response measurements confirmed a 20-40 dB shift in response thresholds to tone pips between 4 and 48kHz. Oregon-Green BAPTA-1 AM was injected into the DCN after preparing slices, and fluorescence measured at 30-100 frames/second. Spontaneous activity was observed throughout the DCN, and was greatest in the pyramidal cell and superficial deep layers. Spontaneous calcium events exhibit similar amplitudes in both the noise-exposed and control groups. This suggests that the generation of calcium signals in the noise-exposed and control groups is fundamentally similar. Conventional ACSF bathing medium contains a higher concentration of calcium than physiological ACSF, which has been shown to suppress spontaneous activity. When immersed in physiological ACSF (1mm CaCl2), DCN neurons within the molecular and pyramidal cell layers displayed higher synchrony (measured as the analog cross-correlation of the calcium signals) in noise-exposed mice (R=0.3-0.4) when compared to age-matched controls (R=0.1-0.2). In conventional ACSF (2.5mM CaCl2), the correlation amplitude was reduced by a factor of 2, but the difference in synchrony remained. Synchronous signals were consistently interspersed with intervals of asynchronous activity in all conditions. These data suggest noise-exposure may enhance the inherent synchrony of spontaneous activity in the DCN, which may ultimately transmit an abnormal percept of sound to higher centers. Supported by NIDCD grant R01 DC000425.

A Model for Tinnitus Generation Based in the Ventral, Not Dorsal, Cochlear Nucleus

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Many neural representations have been proposed to underlie the tinnitus percept including elevated neural firing rate, abnormal temporal patterns of neural discharge, reorganized tonotopic maps, and increased correlation between neurons. By “increased correlation” we specifically mean that the spontaneous firing patterns of two or more neurons are correlated with one another to an abnormally high degree. Recently, Eggermont and co-workers reported enhanced inter-neuronal correlations within the auditory cortex of animals having a pattern of peripheral damage often associated with tinnitus. But cortex may not be special in showing such enhanced correlations. We suggest that cochlear nucleus neurons directly innervated by the cochlear nerve could show enhanced inter-neuronal correlation following peripheral deafferentation and that the spherical bushy cells of the ventral cochlear nucleus are particularly likely candidates for exhibiting this phenomenon. We will explain how several structural and functional aspects of cochlear-nerve fibers and spherical bushy cells may conspire to increase the degree to which spherical bushy cells are correlated with one another following cochlear hair cell or spiral ganglion loss. We will also discuss how these correlations might help account for various aspects of tinnitus phenomenology including, differences between people in the quality of the tinnitus percept, onset of tinnitus immediately following acoustic over-exposure, and the occurrence of tinnitus in some ears, but not others with seemingly identical damage.
Effects of Inferior Colliculus Ablation on Noise-Induced Hyperactivity in the Dorsal Cochlear Nucleus
ARO-abstract
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Hyperactivity in the central auditory system, manifest as increases in spontaneous activity and/or increases in bursting activity, has been implicated as an important correlate of tinnitus induced by noise and other tinnitus-inducing agents. We have been investigating the influences of descending pathways as potential modulators of noise-induced hyperactivity in the dorsal cochlear nucleus (DCN) of hamsters. In this study we were interested in the potential modulatory influence of descending pathways to the DCN from the auditory midbrain. Hyperactivity was induced in the DCN of hamsters by exposure to intense sound (10 kHz, 115 dB SPL, 4 hrs). Recordings were conducted at tonotopic locations in the DCN where spontaneous activity was clearly elevated relative to control levels (i.e., where rates were above 40 events/s). Following this initial recording, input to the DCN from the contralateral inferior colliculus (IC) and higher levels was removed by ablation. Ablation was accomplished by electrocautery against the caudal wall of the inferior colliculus until the bulk of the IC was removed. Examples have been obtained in which removal of the contralateral IC resulted in an enhancement of the level of hyperactivity in the DCN. In other cases, IC removal produced a transient loss of DCN activity which recovered gradually to pre-ablation levels over a period of 15-20 minutes. These results are still preliminary, but they do suggest that DCN hyperactivity persists and may even be enhanced following IC ablation. This further supports the view that DCN hyperactivity does not follow a top-down explanation, although the descending input to the DCN from the IC or higher order structures may exert an overall inhibitory effect on DCN hyperactivity. (Supported by NIH grant R01 DC009097).

Longitudinal Changes in Gap Detection and Prepulse Inhibition Following Noise Exposure in Adult Mice
ARO-abstract
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Six-month-old mice on a mixed C57Bl6 x 129 background were anesthetized with isoflurane and exposed to unilateral noise (n=9), or sham exposure for controls (n=5), for one hour (16 kHz octave band signal, 116 dB SPL). Gap detection and prepulse inhibition were tested at 60 dB SPL (1,000 Hz bands centered at eight frequency bands) before and at post-exposure time points of 1, 3-4, 7, 14, 21, and 30 days, and monthly thereafter until 7 months post exposure. Auditory brainstem response thresholds were measured before and after the noise exposure, and 7 mo post exposure. Brains were then perfusion fixed, harvested, and frozen for later immunohistochemical analysis of vesicular glutamate transporter distributions that are altered after cochlear damage (Zeng et al., J. Neurosci., 2009). Noise exposed mice displayed changes in gap detection and prepulse inhibition behavior for 24 kHz stimuli consistent with the presence of tinnitus at that frequency. Several time points following noise exposure suggested evidence of hyperacusis (stronger responses to gap detection and prepulse inhibition) which was followed by the development of deficits in gap detection by 6 months post exposure. The temporal development of these changes following noise exposure are discussed in the context of the interactions between aging, noise exposure and the associated neurochemical changes that occur at early stages of auditory processing. Supported by the Tinnitus Research Initiative, NIH P01 DC00078 and NIH R01 DC004825 (SES) NIH R21 DC008357 (JGT)
Differential Effects of Prolonged Sound Exposure on the Enlargement of Auditory Neurons in the Brainstem
ARO-abstract

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In our previous study (Lu et al, 2009) we have showed that neurons at the auditory cortex enlarged their size markedly (~30%) following prolonged sound exposure at moderate levels, suggesting plastic changes as the result of over-activity. If so, similar changes should be observed in the subcortical auditory structures. To test this hypothesis, we measured cyto-histologically two obligatory brainstem auditory stations: inferior colliculus (IC) and cochlear nucleus (CN) the after exposing juvenile rats (4 weeks old, n=5) to a monotone (4 kHz, 65 dB SPL) for 7 days (10 hrs/day). Neuronal profiles (nuclei and perikarya) in the IC (central and external subdivisions) and CN (anterior ventral, dorsal and posterior ventral subdivisions) were digitized and measured on photomicrographs taken from 7 (m-thick histological sections stained with toluidine blue. To facilitate accurate measurement, we used image-analysis software (Image ProPlus) that contained a confocal-like image-merging function to sharpen edges of the nuclei and perikarya. Sound exposure expanded cell volumes (both nuclei and perikarya) at the IC markedly (~65%) compared with control (p<0.0001, Student’s t-test). Such sound-induced changes were however not found in the CN. Neurons in other non-auditory structures (visual cortex and superior colliculus) were also unaffected by the same sound exposure. Results showed that the prolonged sound exposure had produced effects that cannot be explained by a simple mechanism linking over-activity with cell enlargement, but might involve a sensitive or critical period that determines whether or not over-activity can exert effects on cytomorphology. That sound has induced marked changes at the IC and the auditory cortex without affecting the CN also suggested the occurrence of tinnitus in these animals as likely induced by long-term sound exposure during their young age. Further behavioral experiments are necessary to confirm such conjecture.

Keywords: over-activity, neural plasticity, auditory brainstem, inferior colliculus, cochlear nucleus, tinnitus


Sustained, High Dose Treatment with Sodium Salicylate Disrupts the Rat Auditory Brainstem Response
ARO-abstract

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High doses of salicylate (aspirin) are a well known cause of mild-to-moderate hearing loss and tinnitus mainly due to its ototoxic effect on outer hair cells. Hearing loss from high-dose salicylate treatment is considered temporary, but the effects of prolonged, high-dose treatment and potential neural effects are poorly understood. In our study we focused on the effects of a long-term, high-dose administration of salicylate on the central auditory pathway. A daily dose of 200 mg/kg of sodium salicylate was administrated to ten male Sprague-Dawley rats for 15 days. Auditory Brainstem Response (ABR) threshold and distortion product otoacoustic emission (DPOAE) 2f1-f2 were measured for all animals before and after the end of the treatment (3 days, 2 and 4 weeks). The results showed in accordance with the literature a reversible decrease of DPOAEs with a full recovery of DPOAE. In contrast, the ABR showed abnormalities in the waveforms with a moderate to large reduction in amplitude of waves I thru IV. For frequencies below 20 kHz, the amplitude of wave II (i.e., P2-N2) measured at 100 dB SPL was significantly decreased. ABR thresholds were increased at all post-administration times. These findings demonstrate a reversible peripheral effect and a permanent central effect as reflected in ABR waveforms. Research supported in part by Tinnitus Research Initiative and NIH (R01DC009091; R01DC009219).
In Vitro and In Vivo Studies of GABAA Mediated Inhibition in Rat Medial Geniculate Body
ARO-abstract

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Age-related hearing loss is a complex disorder affecting 30% of the US population aged 65 to 74 years, and 50% of the population 75 years of age and older. The present in vivo and in vitro studies examined the nature of GABAA receptors (GABAARs) at the level of the medial geniculate body (MGB). The MGB receives lemniscal and extralemniscal ascending inputs as well as reticular, limbic and descending inputs from auditory and nonauditory cortices. Subcortical temporal coding studies suggest that inhibitory GABA circuits gate input-output functions and are involved in coding temporal features of complex acoustic signals. Preliminary iontophoretic, receptor binding and measures of GABAA subunit protein suggest the presence of one specific GABAA receptor subtype is highly concentrated in MGB. These extrasynaptic α4δ containing GABAARs mediate a tonic current and are thought to function as "spillover receptors" during periods of high neuronal activity. A MGB slice preparation was used to establish the presence of this extrasynaptic subclass of GABAARs. In vitro voltage-clamp studies revealed a tonic chloride current, induced by bath application of GABA (1-10 μM) or the α4δ GABAAR subunit selective compound, gaboxadol (GBX)(0.1-5 μM). This current was revealed by focal application the GABAA antagonist, gabazine (50 μM). In vivo studies, in urethane anesthetized rat MGB, found that iontophoretic application of GBX rapidly shut down tone-evoked firing of most MGB neurons tested. GBX appeared more efficacious than GABA in inhibiting MGB tone-evoked responses. GABAA receptor blockade had limited effects on the shape of rate-level functions but significantly altered response to modulated stimuli. Collectively, these studies begin to characterize the functions of GABAergic projections onto MGB neurons and could provide a basis for development of selective agents which could potentially ameliorate certain kinds of tinnitus or age-related deficits. Supported by NIH DC00151.

Low Level Blast Overpressure Exposures Initiate Brain Microvascular Remodeling and Repair
ARO-abstract

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Blast-induced, traumatic brain injury (BI-TBI) is a common battlefield injury in Iraq and Afghanistan. Symptoms of mild BI-TBI include tinnitus, hearing loss, emergent and delayed post-traumatic balance disorders, and migrainous disorders in the absence of overt histological or radiological evidence of damage. This study examines the effects of low intensity (4-18 psi) blast overpressure (BOP) in Sprague-Dawley rats, delivered as a single Friedlander wave with a pneumatic shock tube Brain tissues were analyzed with quantitative PCR arrays and histological markers of injury at 2, 24 and 72 h after BOP exposure. Behavioral measurements were performed on other animals out to 21 days post-BOP exposure. A battery of rat vascular remodeling mRNAs and interleukins showed BOP related up- or down-regulation (≥1.8-fold) of greater magnitude and/or duration with increasing BOP intensity (ANOVA, p<0.01). This group included mRNAs for angiopoietin 1, inhibitor of DNA binding 1, endothelial differentiation sphingolipid G-protein-coupled receptor 1, endothelial PAS domain protein 1, α-laminin, endothelial cell growth factor 1 (platelet-derived), matrix metalloproteinase 2, Fibronectin 1 and Platelet/ endothelial cell adhesion molecule. Other mRNAs were affected at higher threshold (~15 PSI peak), including mRNAs for vascular endothelial growth factors A and B, tissue inhibitors of metallopeptidase 2 and 3, thrombospondin 4, mitochondrial superoxide dismutase 2 and Bcl2-associated X protein. A late up-regulation (72 hours after blast wave exposure) was also observed for a number of stress genes (e.g., Bax, Nos1, Sod1, Sod2, Hsp family genes, Hmox1 and Hmox2) at the higher exposures, suggesting more severe direct and secondary brain injury at the higher peak intensity exposures. Histological findings from decalcified whole heads were consistent with a primary vascular (venous) mechanism of injury. Brain parenchyma appeared normal. There were microthrombi in small veins and limited areas of protein extravasation and hemorrhage near veins within the subdural and subarachnoid...
spaces, particularly in the velum interpositum. The extravasated protein often contained cellular infiltrate, presumably from the adjacent veins. Within the subarachnoid space, the superficial cortical veins appear to have more injury than veins in the choroidal fissure. Immunohistochemical findings included upregulated angiopeptin 1 staining of superficial vessels and upregulated C-X-C receptor 3 staining throughout telecephalic white matter. These findings are consistent with a tissue injury response to microvascular wounds that increased with peak shock overpressure intensity in mild BI-TBI.

**Neural Mechanisms of Tinnitus**
ARO-abstract

**Jos J. Eggermont**
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Tinnitus resulting from different etiologies has different ignition mechanism, albeit that the way it is represented in cortex is likely the same. Because of the strong neural feedback loops from the cortex to thalamus, midbrain and lower brainstem, the neural mechanisms of long-standing tinnitus may involve the entire auditory system network. In addition the amygdala may be involved and be at the basis for the strong emotional content of certain forms of tinnitus. Animal research and non-invasive studies in humans have suggested that tinnitus is often accompanied by increased spontaneous firing rates and increased neural synchrony. In case noise-induced hearing loss is the etiology there are indications that changes in the auditory cortical frequency place (tonotopic) map may also be present. The underlying mechanisms are likely a (temporary) imbalance in the level of excitation and inhibition cause by the reduction of afferent input or by an increase thereof (potentially in the case of somatic tinnitus).

**Central Tinnitus as Prime Example of Thalamocortical Dysrhythmia**
ARO-abstract

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Tinnitus, and auditory dysfunction of central or peripheral origin, is characterized by the perception of auditory noise, most commonly a whistling or a roaring sound, in the absence of an objective physical sound source. While it is now universally accepted that central tinnitus is a disconnection syndrome the underlying neuronal mechanism is presently unresolved. Indeed, central tinnitus provides a unique opportunity to define the intrinsic neuronal and ionic mechanisms capable of supporting such stable auditory hallucination. A very likely mechanisms relate to recurrent thalamo-cortical resonance known as thalamocortical dysrhythmia. This presentation will address such possibility.

**Excitatory and Inhibitory Synaptogenesis in the Cochlear Nucleus**
ARO-abstract

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Interplay between excitation and inhibition is essential for signal processing in the cochlear nucleus. An imbalance between excitation and inhibition may be involved in disorders such as sensorineural hearing loss or tinnitus and such an imbalance may be even more critical when produced during development. In this regard, developmental studies are essential to understand pathological responses involving excitatory and inhibitory neurotransmission. Vesicular neurotransmitter transporters fill synaptic vesicles with specific neurotransmitters, thus contributing to neurotransmitter phenotype. There are three known vesicular glutamate transporters (VGluT1, 2 and 3). VGluT1 is involved in excitatory neurotransmission in the adult rat cochlear nucleus. The vesicular inhibitory amino acid transporter
(VIAAT) carries both GABA and glycine into synaptic vesicles. Because of the specificity of these two markers for labelling inhibitory and excitatory terminals, respectively, they may be used to study synaptic circuit development. Using specific antibodies, we are investigating the developmental distribution of VIAAT and VGLUT1 in the rat cochlear nucleus by immunohistochemistry. VIAAT and VGLUT1 immunoreactivity are differentially distributed across different subdivisions of the cochlear nucleus during postnatal development. Immunoreactivity patterns undergo quantitative and qualitative changes during development, notably before (P7) and after (P15), after hearing onset. Results indicate that VIAAT immunoreactivity precedes VGLUT1. This may reflect neurotrophic effects mediated by GABA and/or glycine, a delayed auditory nerve arrival compared to interneuron maturation, or both. The correlation between hearing onset and immunoreactivity changes may reflect possible causal effects to be further studied. Supported by: MEC (BFU2006-13974) and JCCM (GCS2006C-15, SAN06-009, PEII0901526233, MOV-2007_IE/05).

Salicylate Induces Spiral Ganglion Neuron Degeneration
ARO-abstract

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High doses of salicylate (aspirin) can cause up to 40-50 dB of hearing loss as well as intense tinnitus. Salicylate treatment known to cause tinnitus in animals raises salicylate concentration in CSF to 1.4 mM. While salicylate-induced hearing loss and tinnitus are thought to be completely reversible, some data suggest that prolonged treatment, might damage the inner ear. To investigate this possibility, we treated cochlear organotypic cultures from postnatal day 3 rats with salicylate doses between 1 and 10 mM for 48 h. Spiral ganglion neurons (SGN) showed obvious salicylate-induced histopathologies characterized by a dose-dependent shrinkage of SGN size; significant size reductions were seen with doses as low as 1 mM. Pathological changes were restricted to SGN since hair cells in the same culture showed no signs of damage even with doses as high as 10 mM. Salicylate-treated SGN showed positive TUNEL staining, an indication of DNA fragmentation in cells undergoing apoptosis. Salicylate treatment also induced caspase-labeling implicating the caspase pathways in SGN cell death. To test the hypothesis that salicylate induces SGN degeneration by enhancing NMDA currents, we blocked NMDA receptors with high concentrations of magnesium. The salicylate-induced decrease in SGN size was only partially blocked by magnesium treatment. These results indicate the high doses of salicylate can induce caspase-mediated SGN degeneration in postnatal cochlear cultures. SGN degeneration appears to be mediated in part by the influx of calcium through NMDA receptor; however, other cell death signaling pathways are likely to be involved.

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Mapping Tinnitus in Auditory Related Brain Regions Across Two Rat Models Using Manganese Enhanced MRI
ARO-abstract

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There are no reliable biomarkers for diagnosis and treatment of tinnitus, although advances in rapid tinnitus screening have recently gained ground. Combining gap inhibition of the acoustic startle reflex (gASR) with the manganese-enhanced MRI (MEMRI) method we contrast brain region activity prior to and following the onset of tinnitus across two different rat models. The gASR was used to determine tinnitus status, while brain regions associated with the perception of tinnitus in awake freely moving subjects was shown using MEMRI. Tinnitus was induced either with repeated doses of salicylate or a single noise exposure. Salicylate induced tinnitus resulted in wide spread changes in brain activity when compared to noise induced tinnitus which showed much more restricted changes in activity.
However, there were regions of overlap suggesting that a fundamental component of tinnitus may be identifiable/common regardless of the manner in which the tinnitus was induced. Therefore, we demonstrate that the combination of gASR and MEMRI provides a non-invasive, sensitive metric for using changes in activity level to identify tinnitus related brain regions specific to the method of tinnitus induction as well as across methods in animal models of tinnitus. Our results provide the foundation for future studies aimed at correlating the severity and longevity of tinnitus with neuronal activity, the role of hearing loss and evaluation of the efficacy of treatment across paradigms.

Sound-Evoked Forward Suppression of Spontaneous Firing in Auditory Neurons May Relate to Residual Inhibition in Tinnitus

ARO-abstract

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Recently, we observed that sounds lasting a few milliseconds can suppress spontaneous firing in inferior colliculus neurons for several hundreds of milliseconds. The aim of this study was to extend this research by determining whether the duration of this suppression depends on sound duration. Extracellular responses of inferior colliculus (IC) neurons exhibiting spontaneous firing were recorded in awake CBA/CaJ mice. Stimuli were presented as pure tones at the characteristic frequency for IC neurons or broadband noise. Duration of the stimuli ranged from 50 ms to 1500 ms, and they were presented once every 30 sec. The vast majority of neurons (93%) showed spontaneous firing ranging from 0.4 to 43 spikes/second (sp/s) with median of 5.2 sp/s. Neurons could be divided into two groups based on their response pattern. First, a large population of neurons (74%) exhibited an onset or/and offset response pattern. A relatively small population of neurons (26%) fired during the entire duration of the stimulus. The vast majority of neurons from both populations (82%) showed sound-evoked suppression of spontaneous firing; however, the suppression duration was remarkably different for these populations. The neurons exhibiting an onset or/and offset response pattern also exhibited a short suppression lasting a few tens of milliseconds right after on-off responses occurred. Neurons that fired during the duration of the sound stimulus also showed suppression of spontaneous firing as long as several seconds. Duration of this suppression increased with an increase in the duration of the stimulus. Hyperexcitability or elevated spontaneous activity in the central auditory system often correlates with the perception of tinnitus in humans; thus we hypothesize that sound-evoked suppression of spontaneous firing may underlie residual inhibition, the phenomenon whereby tinnitus is suppressed by long duration sounds. Supported by NIH R01 DC00537.

Salicylate-Induced Tinnitus: Alterations in Neuronal Activity in the Inferior Colliculus of Tranquilized Mice

ARO-abstract

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Tinnitus, the perception of a phantom sound, affects ~14% of the population. Sodium salicylate (SS), the active component of aspirin, induces transient tinnitus in humans and animals, and is often used to investigate its neural mechanisms. The purpose of this study was to investigate changes in neuronal firing patterns across the tonotopic axis of the central nucleus of the inferior colliculus (ICC), a midbrain auditory region which receives inputs from many other brain regions and is a gateway for processing both spectral and temporal properties of sounds. Extracellular recordings were made from the ICC of tranquilized mice (CBA/CaJ) using vertically oriented 16-channel Michigan probes, which allowed for sampling of multi-unit (MU) activity across the entire tonotopic axis of the ICC. Recordings were made from the same location pre-SS, and 0.5, 1, 2, and 3 h post-SS administration (250 mg/kg IP).
Frequency-response area (FRA) maps were generated from the MU response to brief tones (1-72 kHz; 0-80 dB SPL) from a speaker placed 30° in the contralateral hemifield. FRA maps showed a progressive increase in minimum threshold (MT) following SS, ultimately reaching ~40 dB SPL shift by 3 h post-SS, result consistent with SS-induced outer-hair cell dysfunction. In addition, for many units FRAs underwent significant SS-induced changes presumably due to alterations in the normal balance of excitation and inhibition. Neural correlates of temporal processing were assessed using the gap-in-noise paradigm (1-96 ms in duration) and the minimum gap threshold (MGT). Following SS administration, there was a significant increase in the mean MGT from 2 ms pre-SS to 4 ms at 30 m post-SS (p < 0.001), and 5 ms at the 1, 2 and 3 h post-SS time points (p < 0.001). Finally, spontaneous rates (10 min recording) across the entire population of units decreased following SS. Inter-spike intervals and k'-1, a measure of neural synchrony using the cross-correlations of units across different frequency bands, were also assessed. The significant increase in MGT and the change in FRA shapes of ICC neurons following acute SS intoxication may reflect an alteration in the normal balance of excitation and inhibition known to sculpt many of the response properties of ICC neurons. Supported in part by grants from the NIH (R03DC008685, R01DC009219, R01DC009091)

**Blast and Acoustic Trauma-Induced Tinnitus: Auditory and Non-Auditory Aspects**

ARO-abstract

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Tinnitus has complex etiology, involving both auditory and non-auditory factors. Although efforts have centered around the auditory contribution to tinnitus, less attention has been paid to the non-auditory aspects. In this study, we investigated the auditory and non-auditory attributes of tinnitus following blast and noise exposures. In the first experiment, 9 Long-Evans rats were blasted in a shock tube at 14 psi (194 dB SPL). Behavioral manifestation of tinnitus and hearing loss using startle reflex paradigm and MRI diffusion tensor imaging (DTI) in auditory and non-auditory structures were evaluated following blast exposure. Our results showed that blast exposure induced temporary tinnitus and hearing loss, as well as significant changes in the dorsal cochlear nucleus and the corpus callosum. In the second experiment, we investigated the relationship between tinnitus and non-auditory function such as memory and anxiety. In this study, 14 Long-Evans rats were exposed to a 10 kHz tone at 120 dB SPL for 2-3 hours. Using the same procedures, rats were behaviorally tested for tinnitus and hearing loss. After tinnitus development, they were tested for spatial memory and anxiety using Morris Water Maze (MWM) and Elevated Plus Maze (EPM), respectively. Our results showed that tinnitus positive animals performed better at various stages difference in EPM was found between the two groups. The results point out that enhanced memory function may be necessary to sustain the behavioral manifestation of tinnitus. Taken together, our data supports previous findings that tinnitus is closely related to hearing loss and trauma-induced plastic changes in auditory and non-auditory brain structures. The enhanced memory function in tinnitus positive animals suggests that maintenance of tinnitus may entail increased input from the limbic system, and may not unilaterally impair cognitive and other limbic functioning.
Salicylate-Induced Tinnitus: Alterations in Neuronal Activity in the Auditory Cortex of Anesthetized Rats

ARO-abstract

Daniel Stolzberg, Guang-Di Chen, Richard Salvi

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Neuroplastic alterations and increased synchronization of neuronal discharges in the auditory cortex (AC) and related brain regions may be related to the phantom sensation of sound, tinnitus. Our previous study revealed that a high-dose salicylate injection in rats induced tinnitus-like behavior around 16 kHz and enhanced local field potentials (LFP) in the tinnitus frequency-region (Yang et al., 2007, Hear. Res. 226, 244-253). This experiment was designed to further investigate alterations in neural activity in rat auditory cortex following salicylate injection (300 mg/kg). Spontaneous unit discharges, response maps, and peri-stimulus time histograms of neurons in the AC were assessed at different times before and after the salicylate treatment along with LFPs. Sixteen-channel microelectrodes were used to record AC activity and single microelectrodes were used for recording LFPs from the hippocampus (HC). This report will present the salicylate-related alterations in neuronal discharges and cross correlations between neuronal discharges and LFPs from the AC and the HC. Interestingly, salicylate-treatment caused many neurons to expand and shift their response maps towards the tinnitus region (i.e. high-frequency neuron maps expanded towards lower frequencies and the low-frequency neuron maps expanded towards higher frequencies) leading to concentration of units tuned to where tinnitus-like behavior was observed. Map-expansion appeared to emerge prior to the threshold shift. The mechanisms underlying the salicylate-related re-organization are currently unclear, but may be related to diminished GABAergic-signaling reported by others. This study was supported by grants from NIH (R01DC009091; R01DC009219) and TRI to Salvi.

Salicylate-Induced Modulation of Gene and Protein Expression in Rat Auditory Cortex Correlates with Behavioral Phenotype of Central Tinnitus

ARO-abstract

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Tinnitus, the perception of a phantom auditory sensation, can be highly disturbing causing anxiety, depression, stress, and sleep disturbance. Administering large dose of sodium salicylate is a highly reliable and effective method for inducing temporary tinnitus in humans and animals and this pharmacologic approach has been used extensively to investigate the neural and biological mechanisms that give rise to tinnitus. While the peripheral auditory system may be an important neural generator of tinnitus, central auditory pathways are thought to play a major role, possibly by down regulating centrally-mediated inhibition. Considerable effort has gone into identifying the neural correlates of salicylate-induced tinnitus at multiple sites along the auditory pathway, but few studies have examined the molecular mechanisms that give rise to salicylate-induced tinnitus. We have used a large antibody microarray targeting 725 proteins to screen for significant changes in protein expression occurring in the auditory cortex (AC) of Sprague-Dawley rats with salicylate-induced tinnitus. Salicylate treatment (250 mg/kg, IP) induced significant (p<0.05) protein expression changes of 15-25% in 23 proteins (p<0.05). Expression of 7 proteins decreased compared to saline-treated controls while expression increased in the remaining 16. Subsequent gene expression results with a custom qRT-PCR array yielded results consistent with the proteomic data. Salicylate-induced tinnitus was associated with significant changes in the expression of 3 functional groups AC proteins; those involved with (1) neuronal maturation and differentiation (Inexa, Smn1, Rab6ip2, Hnrnp, Cnp, Myd88, Cttn), (2) cell cycle and (Cdc2, Ccna2, Prmt6, Cdc14a) (3) glucose metabolism (Pdia3, Grb2). Ppp2ca and Ppp2r2c appear in all three classifications. Another, GSK3b, functions both in metabolism and synaptic signaling. Research supported in part by NIH grants R01DC009091 and R01DC009219.
Effects of Age on Pre-Pulse, Variable and Fixed Gap Inhibition of the Acoustic Startle Response Amplitude in HET4 Mice
ARO-abstract
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Age-related hearing loss and auditory processing problems are common conditions. A hearing loss of sufficient magnitude to cause difficulty in understanding conversational speech occurs in close to 50 percent of people 75 and older. The incidence of central auditory processing disorders (CAPD) and tinnitus increase in this population. The mechanisms underlying CAPD and tinnitus are unknown, although loss of synaptic strength from inhibitory amino acid transmitters might be involved. There is a lack of animal models describing changes in auditory processing with age. Here we incorporate a behavioral response measure with the auditory brainstem response in an outbred strain (HET4) of middle-aged (9-16 mon) and geriatric (22-24 mon) mice.

The acoustic startle reflex (ASR) is a sound-induced movement from the animal that can be measured and used as an unbiased metric. This startle response can be inhibited by a pre-pulse or a gap in an ongoing noise. We now use this metric to characterize the ASR amplitude I/O functions in quiet and in nine different background noise conditions that vary by center frequency and level. Pre-pulse inhibition (PPI) and gap inhibition (GI) using the same nine noise conditions are also compared in the middle-aged vs. old mice.

The preliminary findings show that the middle-aged mice, compared to the old, show lower ASR thresholds and larger startle amplitudes in quiet. In quiet, startle amplitudes reach a maximum around 100dB SPL. In the presence of background noise, startle thresholds are elevated but maximum startle amplitudes are increased compared to the quiet condition. In the older mice, startle amplitudes are roughly correlated with ABR thresholds. In preliminary results, geriatric mice with low ABR thresholds, compared to the middle-aged mice with comparable thresholds, tend to have less inhibition from a preceding gap, indicating a possible presence of tinnitus or CAPD. We will present data from variable-width gap assays to further quantify effects of CAPD and/or tinnitus in geriatric mice.

Supported by NIH Grant P30DC05188 and P01AG025164.

Tinnitus: From Rats to Humans - Validation of the Acoustic Gap Startle Paradigm
ARO-abstract
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Background: The acoustic startle reflex is a primitive reflex produced by a sudden and unexpected loud sound. It can be inhibited by inserting a weak sound (a prepulse sound) a few milliseconds before the startle sound. A modified version of prepulse modulation was recently developed to model tinnitus in animals, by using a silent gap rather than a prepulse. In normal rats, the gap decreases the startle reflex, similar to a prepulse. In contrast, in rats with salicylate- or noise- induced tinnitus, there is no inhibition of the startle reflex, presumably because the gap is filled with the tinnitus sound. The lack of inhibition is specific to background noise of frequency close to tinnitus frequency, and is therefore used to objectively demonstrate the presence of tinnitus. We propose that, transposed to human subjects, the startle reflex may provide an effective paradigm to measure tinnitus objectively.

Objectives: Our objectives were to 1) validate the efficiency of the gap to inhibit the acoustic startle reflex, using high- and low- frequency background noise, in normal-hearing human participants, and 2) examine how it compares with inhibition induced by a prepulse.

Methods: Young participants without hearing loss or tinnitus were recruited. STARTLE-only trials consisted of a 50ms white noise 105dB(A) burst. GAP trials consisted of a 50ms silent gap inserted into either high- or low- frequency background noise set at 65dB(A), followed by a startle sound. PREPULSE trials consisted of either 50ms bursts of low- or high- frequency noise at 65dB(A) presented in quiet, followed by a startle noise. Electromyographic responses of eyeblink amplitude to the three types of
stimuli were measured. Results: Preliminary results show that prepulse sounds were very effective in inhibiting the acoustic startle reflex, by as much as 2-3 fold, a finding consistent with previous studies in human subjects. The gap, however, was not as effective in inhibiting the reflex, especially in the high frequency range. Conclusion: Although the gap-in-background noise paradigm may not be as effective as the prepulse paradigm in inhibiting the acoustic startle reflex in normal-hearing subjects, it is a promising approach to objectively measure tinnitus in humans.

**Gap Induced Reduction of the Acoustic Startle Response as a Behavioural Test for Noise Induced Tinnitus in Guinea Pigs**

ARO-abstract

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Gap induced reduction of the acoustic startle response has now been used reliably to assess tinnitus in rats (Turner et al., Behav. Neurosci, 2006). This test, which is based on the assumption that if a background acoustic signal was qualitatively similar to the rat's tinnitus, poorer detection of a silent gap in the background would result. Here, we used a short gap (20ms) in a continuous background noise to assess the usefulness of this technique in guinea pigs. Guinea pigs were exposed to a unilateral, 97dB SPL RMS, 1/4 octave band noise with a center frequency of 7kHz for two hours. In some animals this noise exposure was repeated 2 weeks after the first exposure. A control group of animals received a sham noise exposure (normal background sound level inside the sound booth). Auditory brainstem responses (ABRs) were recorded before and after noise exposures to quantify the immediate effect of the exposure, which was a 30-90dB shift with a maximum at 8 or 9kHz. ABRs were recorded weekly after the exposure to document the recovery from exposure, which in most animals was complete one week after the exposure. After noise exposure the gap induced reduction of the startle response was diminished for the 8-, 12- or 16 kHz noise bands, which is interpreted as a behavioural correlate of tinnitus at those frequencies. The same animals were also tested for a prepulse-induced reduction of the startle response, which is assumed to test the hearing threshold, however in our data set this did not correlate with the results of ABR recordings.

Supported by the Tinnitus Research Initiative and NIH P01 DC00078

**Too Much of a Good Thing: Long-Term Treatment with Salicylate May Strengthen Outer Hair Cell Function But Damage Auditory Sensitivity**

ARO-abstract

**Guang-Di Chen, Mohammad Habiby Kermany, Alessandra D'Elia, Massimo Ralli, Chiemi Tanaka, Eric Bielefeld, Dalian Ding, Richard Salvi, Donald Henderson**

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Aspirin has been extensively used in clinical settings. Its side effects on auditory function, including hearing loss and tinnitus, seem only a temporary event. A recent promising finding is that a chronic treatment with a high-dose salicylate (the active ingredient of aspirin) enhances expression of the outer hair cell (OHC) motor protein (prestin), resulting in a strengthened OHC electromotility and distortion product otoacoustic emissions (DPOAEs). We have used salicylate in our lab for two different purposes: (1) to strengthen prestin expression for restoration of cochlear function; and (2) to induce tinnitus in an animal model. Unexpectedly, a permanent loss of cochlear sensitivity was often observed after the chronic salicylate treatment. In the current experiment, rats of different strains and ages were injected with salicylate at a dose of 200 mg/kg/day for 5 days per week for 3 weeks or at higher dose levels (250-350 mg/kg/day) for 4 days per week for 2 weeks. The salicylate treatments induced a permanent reduction of auditory brainstem response (ABR), cochlear compound action potential (CAP), and
cochlear microphonics (CM), and also occasional OHC loss, while the DPOAEs were enhanced or remained at the pre-exposure levels. Interestingly, with an increased interval between injections from 1/day to once or twice per week, a similar amount of salicylate treatment as above enhanced DPOAEs, but did not show a salicylate-related ototoxicity. The mechanisms underlying the permanent salicylate ototoxicity are discussed. Hearing restoration may be achieved by using an optimized salicylate treatment paradigm.

**III Diagnostics**

**Experience with a medicolegal decision-making system for occupational hearing loss-related tinnitus.**


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Owing to an increasing number of requests for compensation, a medicolegal decision-making system for tinnitus related to noise-induced hearing loss (NIHL) has been elaborated at the Federal Belgian Institute of Occupational Diseases. Experience with 113 patients, all of them claiming compensation for NIHL and tinnitus, is now available. The patients underwent an exhaustive audiological investigation, and their professional career and noise exposure were carefully and objectively documented. We reviewed the group of 35 “accepted” cases (i.e., with chronic tinnitus recognized as related to NIHL and financially compensated as an occupational disease) and analyzed the medicolegal arguments for acceptance or rejection. In these patients, tinnitus was mostly bilateral, was perceived on average at a frequency of 4 KHz and with a supraliminal intensity of 7.2 dB, and lasted on average for 7.3 years. To gain better insight into the relationship between cochlear damage and chronic tinnitus, we compared our group to a control group of 35 patients with similar hearing thresholds at 3 and 4 KHz but free of tinnitus. The main difference is a significantly steeper slope of the audiometric curve between 2 and 3 KHz in the tinnitus group. Furthermore, a notch in the distortion product-gram is noticed in 60% of the ears affected by tinnitus versus 9% of the ears in the control group. This abrupt discontinuity in the activity along the tonotopic axis of the auditory system—the main characteristic of NIHL—could be a factor eliciting tinnitus, as a correspondence between the audiometric notch and tinnitus frequency appears to exist.

**Neurootological differentiations in endogenous tinnitus.**


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Vertigo and tinnitus are very frequent complaints. Often, we find multisensory syndromes combined with tinnitus, hearing impairment, vertigo, and nausea. From more than 10,000 cases, we evaluated 757 randomly selected neurootological patients suffering from endogenous tinnitus. First, we classified the 10,000 patients into those suffering from the basic tetrad of tinnitus forms: bruits, endogenous (maskable) tinnitus, exogenous (nonmaskable) tinnitus, and other syndromes such as the slow brainstem syndrome. Then, of all the endogenous tinnitus patients, we randomly selected our study sample (n = 757), and those patients underwent a complex neurosensory investigation, including neurootological history; classic audiometry; acoustic brainstem-evoked potentials; acoustic cortically evoked potentials; visually evoked potentials; electroneystagmography of spontaneous, caloric, rotatory, and optokinetic nystagmus; and craniocorpography with several vestibulospinal tests. For this study, we primarily examined the historical findings. The statistical results demonstrate that tinnitus is interconnected to a multifactorial disease background with a broad spectrum of individual complaints. Finally, the topodiagstics of the functional neurootometric analysis shows that this type of endogenous tinnitus constitutes decidedly more central than peripheral statoacoustic pathology.
The value of transcranial cerebral sonography in diagnosing neurootological disorders.

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Transcranial cerebral sonography (TCCS) is a noninvasive technique that allows the clinician to detect abnormal intracranial-inner-ear fluid interactions in terms of nanoliter tympanic membrane displacements. The displacements recorded in TCCS are evoked either by the acoustic stapedius reflex or spontaneous movements generated by intracranial cardiovascular or by respiratory pressure waves transmitted through the inner ear to the stapes and thence to the tympanic membrane. Analysis of the amplitude and direction of these displacements has enabled neurosurgeons and neurologists to estimate cerebrospinal fluid pressures in patients evaluated by TCCS. This procedure allows for applications in neurootology, particularly in those patients who present with symptoms of pulsating tinnitus, dizziness and imbalance, or hearing loss. This study describes the application of TCCS tests in a series of patients whose diagnoses included perilymphatic fistula and a variety of neurological conditions such as idiopathic intracranial hypertension, type I Arnold-Chiari malformation, sigmoid sinus thrombosis, hydrocephalus, and cerebrovascular malformations. We conclude that both raised intracranial pressure and abnormal intracranial pressure waves are associated with common neurootological symptoms, including tinnitus, dizziness, and hearing dysfunction. Furthermore, TCCS is a valuable addition to neurootologists' test batteries.

Quantitative electroencephalography for tinnitus--a means for data collection, analysis, and translation.

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Quantitative electroencephalography (QEEG) is the technique whereby brain electrical activity in individuals is recorded as they sit quietly with their eyes closed. The electrical activity is quantified with a variety of statistical measures to characterize the huge variation in combinations of emissions from the brain. Neuroscience research has demonstrated that such resting brain activity measures may be consistently altered in conditions such as depression or dementia. A wide variety of ongoing efforts are attempting to find characterizations that reliably denote other neurological conditions. In research on tinnitus, a variety of groups have been working to characterize QEEG changes related to the presence of the abnormal sensation of sound and to the emotional distress associated with it. QEEG changes related to the tinnitus percept are in the gamma electroencephalography (EEG) band recorded from temporal lobes. Clinical depression has a reliable marker in the depression of posterior cerebral alpha EEG frequency band activity, and this same activity is found in patients with tinnitus of the severe disabling type. In the past, QEEG has suffered from inconsistent recording methods, closed data sets, and noncompatible analytical techniques. Now in the modern era, when reliable data sets are shared and hardware and software are less expensive, regular use of QEEG will be clinically important. Those prepared to make the minor investment in equipment and training will reap the benefit of objective measures of brain activity. Knowing patterns of QEEG activity related to tinnitus and its associated depression will help clinicians better manage these patients.
**Impact of tinnitus on quality of life, loudness and pitch match, and high-frequency audiometry.**

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Our objective was to compare quality of life, high-frequency audiometry, and loudness-pitch match in individuals with tinnitus with and without hearing loss. We divided 52 individuals into two groups: one with hearing impairment (HI; n = 24) and the other with no hearing loss (NL; n = 28). All participants underwent loudness-pitch match and high-frequency audiometry and responded to the Tinnitus Handicap Inventory (THI) and World Health Organization Quality of Life (WHOQOL) questionnaires. On high-frequency audiometry, older individuals required 77.15% more intensity than did young individuals. On the THI questionnaire, individuals in the NL group exhibited mild handicap, whereas those in the HI group exhibited moderate handicap. On the WHOQOL questionnaires, the HI group demonstrated greater impairment on the physical and psychological domains than did the NL group. Individuals with HI experienced greater discomfort with tinnitus. On high-frequency audiometry, individuals with tinnitus and HI exhibited higher thresholds, with complete hearing loss at some frequencies. The WHOQOL and THI questionnaires revealed that individuals with HI experienced a poorer quality of life than did those with normal hearing.

**Blunt and blast head trauma: different entities.**

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Mild traumatic brain injury (mTBI) caused by blast-related and blunt head trauma is frequently encountered in clinical practice. Understanding the nuances between these two distinct types of injury leads to a more focused approach by clinicians to develop better treatment strategies for patients. In this study, we evaluated two separate cohorts of mTBI patients to ascertain whether any difference exists in vestibular-ocular reflex (VOR) testing (n = 55 enrolled patients: 34 blunt, 21 blast) and vestibular-spinal reflex (VSR) testing (n = 72 enrolled patients: 33 blunt, 39 blast). The VOR group displayed a preponderance of patients with blunt mTBI, demonstrating normal to high-frequency phase lag on rotational chair testing, whereas patients experiencing mTBI from blast-related causes revealed a trend toward low-frequency phase lag on evaluation. The VSR cohort showed that patients with posttraumatic migraine-associated dizziness tended to test higher on posturography. However, an indepth look at the total patient population in this second cohort reveals that a higher percentage of blast-exposed patients exhibited a significantly increased latency on motor control testing as compared to patients with blunt head injury (p < .02). These experiments identify a distinct difference between blunt-injury and blast-injury mTBI patients and provide evidence that treatment strategies should be individualized on the basis of each mechanism of injury.

**Systematic Screening for Nonspecific Autoantibodies in Idiopathic Sensorineural Hearing Loss: No Association With Steroid Response.**
Otol Neurotol. 2010 Apr 15. [Epub ahead of print]

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Objective: An autoimmune pathogenesis has been suggested for idiopathic sensorineural hearing loss (iSHL). Specific tests have been developed to detect inner ear autoantibodies and have been shown to
correlate with treatment outcome. However, the disease is rare, and specific tests are not easily available. We aimed to analyze the correlation between positive systemic autoimmune test results and steroid treatment outcome in patients with iSHL. Study design: Prospective, single-center, open trial. Setting: All patients younger than 60 years seen in the ENT department from 1999 to 2007 and fulfilling the criteria for iSHL were tested for systemic autoimmunity. Patients: Patients were classified into 2 groups, according to the presence or absence of autoimmunity. Intervention: Clinical evaluation and audiologic tests. Main outcome measures: The outcomes of steroid treatment were compared between these 2 groups. Results: Forty-nine patients were included; the mean age at iSHL onset was 36.1 years. Hearing loss was often bilateral (89.8%). Tinnitus and vertigo were present in 75.5% and 51%, respectively. On audiograms, disease severity was correlated with disease duration. Nine patients (18.4%) had positive autoimmune tests: anti-neutrophil cytoplasmic antibody (n = 1), antinuclear antibody (n = 3), rheumatoid factor (n = 3), and antiphospholipid (n = 2). Twenty-five courses of oral steroids were evaluated after 1 month: 52% of cases experienced some improvement. There were no differences in outcome associated with autoimmunity status (p = 0.85). Conclusion: The results of this study suggest that positive autoimmune tests in patients with iSHL are not predictive of improvement after a 1-month steroid course. Therefore, systematic screening does not seem to be useful, and specific inner ear autoantibody tests need to be developed.

**CT imaging of superior semicircular canal dehiscence: added value of reformatted images.**
Acta Otolaryngol. 2010 Mar 8. [Epub ahead of print]

Ceylan N, Bayraktaroglu S, Alper H, Savaş R, Bilgen C, Kirazli T, Güzelmansur I, Ertürk SM.

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Abstract
Conclusion: Superior semicircular canal dehiscence (SSCD) syndrome may present with various symptoms. CT scans previously interpreted as normal may show SSCD, especially if special reconstructions tailored for superior canal evaluation are added. Objectives: The purpose of this study was to investigate prevalence of SSCD, its length and its correlation with symptoms in patients who had previously undergone temporal bone CT examination that was reported normal and to demonstrate the importance of reformatted images in the diagnosis of SSCD. Methods: We retrospectively reviewed 108 patients who had undergone temporal bone CT examination for various symptoms and were reported as normal. High-resolution temporal bone CT imaging was performed with 1 mm slice thickness in the transverse plane. Each of the superior semicircular canals was evaluated in the plane of Pöschl and Stenver reformatted images together with axial images. Results: Ninety-three patients were included in the study. Nineteen patients with semicircular canal dehiscence were detected. The mean age of the study group was 45 years. Radiologic evidence of SSCD occurred in 23 of 186 temporal bones with a radiologic prevalence of 12%. The most common symptoms in dehiscent patients were vertigo, hearing loss and tinnitus. Defect lengths varied between 1 mm and 6.5 mm.

**Osteoid Osteoma Invading the Posterior Labyrinth of the Petrous Bone.**

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SUMMARY: We report a painless osteoid osteoma of the inner ear in an elderly woman presenting with hearing loss, tinnitus, and vertigo. CT showed a heterogeneous mass containing calcifications involving the posterior labyrinth, which heterogeneously enhanced on postcontrast MR images. Osteoid osteoma should be included in the differential diagnosis of an osteolytic petrous bone lesion with central calcification and enhancement.
Tinnitus and psychological comorbidities.

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Comorbidity is the presence of one or more disorders in addition to the main disorder. Comorbidities negatively influence the development of the main disease. For patients with tinnitus a comorbidity is an additional component complicating the habituation of ear noise and patients with decompensated tinnitus often have psychological comorbidities, e.g. affective, somatoform or anxiety disorders. At the time of first presentation and also during further follow-up, it is essential to pay particular attention to the presence of potential comorbid mental disorders. This is of special importance for patients with decompensated ear noise (severity grades 3 and 4). For ENT specialists it is important that the mental discomfort of patients must be taken seriously and should be identified through a targeted diagnosis. Effective treatment of the co-symptoms using cognitive behavior therapy (CBT) in conjunction with medication often reduces the severity of tinnitus perception and discomfort.

Meningioma as the cause of ear problems

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A 45-year-old woman with long-term unilateral ear problems, hearing loss, vertigo and tinnitus was diagnosed with a meningioma in the middle ear. Magnetic resonance imagining (MRI) revealed that the meningioma penetrated the petrous bone into the middle ear. The meningioma was removed to avoid further hearing loss. Patients with long-term unilateral ear problems that are resistant to conventional therapy should be referred to computed tomography, MRI and explorative tympanotomy. Surgery is indicated if progressions in neurological deficits are seen, but surgery may cause serious neurological deficits

The relationship between tinnitus pitch and the edge frequency of the audiogram in individuals with hearing impairment and tonal tinnitus.

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Some theories of mechanisms of tinnitus generation lead to the prediction that the pitch associated with tonal tinnitus should be related to the „edge frequency“ of the audiogram, f(e), the frequency at which hearing loss worsens relatively abruptly. However, previous studies testing this prediction have provided little or no support for it. Here, we reexamined the relationship between tinnitus pitch and f(e), using 11 subjects selected to have mild-to-moderate hearing loss and tonal tinnitus. Subjects were asked to compare the pitch of their tinnitus to that of a sinusoidal tone whose frequency and level were adjusted by the experimenter. Prior to testing in the main experiment, subjects were given specific training to help them to avoid octave errors in their pitch matches. Pitch matches made after this training were generally lower in frequency than matches made before such training, often by one or two octaves. The matches following training were highly reproducible. A clear relationship was found between the values of f(e) and the mean pitch matches following training; the correlation was 0.94. Generally, the pitch matches were close in value to the values of f(e). 2010 Elsevier B.V. All rights reserved.
Clinical spectrum of patients with erosion of the inner ear by jugular bulb abnormalities.

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OBJECTIVES/HYPOTHESIS: Anatomic variants of the jugular bulb (JB) are common; however, abnormalities such as large high riding JB and JB diverticulum (JBD) are uncommon. Rarely, the abnormal JB may erode into the inner ear. The goal of our study is to report a large series of patients with symptomatic JB erosion into the inner ear. STUDY DESIGN: Retrospective review in an academic medical center. METHODS: Eleven patients with JB abnormality eroding into the inner ear were identified on computed tomography (CT) scan of the temporal bone. RESULTS: Age at presentation was from 5 years to 82 years with six males and five females. The large JB or JBD eroded into the vestibular aqueduct (n = 9) or the posterior semicircular canal (n = 4). The official radiology report usually identified the JB abnormality; however, erosion into these structures by the JB was not mentioned in all but one case. All patients were symptomatic with five having conductive hearing loss (CHL) and three complaining of pulsatile tinnitus. Those with pulsatile tinnitus and four of five with CHL had erosion into the vestibular aqueduct. Vestibular evoked myogenic potential (VEMP) findings in three of six patients were consistent with dehiscence of the inner ear. CONCLUSIONS: High riding large JB or JBD can erode into the inner ear and may be associated with CHL and/or pulsatile tinnitus. CT scan is diagnostic and should be examined specifically for these lesions. As patients with pulsatile tinnitus may initially undergo a magnetic resonance imaging scan, identification of JB abnormality should prompt CT scan or VEMP testing to evaluate for inner ear erosion.

Vestibular schwannoma: when to look for it?

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OBJECTIVES: (1) To compare audiometric parameters in patients with vestibular schwannoma and in those with asymmetric hearing loss from other causes; and (2) to assess proposed screening criteria by comparing published protocols. METHODS: Audiometric data from 199 vestibular schwannoma patients and 225 non-tumour patients were compared. Eight screening protocols were tested on these 424 patients. RESULTS: Vestibular schwannoma and non-tumour patients with little or no hearing loss in the unaffected ear were inseparable; however, vestibular schwannoma patients with hearing loss in the unaffected ear had greater audiometric asymmetry, compared with non-tumour patients with the same pattern of hearing loss. The sensitivity of screening protocols varied from 73 to 100 per cent; parallelism was observed between sensitivity and screening rate. CONCLUSION: As regards vestibular schwannoma screening protocols, the best compromise between sensitivity and screening rate was offered by a criterion comprising either: (1) > or =20 dB asymmetry at two neighbouring frequencies, or unilateral tinnitus, or (2) > or =15 dB asymmetry at two frequencies between 2 and 8 kHz.

Quantitative analysis of cochlear active mechanisms in tinnitus subjects with normal hearing sensitivity: multiparametric recording of evoked otoacoustic emissions and contralateral suppression.

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OBJECTIVE: Aim of this study was to investigate the possible role played by outer hair cells and cochlear efferent system functionality when tinnitus develops in normal hearing ears.
A multiparametric approach was used, entailing recording and analysis of a set of otoacoustic emissions (OAEs): distortion product (DPOAEs), transient evoked (TEOAEs) and efferent-mediated TEOAE suppression in the presence of contralateral acoustic stimulation (CAS). METHODS: Fifty-four subjects with normal hearing sensitivity participated in the study. Twenty-three suffered from chronic subjective tinnitus whereas thirty-one did not have tinnitus and acted as control subjects. DPOAEs were measured with eliciting tones of frequency ratio 1.22 and intensity 65 and 55dB SPL in the frequency range 0.5-8kHz. TEOAEs were recorded with the ‘linear’ protocol using clicks at 60dB peak SPL both in the absence and in the presence of CAS at two different intensities. DPOAE amplitude, TEOAE amplitude, and TEOAE suppression were analysed as relevant parameters. RESULTS: Significantly reduced DPOAE amplitude in the frequency range 1.5-8kHz, lower TEOAE amplitude, and slightly decreased TEOAE suppression were measured in tinnitus subjects compared to non-tinnitus controls. In particular, 74% of tinnitus subjects exhibited abnormal DPOAEs, 13% had abnormal TEOAEs, whereas abnormal TEOAE suppression was found in 9% of patients. CONCLUSION: Overall, the present work revealed the presence of abnormal OAEs, in particular at higher frequencies, in tinnitus subjects with normal hearing sensitivity. A minor (i.e., sub-clinical) outer hair cell dysfunction, particularly in high-frequency cochlear regions, might thus be assumed in normal hearing tinnitus subjects. In order to better put in light the possible role played by outer hair cells in low-frequency cochlear regions, or by the cochlear efferent system, additional analyses would be needed. Copyright (c) 2009 Elsevier Ireland Ltd All rights reserved

A compartment-based approach for the imaging evaluation of tinnitus.

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Tinnitus affects 10% of the US general population and is a common indication for imaging studies. We describe a sequential compartment-based diagnostic approach, which simplifies the interpretation of imaging studies in patients with tinnitus. The choice of the initial imaging technique depends on the type of tinnitus, associated symptoms, and examination findings. Familiarity with the pathophysiologic mechanisms of tinnitus and the imaging findings is a prerequisite for a tailored diagnostic approach by the radiologist

[Aberrant internal carotid artery as a cause of pulsatile tinnitus: a difficult diagnosis in MRI?]
[Article in German]

Soyka MB, Schuknecht B, Huber AM.

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We present the case of a 43-year-old patient with sensorineural hearing loss and the finding of an aberrant internal carotid artery in the left tympanic cavity that was causing pulsatile tinnitus. The aberrant vessel was initially invisible on magnetic resonance imaging (MRI) and was confirmed by high-resolution computed tomography and MR angiography (MRA). Recognition of an aberrant course of an internal carotid artery often requires a combination of MRI and MRA to establish the diagnosis and rule out other differential diagnoses.
Auditory Peripheral Dysfunction in Tinnitus Subjects with Clinically Normal Audiograms

ARO-abstract

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The occurrence of tinnitus in people with clinically normal audiograms raises an important unanswered question: Is peripheral auditory dysfunction necessary for the development of tinnitus? We examined peripheral auditory function in 35 ears of 22 men (30-49 yrs), 10 of whom had tinnitus. All subjects had pure-tone thresholds ≤20 dB HL for all standard audiometric frequencies from 0.125-8 kHz. Measurements in each subject included some or all of the following: pure-tone thresholds from 9–16 kHz, distortion-product otoacoustic emissions (DPOAE: L1, L2=63, 60 dB SPL, f2/f1=1.2, f2=0.5–8 kHz, 14-28 pts/oct), DPOAE with and without 60 dB SPL contralateral broadband noise (L1, L2=55, 40 dB SPL, f2/f1=1.2, f2=1–8 kHz, 28 pts/oct), loudness discomfort levels (LDL), and stapedial reflex strength (ear canal pressure change to contralateral noise at 80 dB SPL). Measures were compared between tinnitus and non-tinnitus groups comprising subjects matched pair-wise in age and poorest threshold at or below 8 kHz. 

1) Thresholds for both groups averaged 2-9 dB at and below 8 kHz, but indicated hearing loss above 8 kHz. Thresholds were subtly (although not significantly) greater in the tinnitus group by approx. 3 dB. 2) DPOAE magnitudes for f2=2-4 kHz were significantly lower in tinnitus subjects. 3) The average reduction in DPOAE produced by contralateral noise was similar for the two groups. 4) LDL was not correlated with DPOAE magnitude (f2=2-4 kHz). 5) Stapedial reflex strength did not differ between the two groups. The data are consistent with diminished outer hair cell function and perhaps subtly greater deafferentation in the tinnitus subjects. These abnormalities may be causally related to tinnitus and/or correlate with additional pathology (e.g., loss of high-threshold afferents), which plays a causative role.

Funded by the Tinnitus Research Consortium

Tinnitus Spectrum and Its Real-Time Visualization Based on a 134 Band Cochlear Model

ARO-abstract

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The existing method for matching tinnitus relies on the paradigm for listening single pure tone or band pass filtered noise. There are many types of tinnitus spectrum in accordance with hearing loss regions; 1) single pure tone, 2) multiple pure tones (harmonic or non-harmonic complex tone), 3) single filtered noise, 4) multiple filtered noise, and 5) the combination of 1) ~ 4). In this respect, a new method has been designed to achieve accurate performance for finding various types of tinnitus spectrum. This study introduces two inventions; 1) tinnitus taxonomy based on 10 types of tinnitus spectrum and 2) a method for visualization of tinnitus spectrum using a 3D cochlear model with 134 band (1/24 Oct) frequency resolution.

The Relation Between the Tinnitus Spectrum and the Tone Audiogram

ARO-abstract

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The tinnitus spectrum is a representation of the frequency content of subjective tinnitus.

The subjects’ tinnitus ear or ears were presented with a number of tones of varying frequency, and the subjects were asked to rate the degree to which the tone is present in his tinnitus between 0 to 100. This results in a tinnitus spectrum, that displays the “likeliness” vs. frequency. We studied the correspondence
between the tinnitus spectrum and the tone audiogram, recorded of 81 subjects.

The subjects were assigned to one of six groups based on their hearing loss. Patients in groups 1 through 4 had hearing thresholds of 20dB or better up to 500Hz, 1kHz, 2kHz and 4kHz, respectively. Subjects in group 5 had no hearing loss, and group 6 contained the subjects that did not qualify for groups 1 through 5. For each group the average tinnitus spectrum was determined. The average tinnitus spectrum increased with the frequency for groups 1-4. For group 4, the spectrum also increased rapidly but only from 3kHz and up. The group without hearing loss showed an increase of the likeliness from 1kHz up.

One hypothesis relates tinnitus to neuronal de-afferentiation, arising from peripheral hearing loss. This hypothesis predicts that the pitch content of a tinnitus percept is related to the shape of the tone audiogram. The presented data generally match this hypothesis. However, the de-afferentiation hypothesis does not account for the origin of the tinnitus in normal-hearing subjects. An increase in synchronicity across neuronal networks has also been proposed as a cause for tinnitus. Neural synchronicity (phase-locking) primarily occurs in response to low-frequency stimuli (upper limit 2.5kHz). Synchronicity across high-frequency neurons may be particularly unusual in healthy subjects. Hence, it is conceivable that it easily leads to an abnormal percept, i.e. high-frequency tinnitus in normal hearing individuals.

IV Imaging

Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. BMC Neurosci. 2010 Mar 24;11(1):40. [Epub ahead of print]

Moazami-Goudarzi M, Michels L, Weisz N, Jeanmonod D.

BACKGROUND: The physiopathological mechanism underlying the tinnitus phenomenon is still the subject of an ongoing debate. Since oscillatory EEG activity is increasingly recognized as a fundamental hallmark of cortical integrative functions, this study investigates deviations from the norm of different resting EEG parameters in patients suffering from chronic tinnitus. RESULTS: Spectral parameters of resting EEG of male tinnitus patients (n=8, mean age 54 years) were compared to those of age-matched healthy males (n=15, mean age 58.8 years). On average, the patient group exhibited higher spectral power over the frequency range of 2-100 Hz. Using LORETA source analysis, the generators of delta, theta, alpha and beta power increases were localized dominantly to left auditory (Brodmann Areas (BA) 41,42, 22), temporo-parietal, insular posterior, cingulate anterior and parahippocampal cortical areas. CONCLUSIONS: Tinnitus patients show a deviation from the norm of different resting EEG parameters, characterized by an overproduction of resting state delta, theta and beta brain activities, providing further support for the microphysiological and magnetoencephalographic evidence pointing to a thalamocortical dysrhythmic process at the source of tinnitus. These results also provide further confirmation that reciprocal involvements of both auditory and associative/paralimbic areas are essential in the generation of tinnitus.


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Amplitude and phase of steady-state signals recorded in response to amplitude-modulated (AM) sine tones vary over time, suggesting that the steady-state response (SSR) reflects not only stimulus input but also its interaction with other input streams or internally generated signals. Alterations of the interaction between simultaneous SSRs associated with tinnitus were studied by recording the magnetic
field evoked by AM-tones with one of three carrier and one of three modulation frequencies. Single AM-tones were presented in single presentation mode and superpositions of three AM-tones differing in carrier and modulation frequency in multiple presentation mode. Modulation frequency-specific SSR components were recovered by bandpass filtering. Compared with single mode, in multiple mode SSR amplitude was reduced in healthy controls, but increased in tinnitus patients. Thus, while in controls multiple response components seem to reciprocally inhibit one another, in tinnitus reciprocal facilitation seems to predominate. Reciprocal inhibition was unrelated to the phase coherence among SSR components, but was correlated with the frequency of phase slips, indicating that the lateral interaction among SSR components acts in a quasi-paroxysmal manner and manifests itself in terms of a random train of phase reset events. Phase slips were more frequent in patients than controls both in single and multiple mode. Together, these findings indicate that lateral or surround inhibition of single units in auditory cortex is reduced and suggest that in-field inhibition is increased in tinnitus. (c) 2010 IBRO. Published by Elsevier Ltd. All rights reserved

Functional and structural aspects of tinnitus-related enhancement and suppression of auditory cortex activity.

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The steady-state auditory evoked magnetic field was recorded in tinnitus patients and controls, both either musicians or non-musicians, all of them with high-frequency hearing loss. Stimuli were AM-tones with two modulation frequencies and three carrier frequencies matching the „audiometric edge“, i.e. the frequency above which hearing loss increases more rapidly, the tinnitus frequency or the frequency 1 1/2 octaves above the audiometric edge in controls, and a frequency 1 1/2 octaves below the audiometric edge. Stimuli equated in carrier frequency, but differing in modulation frequency, were simultaneously presented to the two ears. The modulation frequency-specific components of the dual steady-state response were recovered by bandpass filtering. In both hemispheres, the source amplitude of the response was larger for contralateral than ipsilateral input. In non-musicians with tinnitus, this laterality effect was enhanced in the hemisphere contralateral and reduced in the hemisphere ipsilateral to the tinnitus ear, especially for the tinnitus frequency. The hemisphere-by-input laterality dominance effect was smaller in musicians than in non-musicians. In both patient groups, source amplitude change over time, i.e. amplitude slope, was increasing with tonal frequency for contralateral input and decreasing for ipsilateral input. However, slope was smaller for musicians than non-musicians. In patients, source amplitude was negatively correlated with the MRI-determined volume of the medial partition of Heschl’s gyrus. Tinnitus patients show an altered excitatory-inhibitory balance reflecting the downregulation of inhibition and resulting in a steeper dominance hierarchy among simultaneous processes in auditory cortex. Direction and extent of this alteration are modulated by musicality and auditory cortex volume. 2010 Elsevier Inc. All rights reserved.

Functional brain abnormalities localized in 55 chronic tinnitus patients: fusion of SPECT coincidence imaging and MRI.


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Tinnitus is often defined as the perception of sounds or noise in the absence of any external auditory stimuli. The pathophysiology of subjective idiopathic tinnitus remains unclear. The aim of this study was
to investigate the functional brain activities and possible involved cerebral areas in subjective idiopathic tinnitus patients by means of single photon emission computerized tomography (SPECT) coincidence imaging, which was fused with magnetic resonance imaging (MRI). In this cross-sectional study, 56 patients (1 subject excluded) with subjective tinnitus and 8 healthy controls were enrolled. After intravenous injection of 5 mCi F18-FDG (fluorodeoxyglucose), all subjects underwent a brain SPECT coincidence scan, which was then superimposed on their MRIs. In the eight regions of interest (middle temporal, inferotemporal, medial temporal, lateral temporal, temporoparietal, frontal, frontoparietal, and parietal areas), the more pronounced values were represented in medial temporal, inferotemporal, and temporoparietal areas, which showed more important proportion of associative auditory cortices in functional attributions of tinnitus than primary auditory cortex. Brain coincidence SPECT scan, when fused on MRI is a valuable technique in the assessment of patients with tinnitus and could show the significant role of different regions of central nervous system in functional attributions of tinnitus.

Cortical activation during a pitch discrimination task in tinnitus patients and controls--an fMRI study.

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Chronic subjective tinnitus has been associated with aberrant activation of cortical areas involved in the perception of auditory information. This leads to the hypothesis that neural correlates of altered auditory perception may be found in tinnitus patients using functional magnetic resonance imaging. To study brain activation patterns due to acoustic stimulation in a pitch discrimination task, 6 tinnitus patients and 6 age-matched controls were investigated. Tones were presented binaurally at 5 beeps/s with three different frequencies in a block design. Using Statistical Parametrical Mapping, we found activation of secondary auditory areas in both groups. Furthermore, controls showed activation of the right-hemispheric anterior insula, whereas the middle frontal gyrus, putamen and left-hemispheric insula were activated in tinnitus patients. In the between-group analysis, activation of the caudate nucleus, superior frontal gyrus (Brodmann area 8) and cingular cortex was more pronounced in patients than in controls suggesting the perception of auditory inputs in a more emotional context in our patient group compared to controls. 2009 S. Karger AG, Basel

Real-time fMRI feedback training may improve chronic tinnitus.

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OBJECTIVES: Tinnitus consists of a more or less constant aversive tone or noise and is associated with excess auditory activation. Transient distortion of this activation (repetitive transcranial magnetic stimulation, rTMS) may improve tinnitus. Recently proposed operant training in real-time functional magnetic resonance imaging (rtfMRI) neurofeedback allows voluntary modification of specific circumscribed neuronal activations. Combining these observations, we investigated whether patients suffering from tinnitus can (1) learn to voluntarily reduce activation of the auditory system by rtfMRI neurofeedback and whether (2) successful learning improves tinnitus symptoms. METHODS: Six participants with chronic tinnitus were included. First, location of the individual auditory cortex was determined in a standard fMRI auditory block-design localizer. Then, participants were trained to voluntarily reduce the auditory activation (rtfMRI) with visual biofeedback of the current auditory activation. RESULTS: Auditory activation significantly decreased after rtfMRI neurofeedback. This reduced the subjective tinnitus in two of six participants. CONCLUSION: These preliminary results
suggest that tinnitus patients learn to voluntarily reduce spatially specific auditory activations by rtfMRI neurofeedback and that this may reduce tinnitus symptoms. Optimized training protocols (frequency, duration, etc.) may further improve the results.

**Somatosensory Modulation of Tinnitus, an FMRI Study**

**ARO-abstract**

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Jaw protrusion may lead to a change of tinnitus. To identify the neural mechanisms that are responsible for this somatic modulation, we measured the fMRI response to jaw protrusion. Thirteen patients with tinnitus and 20 healthy controls were included in an fMRI experiment. All patients were able to modulate their tinnitus by performing jaw protrusion. Experiments were performed on a 3T Philips scanner, using sparse sampling (TR=10s). Experimental conditions consisted of (1) bilateral broadband noise, (2) jaw protrusion, (3) the combination of both and (4) a baseline condition. A region of interest analysis was performed to quantify responses to the experimental stimuli. A group analysis of the response to sound showed activity in the auditory pathway, consisting of the cochlear nucleus (CN), the inferior colliculus (IC), the medial geniculate body, and the primary and secondary auditory cortex. Jaw protrusion activated the following structures: the cerebellum, the ventrolateral nucleus of the thalamus, the putamen, the motor cortex and the somatosensory cortex. In addition, the auditory pathway showed significant responses to jaw protrusion. In contrast, the somatosensory cortex only showed a response to jaw protrusion and not to sound stimuli. A difference between subject groups was found in the CN and the IC, where patients showed a larger response to protrusion than controls. These data show that the brainstem auditory nuclei play a role in the somatic modulation of tinnitus.

**Auditory Evoked Potentials in People with Tinnitus: A Relationship to Sound-Level Tolerance?**

**ARO-abstract**

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A recent fMRI study of tinnitus and non-tinnitus subjects showed that (1) sound-evoked activation of auditory midbrain, thalamus, and primary cortex increases with decreasing sound-level tolerance (ST) gauged by loudness discomfort level and a questionnaire and (2) elevated activation in primary cortex is also associated with tinnitus. We measured auditory evoked potentials (AEPs) and assessed ST in threshold- age- and sex-matched tinnitus and non-tinnitus subjects to determine whether the synchronously active neurons producing AEPs contribute to the elevated activation seen with fMRI. AEPs were recorded between vertex, F3, F4 and either the left (binaural stim.) or the stimulated (monaural) ear in 6 men with tinnitus (age 43±2) and 6 without (age 43±1). Mean threshold for the tinnitus and non-tinnitus groups differed on average by 2 dB and by no more than 6 dB at any half-octave interval from 0.125 to 14 kHz. Mean amplitude of auditory brainstem response (ABR) wave I did not differ significantly between the tinnitus and non-tinnitus groups at any level and showed no correlation with ST (monaural 11/s clicks; 30, 50, 70 dB HL). However, mean amplitude for tinnitus subjects was smaller than for non-tinnitus subjects at all sound levels and the difference increased with level. This trend raises the possibility of diminished auditory nerve activity in the tinnitus subjects relative to the non-tinnitus subjects despite a close matching of thresholds between groups. Neither ABR wave V nor cortically-generated N100/P200 differed in amplitude between tinnitus and non-tinnitus subjects or correlated in amplitude with ST (binaural 3/s clicks; 50, 70 dB HL). These preliminary results suggest that neuronal populations generating the highly temporally synchronized activity underlying wave V and N100/P200 do not contribute to elevations in fMRI activation associated with abnormal sound-level tolerance and tinnitus. American Tinnitus Association, Tinnitus Research Initiative.
Sudden hearing loss: a ten-year outpatient experience.

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The aim of this study was to determine the effects of various treatment modalities employed for patients with sudden sensorineural hearing loss (SHL). We retrospectively evaluated the records of patients treated in the sudden hearing loss section of the Otolaryngology Department at Clinic Hospital, School of Medicine, University of São Paulo, Brazil, between 1996 and 2006. Our study included patients with SHL of sudden onset (occurring over a 72-hour period) at equal to or greater than 30 dB at three consecutive frequencies. We divided patients into five groups by profile and treated them with dextran, dexamethasone, acyclovir, nicotinic acid, and papaverine hydrochloride (with or without vitamin A). We performed audiometry at baseline and on days 30, 90, 120, and 180 of treatment. We determined outcome as the difference between day-0 and day-180 pure-tone averages (PTAs). Among the 139 patients evaluated, baseline PTA was similar in all groups. We observed significant improvements in PTAs after 180 days of treatment and noted a significant linear correlation between time from SHL onset to initial visit and recovery. However, no significant difference was evident among the treatment groups. In the treatment of SHL, dextran provided no more benefit than did dexamethasone or acyclovir. Earlier initiation of treatment improves the prognosis for patients with SHL.

Carbamazepine responsive typewriter tinnitus from basilar invagination.

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Comment in:

Basilar invagination due to a congenital skeletal disorder kinked the brainstem at the ponto-medullary junction causing both auditory nerves to make an acute turn at the porus acusticus. The associated bilateral asynchronous clicking tinnitus responded to carbamazepine.

Bojungikgitang and banhabaekchulchonmatang in adult patients with tinnitus, a randomized, double-blind, three-arm, placebo-controlled trial - study protocol.
Trials. 2010 Mar 28;11(1):34. [Epub ahead of print]

Kim NK, Lee DH, Lee JH, Oh YL, Yoon IH, Seo ES, Lee CH.

Background: Tinnitus is the perception of hearing a sound for which there is no external acoustic source. It is often associated with sudden, temporary hearing loss and has a clear impact on a patient's quality of life. Despite numerous trials, there are no treatments that can be considered well established in terms of providing replicable long-term tinnitus reduction. Complementary and alternative medical approaches have been employed to relieve symptoms of tinnitus. Bojungikgitang and banhabaekchulchonmatang are among the most strongly preferred and widely used herbal medicines for tinnitus in Korea, as they cause very few serious adverse effects. We aim to establish basic clinical efficacy and safety data for bojungikgitang and banhabaekchulchonmatang, which are approved as herbal medications by the Korea Food and Drug Administration in adult patients with tinnitus. Methods: This study was a randomised, double-blind, placebo-controlled trial with three parallel arms (bojungikgitang, banhabaekchulchonmatang, and a placebo). Participants included in the study met the following criteria: typical conditions of intermittent or continuous tinnitus, for more than three months, with involuntary
Participants received bojungikgitang, banhabaekchulchonmatang, or a placebo-drug for eight weeks. The total duration of each arm was eleven weeks. Each participant was examined for signs and symptoms of tinnitus before and after taking medication. Post-treatment follow-up was performed two weeks after the final administration of medication. Discussion: This trial provided evidence for the efficacy and safety of bojungikgitang and banhabaekchulchonmatang in adult patients with tinnitus. The primary outcome measure was the Tinnitus Handicap Inventory, an assessment used to identify difficulties that may be experienced due to tinnitus. The secondary measures were included an Acoustic Examination and the Visual Analogue Scale. We employed the Euro-Qol 5-Dimension and the Health Utilities Index Mark 3, a health-related quality of life questionnaire. Safety was assessed by complete blood cell count, erythrocyte sedimentation rate, blood chemistry, urine analysis, PA chest film, brain computed tomography, otologic examination, and vital signs. Trial registration: Current Controlled Trials ISRCTN23691284

**Acute idiopathic sensorineural hearing impairment at frequency exceeding 8 kHz.**
Acta Otolaryngol. 2010 Mar 18. [Epub ahead of print]

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Abstract Conclusions. Acute idiopathic sensorineural hearing impairment at a frequency exceeding 8 kHz (high-frequency range) was recognized in patients suffering from acute tinnitus without hearing loss. The cases in this study may contribute to clarifying the pathogenesis of tinnitus without hearing loss and evaluating its response to steroid therapy. Objectives. The aim of this study was to demonstrate the existence of acute idiopathic sensorineural hearing impairment only in the high-frequency range and to investigate its relation to tinnitus without hearing loss. Methods. Five patients aged 29 years or younger who consulted a hospital within a few days after the onset of unilateral tinnitus without hearing loss were studied. We conducted audiometry involving the high-frequency range on first medical examination and on improvement in tinnitus, and investigated the association between the hearing findings in the high-frequency range and a tinnitus prognosis. Results. All five patients showed abnormalities in the threshold in the high-frequency range on the affected side. In the three cases given prednisolone, tinnitus and the threshold abnormalities were reduced within 20 days. In contrast, tinnitus and the threshold abnormalities showed little change in two patients who were not treated.

**Too much of a good thing: Long-term treatment with salicylate strengthens outer hair cell function but impairs auditory neural activity.**
Hear Res. 2010 Mar 6. [Epub ahead of print]

**Chen GD, Kermany MH, D’Elia A, Ralli M, Tanaka C, Bielefeld EC, Ding D, Henderson D, Salvi R.**
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Aspirin has been extensively used in clinical settings. Its side effects on auditory function, including hearing loss and tinnitus, are considered as temporary. A recent promising finding is that chronic treatment with high-dose salicylate (the active ingredient of aspirin) for several weeks enhances expression of the outer hair cell (OHC) motor protein (prestin), resulting in strengthened OHC electromotility and enhanced distortion product otoacoustic emissions (DPOAE). To follow up on these observations, we carried out two studies, one planned study of age-related hearing loss restoration and a second unrelated study of salicylate-induced tinnitus. Rats of different strains and ages were injected with salicylate at a dose of 200mg/kg/day for 5days per week for 3weeks or at higher dose levels (250-350mg/kg/day) for 4days per week for 2weeks. Unexpectedly, while an enhanced or sustained DPOAE was seen, permanent reductions in the amplitude of the cochlear compound action potential (CAP) and the auditory brainstem response (ABR) were often observed after the chronic salicylate treatment. The mechanisms underlying these unexpected, permanent salicylate-induced reductions in neural activity are discussed. Copyright © 2010 Elsevier B.V. All rights reserved.
Exploring the reasons why melatonin can improve tinnitus.

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Melatonin has been proposed as a treatment for tinnitus, especially on the basis of its favourable effects on sleep and its vasoactive and antioxidant properties. However, to our knowledge no attempts of interpretation have been advanced through a detailed analysis of the various specific properties of melatonin possibly cooperating in a coincidental way to relieve tinnitus: among these, its modulatory effect on central nervous system resulting in a protective mechanism against an exaggerated sympathetic drive; its capacity to induce a more steady hemodynamic condition, through a multifactorial and multi-organ activity, resulting in a more regular labyrinthine perfusion; a possible action on the skeletal muscle tending to a reduction of the muscular tone, which could relieve tinnitus of muscular origin deriving from tensor tympani tonic contractions; its possible reported antidepressive effect, which could indirectly act on tinnitus; a direct regulation of inner ear immunity as proposed in literature when melatonin was reported to be present in the inner ear. All these observations seem to indicate melatonin as a tool deserving a greater attention than other antioxidants in the attempt of relieving tinnitus, justifying its application from a more precise rationale based on a series of physio-pathological aspects. Copyright © 2010 Elsevier Ltd. All rights reserved.

The effects of the Chinese herbal medicine EMF01 on salicylate-induced tinnitus in rats.


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AIM OF THE STUDY: Traditional Chinese medicine (TCM) has been reported to successfully alleviate tinnitus, although well-controlled studies have not been conducted. In this study, we attempted to test a TCM, Er Ming Fang (EMF01) containing Rehmannia glutinosa, Cornus officinalis, Salvia mittiorrhiza, Pueraria, Schisandra chinensis, Poria cocos and Platycodon grandiflorum, on salicylate-induced tinnitus in rats, using a conditioned lick suppression paradigm. MATERIALS AND METHODS: A pilot study examined the effect of 8.75 g/kg and 17.5 g/kg EMF01 (delivered by oral gavage for 20 days) and showed a slight decrease in the suppression ratio (SR) in the 8.75 g/kg group. In order to confirm the possible effect of EMF01 on tinnitus at 8.75 g/kg, a further study was carried out with a larger sample size. RESULTS: While there were statistically significant differences between the treatment groups, post hoc tests revealed that EMF01 did not have any significant effect on salicylate-induced tinnitus. CONCLUSIONS: While this study does not support the efficacy of EMF01 in the treatment of salicylate-induced tinnitus, further studies should be conducted to determine if it alleviates tinnitus associated with acoustic trauma. Copyright (c) 2010 Elsevier Ireland Ltd. All rights reserved.

Protective effect of Korean red ginseng extract on cisplatin ototoxicity in HEI-OC1 auditory cells.

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Ginseng extract is known to have many beneficial effects, including the reversal of pathological and physiological changes induced by ischemia, stress, and aging. Cisplatin, an effective antineoplastic drug, can cause irreversible sensorineural hearing loss and serious tinnitus in humans; thus cisplatin-induced
ototoxicity is a useful experimental model for ototoxicity. This study investigated the protective effects of Korean red ginseng extract on cisplatin-induced ototoxicity in auditory cells. Pretreatment with 2.5 mg/mL of ginseng extract prior to application of 20 microM of cisplatin significantly increased cell viability after 48 h of incubation in auditory cells. Pretreatment with ginseng extract significantly attenuated the cisplatin-induced increase in reactive oxygen species (ROS). Ginseng extract also inhibited the expression of caspase-3 and poly-ADP-ribose polymerase related to cisplatin-induced apoptosis because a major mechanism of cisplatin-induced toxicity involves ROS production. Thus, Korean red ginseng extract can play both an anti-apoptotic and anti-oxidative role on cisplatin-induced ototoxicity in an auditory cell line. Copyright (c) 2009 John Wiley & Sons, Ltd.

Sustained delivery of lidocaine into the cochlea using poly lactic/glycolic acid microparticles.

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OBJECTIVES/HYPOTHESIS: Lidocaine is a local anesthetic that is known to suppress tinnitus via systemic or local application; however, this effect has only limited duration. The current study aimed to establish a method for the sustained delivery of lidocaine into the cochlea using poly lactic/glycolic acid (PLGA) microparticles. STUDY DESIGN: Experimental study. METHODS: Lidocaine-loaded PLGA microparticles were produced and their in vitro-release profiles were examined. The lidocaine concentrations in the perilymph were measured at different time points following the application of the lidocaine-loaded PLGA microparticles to the round-window membranes of guinea pigs. The possible adverse effects of the local application of lidocaine-loaded PLGA microparticles were also examined. RESULTS: The in vitro analyses revealed that the microparticles were capable of the sustained delivery of lidocaine. The in vivo experiments demonstrated the sustained delivery of lidocaine into the cochlear fluid, and the maintenance of high lidocaine concentrations in the perilymph for up to 3 days after application. Nystagmus and inflammation in the middle ear mucosa were not detected after the local application of lidocaine-loaded PLGA microparticles, although temporary hearing loss was observed. CONCLUSIONS: Lidocaine-loaded PLGA microparticles were shown to be capable of the sustained delivery of lidocaine into the cochlea, suggesting that they could be used for the attenuation of peripheral tinnitus.

Pharmacological approaches to the treatment of tinnitus.

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Tinnitus is the conscious perception of a phantom sound in the absence of an external source. For 1 in 100 of the general population, the condition severely affects quality of life. In spite of the fact that the market for a drug indicated for tinnitus relief is huge, there are still no FDA-approved drugs, and the quest for a tinnitus-targeted compound faces important challenges. A wide variety of drugs have been used off-label to treat tinnitus sufferers, with limited but significant effects in subsets of patients. If the compounds being developed at present by the pharmaceutical industry finally reach the market, they will establish a turning point in the treatment of this pathology. 2009 Elsevier Ltd. All rights reserved.
Effects of selective serotonin reuptake inhibitor on treating tinnitus in patients stratified for presence of depression or anxiety.

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We evaluated the effects of a selective serotonin reuptake inhibitor, paroxetine, on treating tinnitus. Tinnitus patients stratified for the presence of depression and anxiety were studied retrospectively. Fifty-six patients were observed for more than 6 months. They were initially treated with paroxetine only at a dose of 10 mg/day for 2-4 weeks; thereafter, the dose was increased to 20 mg/day. Tinnitus distress was evaluated with the Tinnitus Handicap Inventory (THI) and with visual analog scales (VASs) for tinnitus loudness and annoyance. Depression and anxiety were measured with the Self-Rating Depression Scale (SDS) and the trait section of the State-Trait Anxiety Inventory (STAI). The patients were grouped according to their SDS and STAI scores, and each variable was compared at baseline and the 6-month follow-up. Changes among these variables were also examined to determine whether reduced tinnitus distress was related to the improvement of depression or anxiety. Patients with both depression and anxiety showed better results (decrease in THI, VASs, SDS and STAI scores) than patients with anxiety alone, or patients without depression and anxiety. In patients with depression and anxiety, changes in tinnitus variables and changes in depression and anxiety scores were strongly correlated. In other patients, however, changes in tinnitus variables and changes in depression and anxiety scores were not correlated. These results suggest that paroxetine is effective in treating distressed tinnitus patients with depression and anxiety by reducing their tinnitus severity as well as their depression and anxiety. 2009 S. Karger AG, Basel

Paroxysmal staccato tinnitus: a carbamazepine responsive hyperactivity dysfunction symptom of the eighth cranial nerve.

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Comment in:

Hyperactive disorders related to neurovascular compression have been described for several cranial nerves of which trigeminal neuralgia and hemifacial spasm are the best known. The present report on four patients, in conjunction with previous reports, suggests that paroxysmal staccato tinnitus might be considered an auditory hyperactivity disorder of the eighth cranial nerve. The present patients reported attacks, usually lasting 10-20 s, of loud monaural tinnitus with a staccato character (eg, clattering or sounding like a machine gun). The attacks occurred very frequently, sometimes every minute. The attacks were spontaneous but they were also provoked by certain head positions or by exposure to loud sounds. Most of the patients did not reveal any significant eighth cranial nerve sensory loss and thus it is probably not advisable to rely on any specific test result for this diagnosis. Instead, it is suggested that a diagnosis of paroxysmal staccato tinnitus can be based on the history as the symptoms are both stereotypic and very specific. Furthermore, low doses of carbamazepine, although not effective for the general population of tinnitus patients, relieved the symptoms.
Role of GABAergic Activity in Auditory Cortex Gain Control
ARO-abstract

Wei Sun¹, Jianzhong Lu¹, Anchun Deng¹, Edward Lobarias¹, Ron Goodey², Richard Salvi¹

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High doses of salicylate, which cause peripheral hearing loss, can enhance sound-evoked response in the central auditory system (CAS). This enhancement phenomenon suggests that the CAS increases the central gain to compensate the reduced peripheral input. Abnormal increases in central gain may contribute to hyperacusis and tinnitus. To explore the neural mechanisms underlying central gain changes, we examined the effects of GABA receptor agonists and antagonists on AC neural responses. Bicuculline, a GABA-A receptor antagonist, significantly enhanced the firing rate of neurons in AC. In contrast, muscimol, a GABA-A receptor agonist and S-baclofen and R-baclofen, GABA-B agonists, strongly suppressed the firing rate or sound-evoked local field potential. Consistent with previous results, salicylate treatment (systemic injection or local application on the AC) caused a significant increase in sound-evoked AC neural activity and also significantly enhanced the amplitude of the startle reflex, a behavioral manifestation of increased gain. S-baclofen or r-baclofen, GABA-B receptor agonists, reduced the salicylate-induced enhancement of AC firing rate. Similarly, vigabatrin, an anti-seizure drug that increases GABA concentration in the brain, also reduced the salicylate-induced AC response enhancement. Consistent with the central gain hypothesis, vigabatrin and baclofen also reduced the exaggerated startle reflex response induced by salicylate. Our results suggest that salicylate reduces GABA inhibition in the CAS leading to enhancement of the AC response. Increasing GABA-mediated inhibition with baclofen or vigabatrin reduces the central gain and reverses the exaggerated neural and behavioral responses evoked by high dose of salicylate (Supported by RNID, AFAR and NIH).

Characterization of Tinnitus Treatment Drugs in Pentylenetetrazole-Induced Activity Using an in Vitro Model of Auditory Cortex Networks
ARO-abstract

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Tinnitus or “ringing in the ears” affects approximately 30 million people in the USA alone, with 10 million being highly debilitated by the malady. In this study, we have used an in vitro model to test the efficacy of drugs that attempt to treat tinnitus. Dissociated neurons from auditory cortex of mouse embryos were grown on photoetched microelectrode arrays (MEA) with 64 transparent indium-tin oxide electrodes. The proconvulsant drug pentylenetetrazole (PTZ) was applied on spontaneously active auditory cortex networks (ACNs). Following this, Gabapentin, Linopirdine or L-Carnitine was administered at various concentrations to determine if the activity could be reduced to the pre-PTZ level. Results indicated that a concentration of 1.0 mM PTZ significantly increased neuronal activity, presumably mimicking tinnitus. The selective Ca2+ channel blocker Gabapentin, the potassium channel blocker Linopirdine, and the antioxidant L-Carnitine, reduced the activity in ACNs to or below their pre-PTZ condition. The potency of the drugs was Linopirdine > Gabapentin > L-Carnitine at concentration ranges comparable to clinical levels. This in vitro system is a unique platform for screening drugs to study their efficacy in controlling the induced increase in neuronal firing that may mimic tinnitus-like neural activity in humans.

Baclofen and the Role of GABA Inhibition on Salicylate and Noise Induced Tinnitus
ARO-abstract

Edward Lobarias¹, Ronald Goodey²,³, Richard Salvi¹, Wei Sun¹

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Some forms of tinnitus are believed to arise from abnormal central activity following peripheral ear injury. In the present study, we used Gap Prepulse Inhibition of the Acoustic Startle (GPIAS) in rats to evaluate...
the hypothesis that GABA mediated inhibition could play an important role in modulating either transient or persistent tinnitus. In untreated rats, brief silent gaps presented before a loud startled stimulus significantly suppress startle responses. When animals were treated with high doses of salicylate (250 mg/kg) or exposed to intense narrow band (123 dB SPL, 16 kHz, 100 hz BW) unilateral noise, GPIAS was significantly reduced at 16-20 kHz, suggesting the presence of tinnitus in this frequency region. After rats showed evidence of tinnitus following high doses of salicylate, treatment with the baclofen-S enantiomer caused a dose-dependent decrease in the post-salicylate exaggerated startle response and a partial reversal of gap prepulse inhibition in roughly half the animals tested. In contrast the baclofen-R enantiomer which is stereospecifically active on GABA-B receptors failed to suppress the exaggerated startle response and had little effect on the reduced gap prepulse inhibition.

Two weeks after unilateral noise trauma (16 kHz NBN, 123 dB SPL, 1 h) a subset of rats showed impaired GPIAS 12-24 kHz consistent with the presence of tinnitus. When rats were treated with baclofen-S there was significant reversal of impaired GPIAS 12-16 kHz but 20 kHz remained abnormal. These results suggest that baclofen-S partially reduced the tinnitus percept. In contrast, baclofen-R was ineffective at reducing the presence of tinnitus at all frequencies tested.

Supported by TRI and NIH (R01DC009091; R01DC009219)

VI Auditive Stimulation

Recent experience with the neuromonics tinnitus treatment.

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This study examines the outcomes of patients undergoing the Neuromonics tinnitus treatment protocol at a single, tertiary referral center over a 2-year period. A retrospective review of patient records was performed with the objective of collecting demographic and audiological information and identifying changes in score on an established tinnitus questionnaire (Tinnitus Reaction Questionnaire [TRQ]) after treatment. Forty-seven patients initiated treatment with the Neuromonics device during the study period. Fourteen patients completed treatment, and another 18 were actively undergoing treatment at the end of the study period. The mean pure-tone average for the study group (N = 47) was 23.4 dB for the involved ear. Of those who completed the treatment, the mean posttreatment TRQ score was significantly lower than the pretreatment score (p approximately .001). Fifteen patients (31.9%) returned the device or did not complete treatment. Across all 47 patients, 48.9% achieved a successful reduction of 40% or greater in TRQ score. There was no correlation among pure-tone average, initial TRQ score or duration of use, and percentage change in TRQ score for those with at least one follow-up test. Based on these preliminary findings, treatment with the Neuromonics device is successful in reducing TRQ scores in appropriately selected patients with tinnitus.

Worldwide experience with sequential phase-shift sound cancellation treatment of predominant tone tinnitus.

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OBJECTIVE:To report clinical data from six centres in the US, Western Europe and Asia which have used phase-shift sound wave cancellation for treatment of predominant tone tinnitus, from the first treatment in 2000 to 2009. METHOD:Clinical data were obtained from New York City, London, Erie (Pennsylvania, USA), Antwerp, Grottamare (Italy) and Kuala Lumpur, and summarised. RESULTS:A total of 493 patients were treated. A reduction in tinnitus volume (defined as > or =6 dB) was seen in 49-72 per cent of patients.

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OBJECTIVES/HYPOTHESIS: Audiologic rehabilitation of individuals with profound unilateral sensorineural hearing loss (USNHL) has traditionally been limited to the use of air-conduction contralateral routing of sound (CROS) hearing aids. Treatment for these individuals has expanded with new applications of the bone-anchored hearing aid (BAHA), transcranial hearing aid (t-CROS), and the cochlear implant. In this article, the authors review the literature that addresses these various treatment options. STUDY DESIGN: Contemporary review

RESULTS: Historical information is available that describes the limited efficacy of air-conduction CROS hearing aids in lifting hearing handicap associated with USNHL. Current investigations on providing cross hearing are generally focused on use of the BAHA. Little is known at present whether new developments in hearing aid technology can improve on conventional air-conduction CROS or t-CROS approaches. Interestingly, the cochlear implant seems to be a viable option for individuals with USNHL and tinnitus who also have intact auditory nerve pathways.

CONCLUSIONS: There is indication in the literature that BAHA provides greater relief of hearing handicap associated with USNHL than CROS hearing aids; however, both have been found to provide limited patient satisfaction and seemingly fall short of restoring true sound localization. Adequate trials have not been performed comparing BAHA with the best CROS hearing aid technology. Transcranial hearing aids and cochlear implants are experimental methods to treat USNHL and hold promise, although there remains a lack of studies available to fully support this.


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Phase-shift treatment is a new tinnitus therapy that aims at sound cancelling. This technique is based on a theory advocating that the induction of a sound wave with a 180 degrees phase-shift compared to the sound experienced by the patient could result in sound cancelling, likely by negation of the cortical perception of tinnitus or residual inhibition, which can be partial or complete. The aim of our study is to compare the effect of phase-shifting generated by the tinnitus phase-out device between pure tone tinnitus patients (PTP) and narrow band noise tinnitus patients (NBNP). In present comparative study, we explore the effects of phase-shifting during 6 weeks of phase-out therapy in PTP and NBNP. Thirty-five tinnitus patients were included in the study. Twenty-one patients had pure tone tinnitus and 14 patients had narrow band noise tinnitus. The effects on tinnitus were assessed using three separate visual analogue scales (VAS), the tinnitus questionnaire, the hyperacusis questionnaire, the Beck depression inventory, a categorical scale and audiometric measurements. While no differences in VAS were seen after therapy in NBNP, tinnitus increase could be demonstrated in PTP. This increase could be demonstrated for tinnitus loudness (p = 0.002) and tinnitus annoyance (p = 0.014). In conclusion, implementation of phase-shifting did not lead to significant sound cancelling. Our results are discussed and compared to previous studies investigating the effects of phase-out in tinnitus patients.
Bimodal hearing benefit for speech recognition with competing voice in cochlear implant subject with normal hearing in contralateral ear.

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OBJECTIVES: This project assessed electroacoustic benefit for speech recognition with a competing talker. DESIGN: Using a cochlear implant subject with normal hearing in the contralateral ear, the contribution of low-pass and high-pass natural sound to speech recognition was systematically measured. RESULTS: High-frequency sound did not improve performance, but low-frequency sound did, even when unintelligible and limited to frequencies below 150 Hz. CONCLUSIONS: The low-frequency sound assists separation of the two talkers, presumably using the fundamental frequency cue. Extrapolating this finding to regular cochlear implant users may suggest that using a hearing aid on the contralateral ear will improve performance, even with limited residual hearing.

Acoustic Masking of Noised-Induced Tinnitus in Rats

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Tinnitus, a subjective perception of sound in the absence of acoustic stimulation, is a prevalent condition that causes somatic and psychological disturbances and affects quality of life at various degrees. Acoustic masking in some forms of background noise is a commonly used tool for tinnitus relief. However, the underlying mechanisms are still poorly understood. In this study, we evaluated and characterized the effect of acoustic masking on tinnitus by examining the changes in behavioral evidence and neural correlates of tinnitus. To induce tinnitus, Sprague-Dawley rats (n=16) were exposed to a 10 kHz tone at 120 dB SPL for 3 hours. GAP detection for tinnitus and prepulse inhibition (PPI) for hearing loss across 5 frequency bands were measured pre-/post-noise exposure as well as during acoustic masking with broadband and narrow band noises (10-18 kHz) at 55 dB SPL. Age-matched control rats (n=6) were also studied. In addition, electrophysiology is being conducted to investigate how acoustic masking affects neural correlates of tinnitus along the auditory pathway. Our preliminary results demonstrated that certain noise-exposed animals developed behavioral manifestations of tinnitus across different frequency bands with predominance at 12 kHz, as evidenced by significant gap detection deficits together with PPI. We also found that acoustic masking with broadband noise tended to mask tinnitus at 12 kHz band. However, when using 10-18 kHz band noise at the same level, we found that both GAP detection and PPI deficits at 12-16 kHz were enhanced. Our data in this animal model demonstrate that tinnitus can be masked with a low level broadband noise. Results from the 10-18 kHz masking may suggest that rats were more sensitive to band noise masking at frequencies that are similar to those of their tinnitus. Further investigation is needed to determine the masking effect of a lower intensity narrow band noise on tinnitus.

Sound Therapy and Counseling for Tinnitus

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A variety of counseling and sound therapies have been developed over the past two decades. The counseling approaches follow a broad range, depending on patients needs. Theoretical approaches
vary, focusing on habituation, cognition, behavior, fear, control or acceptance. There is now emerging
evidence that some of these counseling treatments provide relief for the primary handicaps of tinnitus;
changes in 1) thoughts and emotions, 2) hearing, 3) sleep and 4) concentration. Many sound therapy
approaches have also been proposed, including the use of partial and total noise masking, music and
modulation tonal complexes. There is less agreement on the benefit of devices, but my personal clinical
experience is that they help some individuals.

Tinnitus Suppression by Low-Rate Modulated Sounds
ARO-abstract

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Tinnitus affects 10% to 20% of the population and can adversely impact quality of life. Numerous
treatments have been attempted to remedy tinnitus, but a definitive treatment does not exist. Acoustic
stimulation has been used to mask tinnitus, but this is usually effective only when the tinnitus is relatively
soft. In our study, we aimed to find an effective and low-cost means of suppressing tinnitus via modified
acoustic stimulation. Suppression differs from masking in that effective tinnitus suppressors are often
lower in level and with different temporal and spectral properties than the perceived tinnitus, whereas
maskers are often presented at an equal level and share similar temporal and spectral properties as the
perceived tinnitus.

A prospective, observational study design was undertaken to identify customized and patterned acoustic
stimuli in a group of patients whose tinnitus could not be controlled by current conventional methods. We
focused on low-rate amplitude-modulated (AM) or frequency-modulated (FM) sounds because they have
been shown to produce sustained and highly synchronized cortical responses in the brain. In addition
to AM and FM tones, we investigated pure tones, band-pass noise, and white noise, totaling 5 different
sound therapy approaches. These were delivered acoustically via headphones to 25 subjects with
tinnitus.

Amplitude, frequency, and shape of the modulation were modeled alone and in combination with other
subject factors to predict suppression and determine which combination of parameters provided the
best response. More than half of the subjects experienced suppression with either an amplitude- or
frequency- modulated tone. Often, the tones were high-frequency and near the frequency region of
the matched tinnitus. No subject experienced total suppression with white noise, the traditional sound
therapy approach. The present result suggests that sound therapy is an underexplored but promising
area of research for tinnitus treatment.

Tinnitus Retraining Therapy Using Portable Music Player
ARO-abstract

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The aim of this study is to evaluate the tinnitus retraining therapy (TRT) using a portable music player
with environmental sounds as the sound generator.

The patients exist that can have no therapeutic benefit due to the difficulty of volume adjustment
of tinnitus control instrument (TCI) and the tinnitus spectra above 6 kHz. When the tinnitus spectra
are higher than 6 kHz, the tinnitus can not be covered with TCI or hearing aid. The patients using
environmental sounds recorded in portable music player as a substitute for TCI or hearing aid in TRT
were recommended to use the sound of water or waterfall. We analyzed environmental sounds including
the sound of water or waterfall acoustically and examined the effectiveness of the environmental sounds
in TRT.

The subjects were twenty-six patients who had tinnitus as a chief complaint and were followed in the
specialized outpatient department for tinnitus in Kagawa University Hospital between January 2005
and February 2008. They were divided into three groups according to the type of devices; TCI group, hearing aid group and portable music player group. The sound of the murmur of a stream (one of the water sounds) contained a wide-frequency band and a constant strength, whereas the wave sound showed inconstant strength. Therefore, we mainly used the sound of murmur of a stream in the portable music player group. The mean score of Tinnitus handicap Inventory (THI) in portable music player group was decreased one year after the treatment. The efficacy ratio in portable music player group was almost equal to the mean THI score in TCI group and hearing aid group.

In conclusion, TRT using portable music player had good efficacy similar to TCI and hearing aid. The sound of the murmur of a stream was one of the most effective sounds in TRT. TRT using portable music player as sound generator can provide the most cost-effective treatment option for tinnitus patients.

VII Brain Stimulation

Strategies for enhancement of transcranial magnetic stimulation effects in tinnitus patients.

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Tinnitus is an auditory phantom sensation characterized by the perception of elementary sound or noise in the absence of any acoustical sound source. Tinnitus is a frequent disorder and is difficult to treat. Compelling evidence corroborates the perception of chronic tinnitus as associated with regional changes in cortical excitability. Repetitive transcranial magnetic stimulation (rTMS) over the temporal or the temporoparietal cortex has recently been introduced as a new treatment strategy for tinnitus. The technique has been applied in two different ways in tinnitus patients. Single sessions of high-frequency rTMS have been successful in transient reduction of tinnitus perception, whereas repeated sessions of low-frequency rTMS have resulted in longer-lasting tinnitus reduction, indicating therapeutic potential. However, treatment outcome so far is characterized by high interindividual variability and only moderate effect size. This study reviews different approaches for enhancement of rTMS effects in tinnitus patients. The different strategies include the combined stimulation of nonauditory and auditory brain areas, the variation of stimulation frequencies and intensities, and the comparison of different firing modes (burst vs. tonic stimulation). Furthermore, the value of optimum patient selection is discussed. Another approach consists of a combination of rTMS administration with pharmacological intervention. Repetition of rTMS treatment in treatment responders seems to be a promising approach for the prolongation of treatment effects. A pilot study suggests further that treatment effects can be enhanced by combined stimulation of auditory and nonauditory brain areas. Moreover, clinical data such as tinnitus duration and the dimension of hearing loss seem to have an important impact on treatment effects. Successful enhancement of treatment effects will depend on a more detailed understanding of the neuronal correlates of the different forms of tinnitus and the mechanisms by which rTMS exerts its effects.

Repetitive transcranial magnetic stimulation for tinnitus treatment: No enhancement by the dopamine and noradrenaline reuptake inhibitor bupropion

Brain Stimulation, published online 26 April 2010

Kleinjung T, Steffens T, Landgrebe M, Vielsmeier V, Frank E, Burger J, Strutz J, Hajak G, Langguth B.

Repetitive transcranial magnetic stimulation (rTMS) of the temporal cortex has shown beneficial effects in patients with chronic tinnitus. Recent preclinical data in healthy controls suggest that the effects of low-frequency rTMS can be enhanced by dopaminergic drugs. Objective: We investigated whether application of the dopamine reuptake inhibitor bupropion increases the clinical effects of low-frequency rTMS over the auditory cortex in tinnitus patients.
Subjects and Methods: Eighteen subjects with chronic tinnitus received 10 sessions of 1 Hz rTMS (2000 pulses/day, 110% motor threshold) applied to the left temporal cortex. In addition, these subjects received one dosage of 150 mg bupropion (Wellbutrin XL/Elontril) 4 hours before each TMS session. Treatment outcome was assessed with a tinnitus questionnaire over a 3-month period. Treatment effects were compared with a control group of 100 tinnitus patients matched for age, tinnitus duration, and tinnitus questionnaire baseline scores, who received the same rTMS treatment without prior bupropion application.

Results: For the whole sample, there was a significant effect of rTMS treatment over time. There were no significant differences between the bupropion and the control group.

Conclusions: Our data suggest that 150 mg bupropion administration does not enhance the effect of rTMS in the treatment of tinnitus.

Tinnitus as a Symptom of Psychotic Depression Successfully Treated With Electroconvulsive Therapy.
J ECT. 2010 Apr 6. [Epub ahead of print]

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We present the case of a 51-year-old woman with recurrent major depression with psychotic features including severe tinnitus. Her tinnitus resolved with successful treatment of her depressive episode with electroconvulsive therapy. We review the literature on electroconvulsive therapy and tinnitus.

Burst transcranial magnetic stimulation: which tinnitus characteristics influence the amount of transient tinnitus suppression?
Eur J Neurol. 2010 Mar 30. [Epub ahead of print]

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Background: Transcranial Magnetic Stimulation (TMS) is a method capable of temporarily suppressing tinnitus by delivering tonic or burst stimuli. Burst TMS has a high interindividual variability and low effect size. Tinnitus type and laterality, tinnitus-related distress, and tinnitus duration might contribute to this large individual variation. Methods: The effect of burst TMS on the auditory cortex in 100 male individuals is evaluated with coil placed over the auditory cortex. For unilateral tinnitus, this coil was placed contralaterally to the tinnitus, whilst for bilateral tinnitus the coil was placed over the right auditory cortex. The site of maximal tinnitus suppression is determined using 1-Hz stimulation with five pulses per burst (intensity of the stimulation set at 90% of the motor threshold). When tinnitus suppression is noted, the patients are asked to estimate the decrease in tinnitus in percentage using the numeric rating scale. The procedure is repeated with stimulations at 5, 10 and 20 Hz, each stimulation session consisting of 200 pulses. Results: Results demonstrate that burst stimulation can decrease the perceived tinnitus intensity transiently in 57.83% of the patients. Patients with bilateral tinnitus respond better to burst TMS than patients with unilateral tinnitus and highly distressed patients presenting with unilateral pure tone tinnitus fail to burst TMS. Conclusions: Burst TMS modulates both unilateral and bilateral tinnitus, both high and low distress and both pure tones and narrow band tinnitus. However, the suppression effect is moderated by tinnitus type and laterality, tinnitus-related distress, and tinnitus duration.
Contralateral versus ipsilateral rTMS of temporoparietal cortex for the treatment of chronic unilateral tinnitus: comparative study.
Eur J Neurol. 2010 Mar 4. [Epub ahead of print]

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Background: Repetitive transcranial magnetic stimulation (rTMS) applied over left temporoparietal cortex has been reported to have a long-term therapeutic effect on tinnitus. We compare the impact of 1 and 25 Hz rTMS delivered either contralateral or ipsilateral to symptoms in 62 patients with unilateral chronic tinnitus. Material and methods: Patients were randomly assigned to one of four treatment groups: with stimulation at 1 or 25 Hz applied either ipsilateral or contralateral to symptoms. Two thousand pulses per session were given daily for 2 weeks. Changes in tinnitus handicap inventory (THI), self-rating scores of loudness, awareness, and annoyance were measured monthly for 10 months. Duration of residual inhibition (RI) and psychiatric morbidity were evaluated monthly for 3 months. Results: There was a significant main effect of time (P < 0.0001) and a significant time x side interaction (P = 0.032) between groups. This was because of the fact that contralateral stimulation had a greater effect on THI than ipsilateral stimulation; it was also superior to left side stimulation (P = 0.027). Ratings of loudness improved more after contralateral rTMS (P = 0.037). Twenty patients had no remaining tinnitus after 3 months; the remainder had a significant increase in RI. Patients with the shortest history of tinnitus tended to respond better to rTMS. There was a significant correlation between changes in THI score and changes in Hamilton anxiety and depression scores. Conclusion: Ten daily treatments of 1 and 25 Hz rTMS contralateral to the side of tinnitus have a greater beneficial effect on symptoms than either ipsilateral or left side stimulation.

rTMS for the treatment of tinnitus: the role of neuronavigation for coil positioning.

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Tinnitus affects 10% of the population, its pathophysiology remains incompletely understood, and treatment is elusive. Both animal models and functional imaging data in tinnitus patients suggest that tinnitus is associated with increased neuronal activity, increased synchronicity and functional reorganisation in the auditory cortex. Therefore, targeted modulation of auditory cortex has been proposed as a new therapeutic approach for chronic tinnitus. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive method for modulation of cortical activity, has been applied in different ways in patients with chronic tinnitus. Single sessions of high-frequency rTMS over the temporal cortex have been used to transiently interfere with the intensity of tinnitus. Repeated sessions of low-frequency rTMS have been investigated as a treatment for tinnitus. Here, we review data from clinical trials and discuss potential neurobiological mechanisms with special focus on the relevance of the stimulation target and the method of TMS coil positioning. Different functional neuroimaging techniques are used for detecting tinnitus-related changes in brain activity. They converge in the finding of increased neuronal activity in the central auditory system, but they differ in the exact localisation of these changes, which in turn results in uncertainty about the optimal target for rTMS treatment. In this context, it is not surprising that the currently available studies do not demonstrate clear evidence for superiority of neuronavigational coil positioning. Further development of rTMS as a treatment for tinnitus will depend on a more detailed understanding of both the neuronal correlates of the different forms of tinnitus and of the neurobiological effects mediating the benefit of TMS on tinnitus perception.
Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study.
Exp Brain Res. 2010 Feb 26. [Epub ahead of print]

Vanneste S, Plazier M, Ost J, van der Loo E, Van de Heyning P, De Ridder D.

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Tinnitus is considered as an auditory phantom percept. Preliminary evidence indicates that transcranial direct current stimulation (tDCS) of the temporo-parietal area might reduce tinnitus. tDCS studies of the prefrontal cortex have been successful in reducing depression, impulsiveness and pain. Recently, it was shown that the prefrontal cortex is important for the integration of sensory and emotional aspects of tinnitus. As such, frontal tDCS might suppress tinnitus as well. In an open label study, a total of 478 tinnitus patients received bilateral tDCS on dorsolateral prefrontal cortex (448 patients anode right, cathode left and 30 anode left, cathode right) for 20 min. Treatment effects were assessed with visual analogue scale for tinnitus intensity and distress. No tinnitus-suppressing effect was found for tDCS with left anode and right cathode. Analyses show that tDCS with right anode and left cathode modulates tinnitus perception in 29.9% of the tinnitus patients. For these responders a significant reduction was found for both tinnitus-related distress and tinnitus intensity. In addition, the amount of suppression for tinnitus-related distress is moderated by an interaction between tinnitus type and tinnitus laterality. This was, however, not the case for tinnitus intensity. Our study supports the involvement of the prefrontal cortex in the pathophysiology of tinnitus.

Left temporal low-frequency rTMS for the treatment of tinnitus: clinical predictors of treatment outcome - a retrospective study.
Eur J Neurol. 2010 Feb 10. [Epub ahead of print]


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Background: There is increasing evidence that repetitive transcranial magnetic stimulation (rTMS) can reduce chronic tinnitus. However, treatment results are characterized by high interindividual variability. Therefore, the identification of predictors for treatment response is of high clinical relevance. Methods: Clinical data of 194 patients with tinnitus were evaluated. All patients were treated with a standardized rTMS procedure (1 Hz, 10 days, 2000 stimuli/day, over the left temporal cortex). A potential influence on the outcome was analysed for the following parameters: age, gender, depression scores in Beck Depression Inventory (BDI) and tinnitus severity (TQ) before rTMS, lateralization, frequency and duration of tinnitus and extent of hearing loss. Results: An effect of tinnitus laterality was observed. In patients with left-sided or bilateral tinnitus, rTMS resulted in a statistically significant reduction of TQ scores, whereas patients with right-sided tinnitus did not show a significant improvement after rTMS treatment. However, in correlation analyses, we found a trend which did not reach statistical significance that in the subgroup of treatment responders tinnitus duration influenced rTMS outcome. In addition, a multiple regression analysis identified the TQ score at baseline as a significant predictor for treatment outcome. For all other investigated parameters, no statistically significant effects were found. Conclusions: This study suggests that left temporal low-frequency rTMS has beneficial effects in left-sided and bilateral tinnitus, but not in right-sided tinnitus. In line with the results from earlier studies involving smaller samples, tinnitus duration was found to influence rTMS outcome.
Variability in Tinnitus Suppression Via Electric Stimulation

ARO-abstract

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Electric stimulation of the cochlea has been shown to suppress tinnitus, but the parameters of an effective electric stimulus remain unexplored. Furthermore, a clear distinction needs to be drawn between tinnitus masking and suppression, as they utilize different mechanisms. Previously, high-rate pulse trains (4800pps) delivered to the cochlea produced substantial or complete tinnitus suppression in a number of patients (Rubenstein et al. 2003), whereas low-rate (20-200pps) pulse trains completely suppressed tinnitus in a patient with debilitating tinnitus (Zeng et al. presentation at 2007 ARO).

Here we explored a large parametric space of electric stimuli and measured the effects on tinnitus suppression. Stimulation rate, electrode place, and loudness of the stimuli were varied, and electric stimuli were delivered to the cochlear implant for a total of six minutes. Subjective loudness of tinnitus, as well as loudness of the stimulus, was assessed in thirty (30) second intervals. A total of twelve cochlear implant subjects with tinnitus have participated in our study to date.

Eight out of the twelve subjects achieved tinnitus suppression greater than 30% (<30% suppression could be attributed to a placebo effect), with six subjects experiencing complete suppression during electric stimulation. Preliminary analysis of the data, however, indicates no trends across stimulation rate, place, or level. The present results suggest that electric stimulation via a cochlear implant can be an effective therapeutic for those suffering from tinnitus; however, the effective suppression stimulus varies greatly among individuals.

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Electrical Suppression of Tinnitus: A Neuromodulation Approach

ARO-abstract

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Tinnitus is a phantom sound that occurs in the absence of external acoustic stimulation. If chronic, tinnitus can have debilitating effects on patients and it has a significant economic impact on society due to its large prevalence. Although a number of treatment methods have been used, so far there are still no reliable therapies. Recent clinical studies have demonstrated that auditory cortex electrical stimulation (ACES) can suppress tinnitus in patients. However, the large variability in the efficacy of ACES-induced suppression of tinnitus across individuals has hindered its development into a reliable therapy. Due to ethical reasons, many issues cannot be comprehensively addressed in patients. We have developed an animal model of tinnitus suppression through ACES and neuromodulation. In this model, behavioral testing and electrophysiological recordings were conducted following noise exposure to test for behavioral manifestation of tinnitus and its neural correlates. Electrical stimulation of the AC was implemented to determine if ACES suppresses tinnitus and modulates its neural correlates. Our data showed that noise exposure induces tinnitus and the induced tinnitus is significantly suppressed by ACES, which is in line with clinical observations. In addition, we found that ACES induces complex neural responses (inhibition, excitation and no change) in the dorsal cochlear nucleus and inferior colliculus, structures that have been implicated in the etiology of tinnitus. Furthermore, we found that ACES modulates neural interactions across auditory brain structures, suggesting that suppression of tinnitus may involve balancing neural activity or adjusting neural information flow at least along the auditory axis. We expect that an in-depth understanding of the underlying mechanisms of ACES-induced tinnitus suppression will further clinical investigations and stimulate development of specialized neural prosthesis for effective tinnitus suppression.
Repetitive Transcranial Magnetic Stimulation (RTMS) for Treatment of Chronic Tinnitus

ARO-abstract

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[Background and purpose] There is compelling evidence that tinnitus is associated with functional alterations in the central nervous system. Repetitive transcranial magnetic stimulation (rTMS) is a potent tool for modifying neural activity at the simulated area and at a distance along functional anatomical connections. Depending on stimulation parameters, cortical networks can be functionally disturbed or modulated in their activities. Low-frequency rTMS has been shown to result in a decrease in cortical excitability. The technique can alleviate tinnitus by modulating the excitability of neurons in the auditory cortex. We aimed to investigate effects of low-frequency rTMS in the patients and determine the factors that predict a beneficial outcome with rTMS treatment.

[Method] Sixteen patients (male 10, female 6) with chronic tinnitus underwent low-frequency (1Hz) rTMS (intensity: 110% motor threshold, number of stimuli: 1200) to their left auditory cortex. The treatment outcome was assessed with a visual analog scale (VAS) of loudness, annoying and duration, loudness balance test, and tinnitus handicap inventory (THI). Therapeutic success was studied according to the patients’ clinical characteristics.

[Results] A significant reduction in the VAS (loudness and annoying) occurred immediately after rTMS, which gradually returned to pretreatment levels following 7 days. The patients with normal hearing and age-related hearing loss have a tendency to benefit more from rTMS treatment.

[Conclusion] These results support the potential of rTMS as a new therapeutic tool for the treatment of chronic tinnitus. Because this study was performed with a small sample sizes and showed high interindividual variability of treatment effect, further development of the technique is needed before it can be recommended for use in clinical routine.

VIII Behavioral Therapy

Group therapy for patients with tinnitus at the University of Brasilia Medical School.

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Although group therapy for tinnitus is a well documented field in the international literature, as far as we know it has never been held in Brazil. This study represents a successful experience of a group therapy for tinnitus based on the tinnitus retraining therapy associated with behavioral cognitive techniques. The goal of the present study is to assess patients with tinnitus before and after the group therapy based on the tinnitus retraining therapy and the behavioral cognitive therapy. Materials and Methods: Prospective cohort study: 27 subjects signed in for the study, and answered the Tinnitus Handicap Inventory (THI) and the Hospital Depression and Anxiety Scale (HAD), before and after the treatment. We held six structured sessions according to the principles of tinnitus retraining therapy associated with behavioral cognitive techniques. Results: 27 patients started and 19 finished the treatment (8 were taken off). 47.4% men, mean age of 47.6. THI results before and after treatment were respectively: functional: 29 and 14, emotional 24 and 10 and catastrophic 12 and 5 and the HAD scale: anxiety 2 and 9 and depression 10 and 6. Conclusion: The treatment described is effective in improving tinnitus symptoms.
Tinnitus Retraining Therapy (TRT) for tinnitus.

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BACKGROUND: Tinnitus is described as the perception of sound or noise in the absence of real acoustic stimulation. Although an outright cure for tinnitus remains elusive, various management strategies have been developed to help to lessen the impact of the symptom. Following the publication of a neurophysiological model of tinnitus, Tinnitus Retraining Therapy (TRT) was developed. Using a combination of directive counselling and sound therapy in a strict framework, this is one of the most commonly used treatment modalities for tinnitus. Many studies refer to the use of TRT where in fact a modified version of this therapy is actually being implemented. It is therefore important to confirm the use of authentic TRT when reviewing any study that reports its use.

OBJECTIVES: To assess the efficacy of TRT in the treatment of tinnitus.
SEARCH STRATEGY: The search included the Cochrane ENT Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE and reference lists of identified publications. The date of the most recent search was 26 August 2009.

SELECTION CRITERIA: Randomised controlled trials of TRT versus no treatment, or other forms of treatment, in adult patients with tinnitus.

DATA COLLECTION AND ANALYSIS: Both authors critically appraised the retrieved studies for risk of bias and extracted data independently. Where necessary, we contacted the original study authors for further information.

MAIN RESULTS: Only one trial (123 participants) was included in the review. Several excluded trials did not follow the strict protocol for TRT, evaluating instead a modified form of TRT. The included trial showed TRT to be more effective than a tinnitus masking (TM) approach. In this study outcome data for tinnitus severity were presented using three instruments (Tinnitus Handicap Inventory (THI), Tinnitus Handicap Questionnaire (THQ), Tinnitus Severity Index (TSI)) for patients in three groups (participants’ tinnitus being a ‘moderate problem’, ‘big problem’ or ‘very big problem’). At 18 months, improvements for the three groups in the three scores (TRT versus TM) were respectively: ‘moderate problem’ - THI: 18.2 versus 4.6, THQ: 489 versus 178, TSI 7.5 versus 1.6; ‘big problem’ - THI: 29.2 versus 16.7, THQ: 799 versus 256, TSI: 12.1 versus 6.7; and ‘very big problem’ - THI: 50.4 versus 10.3, THQ: 1118 versus 300, TSI: 19.7 versus 4.8.

AUTHORS’ CONCLUSIONS: A single, low-quality randomised controlled trial suggests that TRT is much more effective as a treatment for patients with tinnitus than tinnitus masking.

The relationship between various psychosocial factors and physical symptoms reported during primary-care health examinations.

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OBJECTIVES: The aim of the study was to determine indicators for psychosocial factors and to investigate the associations between them and physical complaints, as well as to examine possible gender-dependent differences. METHODS: This was an observational (cross-sectional) study in primary care (health examinations in several Austrian regions); participants were 312 men and 374 women aged 19-60 years. The impact of psychosocial factors on ten physical symptoms (cardiac complaints, dyspnea, gastric complaints, headaches, joint or muscle pain, dry skin, hearing impairment, tinnitus, decrease of strength and endurance, and insomnia) was analyzed using logistic regression analyses and multiple linear regression models. RESULTS: People with psychosocial stress or dissatisfaction exhibited a higher probability of reporting at least one physical symptom. Age-adjusted odds ratios (95% CI) were as follows: pressure at work 1.72 (1.08-2.73) in men and 2.53 (1.46-4.39) in women, social stress in the workplace 3.37 (1.41-8.05) in men and 3.09 (1.01-9.43) in women, sexual dissatisfaction 4.48 (1.47-13.62) in men and 1.77 (0.80-3.96) in women, discomfort in family/partnership 4.71 (1.34-16.57) in men and 1.76 (0.66-4.67) in women. Among men, the psychosocial parameter most strongly related to the number of physical symptoms was discomfort in family/partnership, followed by social
stress in the workplace, sexual dissatisfaction, and pressure at work with means of 2.00, 1.27, 0.92 and 0.33 symptoms respectively (linear regression model, adjusted for age). Among women the strongest association found was also with discomfort in family/partnership, followed by sexual dissatisfaction, pressure at work and social stress in the workplace with means of 1.32, 1.20, 0.58 and 0.50 symptoms respectively. CONCLUSIONS: The reporting of physical symptoms is often associated with psychosocial factors and these should be taken into account during primary care and, where appropriate, should be further clarified. There are unexpected, gender-related patterns in the association of different psychosocial factors with physical symptoms that warrant further investigation.

The distressed (Type D) personality is independently associated with tinnitus: a case-control study.

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BACKGROUND: Tinnitus is a common and disturbing condition, reported by 10% to 20% of the general population. OBJECTIVE: The authors sought to determine personality characteristics associated with tinnitus patients versus a control group of ear-nose-throat (ENT) patients without tinnitus. METHOD: Adult chronic tinnitus sufferers (N=265) and ENT patients without tinnitus (N=265) participated in a cross-sectional study. The authors evaluated personality characteristics with tests for distressed personality (Type D), neuroticism, extraversion, and emotional stability. RESULTS: As compared with control subjects, tinnitus patients had statistically significant and clinically relevant higher levels of neuroticism, negative affectivity, and social inhibition, on one hand, and lower levels of extraversion and emotional stability on the other hand. Also, tinnitus patients were more likely to have a type D personality. CONCLUSIONS: Neuroticism, reduced extraversion, and reduced emotional stability were associated with tinnitus, but the level of prediction of the model improved with the addition of type D personality to the single traits. This might indicate that personality characteristics, and type D personality, in particular, are associated with having tinnitus and might contribute to its perceived severity.

Type D personality among noncardiovascular patient populations: a systematic review.

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OBJECTIVE: This article reviews all available literature concerning the implications of Type D personality (the conjoint effects of negative affectivity and social inhibition) among patients with noncardiovascular conditions. METHODS: Published papers were included if they studied Type D personality among noncardiovascular patient populations. Twelve articles met our inclusion criteria and were subjected to a methodological quality checklist (e.g., sample size, response rate, Type D measurement). RESULTS: The methodological quality of the selected studies was quite good. The noncardiovascular patient populations included chronic pain, tinnitus, sleep apnea, primary care patients, vulvovaginal candidiasis, mild traumatic brain injury, vertigo, melanoma and diabetic foot syndrome. Type D personality was associated with an increased number or severity of reported health complaints, heightened the perception of negative emotions (e.g., depression and anxiety), had an adverse effect on health-related behaviors, was associated with poor adherence to treatment and significantly reduced effort to perform during diagnostic testing. CONCLUSION: Type D is a vulnerability factor that not only affects people with cardiovascular conditions but also those with other medical conditions. Type D was associated with poor physical and mental health status and poor self-management of the disease. Consequently, including Type D in future studies seems warranted. Copyright 2010 Elsevier Inc. All rights reserved.
The impact of Type D personality on health-related quality of life in tinnitus patients is mainly mediated by anxiety and depression.

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OBJECTIVE: To evaluate the impact of Type D personality on health-related quality of life (HRQoL) and self-reported tinnitus-related distress in chronic tinnitus patients and whether this relationship is mediated by indicators of psychological distress (i.e., vital exhaustion, anxiety, and depression). MATERIALS AND METHODS: Using a cross-sectional study design, 265 consecutive tinnitus patients were asked to complete the Hospital Anxiety and Depression Scale, the Maastricht Questionnaire, the Type D Scale (DS14), the Short-Form Health Survey 36, and the Tinnitus Reaction Questionnaire. RESULTS: The prevalence of Type D was 35.5%. Type D patients were significantly more anxious, depressed, and vitally exhausted, and experienced more impaired HRQoL and increased tinnitus-related distress compared with non-Type D patients. Structural equation modeling showed that Type D personality directly increased symptoms of depression and anxiety, but not vital exhaustion. Type D was also a direct predictor of poor mental and physical HRQoL and increased tinnitus-related distress, although this influence was mainly mediated by symptoms of depression and anxiety. Anxiety, depression, and vital exhaustion had a direct influence on HRQoL and self-reported tinnitus-related distress, with a higher impact on mental HRQoL (R² = 0.74) compared with physical HRQoL (R² = 0.33). Vital exhaustion was a predictor of HRQoL and self-reported tinnitus-related distress; however, its influence was moderated by enhanced levels of anxiety and depression. CONCLUSION: Tinnitus patients with a Type D personality were more likely to be anxious and depressed and to experience poor HRQoL and increased self-reported tinnitus-related distress, with the impact of Type D mainly being mediated by symptoms of anxiety and depression, although Type D also exerted a direct influence on these outcomes. These findings underline that to reduce the impact of tinnitus on HRQoL and self-reported tinnitus-related distress, treatment should be directed toward reducing anxiety and depression, especially in patients with a Type D personality.

Real-time fMRI feedback training may improve chronic tinnitus.

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OBJECTIVES: Tinnitus consists of a more or less constant aversive tone or noise and is associated with excess auditory activation. Transient distortion of this activation (repetitive transcranial magnetic stimulation, rTMS) may improve tinnitus. Recently proposed operant training in real-time functional magnetic resonance imaging (rtfMRI) neurofeedback allows voluntary modification of specific circumscribed neuronal activations. Combining these observations, we investigated whether patients suffering from tinnitus can (1) learn to voluntarily reduce activation of the auditory system by rtfMRI neurofeedback and whether (2) successful learning improves tinnitus symptoms. METHODS: Six participants with chronic tinnitus were included. First, location of the individual auditory cortex was determined in a standard fMRI auditory block-design localizer. Then, participants were trained to voluntarily reduce the auditory activation (rtfMRI) with visual biofeedback of the current auditory activation. RESULTS: Auditory activation significantly decreased after rtfMRI neurofeedback. This reduced the subjective tinnitus in two of six participants. CONCLUSION: These preliminary results suggest that tinnitus patients learn to voluntarily reduce spatially specific auditory activations by rtfMRI neurofeedback and that this may reduce tinnitus symptoms. Optimized training protocols (frequency, duration, etc.) may further improve the results.
The effectiveness of bibliotherapy in alleviating tinnitus-related distress.

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OBJECTIVE: The present study examined the efficacy of bibliotherapy in assisting individuals experiencing distress related to tinnitus. METHODS: One hundred sixty-two tinnitus sufferers from Australia participated in a study designed to examine the effectiveness of a cognitive-behaviorally based self-help book in reducing distress. To maximize the ecological validity of the findings, we excluded no individuals interested in treatment for tinnitus-related distress. RESULTS: The experimental condition lost 35% of participants at postassessment, compared to 10% in the control group. In an analysis of participants who completed postintervention assessment, those assigned to the intervention condition, who received a tinnitus self-help book, showed significantly less tinnitus-related distress and general distress 2 months later compared to those assigned to the waiting list control condition. The intervention group's reduction in tinnitus-related distress and general distress from preintervention to postintervention 2 months later was significant, and these participants maintained a significant reduction in distress on follow-up 4 months after they received the tinnitus self-help book. A long-term follow-up of all participants, who at that time had received the book at least a year previously, showed a significant reduction in tinnitus distress. Although these group differences and pre-post changes were significant, effect sizes were small. Intention-to-treat analyses showed no significant effect for between-groups analyses, but did show a significant effect for the 1-year follow-up pre-post analysis. CONCLUSION: Information on the effectiveness of using a self-help book, without therapist assistance, in alleviating distress is important, as bibliotherapy can provide inexpensive treatment that is not bound by time or place. Copyright 2010 Elsevier Inc. All rights reserved.

Learning Strategy Determines Cortical Plasticity: Implications for Behavioral Treatments of Auditory Disorders
ARO-abstract

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The auditory cortex is now known to be a substrate for auditory learning, in addition to its role in the analysis of sounds. Most extensively studied is the primary auditory cortex (A1): highly-specific physiological plasticity develops when both animal and human subjects learn the meaning of sounds. First discovered in studies of associative learning, frequency receptive fields (RFs) can shift to the frequency of a signal tone (Bakin & Weinberger, Brain Res., 1990), producing a specific increase in its representational area as a direct function of the level of its acquired behavioral importance (Rutkowski & Weinberger, PNAS, 2005). Such learning-induced plasticity provides the neurobiological basis for clinical treatments of disorders such as speech comprehension and tinnitus. Although it is currently assumed that auditory learning is invariably accompanied by cortical plasticity, we have found that how learning occurs is critical to the formation of plasticity. Specifically, auditory tasks can be solved using different learning strategies and plasticity in A1 of animals depends on their use of a particular strategy. We present findings from groups of animals (rats) trained in a variety of tasks. The findings reveal that cortical plasticity in the form of signal-specific increased sensitivity (decreased threshold), increased selectivity (decreased bandwidth) and increased area of representation develop when the learning strategy of subjects depends on attending to acoustic onset transients while ignoring tone offsets. Thus, remedial auditory training regimens that aim to induce learning-related plasticity need to incorporate the use of appropriate specific auditory learning strategies.

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Sound Therapy and Counseling for Tinnitus
ARO-abstract

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A variety of counseling and sound therapies have been developed over the past two decades. The counseling approaches follow a broad range, depending on patients' needs. Theoretical approaches vary, focusing on habituation, cognition, behavior, fear, control or acceptance. There is now emerging evidence that some of these counseling treatments provide relief for the primary handicaps of tinnitus; changes in 1) thoughts and emotions, 2) hearing, 3) sleep and 4) concentration. Many sound therapy approaches have also been proposed, including the use of partial and total noise masking, music and modulation tonal complexes. There is less agreement on the benefit of devices, but my personal clinical experience is that they help some individuals.

Is a Tinnitus Seminar a Successful Treatment Modality?
ARO-abstract

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This study’s aim was to determine if a one-time tinnitus seminar could provide patients significant relief from distress caused by their tinnitus. Measurements were made using the tinnitus reaction questionnaire (TRQ) and by comparing a waitlist control group to a treatment group. The percent of improvement chosen as clinically significant for this study was 20%. The benefit was determined by analyzing the decrease in scores between pre and post treatment TRQs. The tinnitus reaction questionnaire was chosen because it has been shown to have good internal consistency (cronbach's alpha = .96), test-retest reliability (r = .88), and has good correlation values to findings from clinicians (Wilson et al., 1991). There were 33 participants total (10 participants in the waitlist group and 23 participants in the treatment group). Of the 33 participants, 30 completed the study, a 91% completion rate.

There was not a significant difference between pre-post tinnitus reaction questionnaires when comparing the waitlist control group to the treatment group. A one way ANOVA was used to determine the difference between total change by group, \[F(1,28)=1.39, P=0.246]\]. A one way ANOVA performed for 3 different test scores as a function of group was also found to not be statistically significant \[F(1,28)=0.605, P=0.44]\). It may be that statistically significant results were not found between the control and treatment groups due to the small sample size. Other studies using similar criteria with larger group sizes have been able to produce statistically significant results (Henry et al., 2008).

A second questionnaire designed by the researchers to determine perception of the seminar demonstrated positive findings. Further analysis was carried out by dividing the seminar participants into one group demonstrating clinically significant changes and another that did not. The mean score for the participants with clinically significant improvement was 5.75 out of 8. The non-clinically significant group also had a mean score of 5.29 out of 8, (0.046 % difference). Every participant marked that they would recommend the seminar to other tinnitus sufferers, while 95% found the seminar helpful, and followed at least one of the seminar’s recommendations. The vast majority of participants, 90% also felt they had a better understanding of their tinnitus following the seminar.

As many as 50 million people suffer from tinnitus in this country and many of them may be told by health professionals that no treatment options are available to help them. Tinnitus seminars offer a potential benefit to both patients disturbed by their tinnitus as well as the medical community’s approach to procedures for tinnitus at an excellent cost/benefit ratio.
IX Somatic Tinnitus

Exploring Multisensory Integration Using a Three-Dimensional Silicon Microelectrode Array for Simultaneous Ventral and Dorsal Cochlear Nucleus Recording and Stimulation

ARO-abstract

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Somatosensory projections from the spinal trigeminal nucleus (Sp5) to the cochlear nucleus predominantly target the granule cell domains of the dorsal cochlear nucleus (DCN) and ventral cochlear nucleus (VCN). However numerous SP5 terminals are also found in the deep layers of DCN and magnocellular regions of VCN (Shore and Zhou, J. Neurosci Res., 2004; Haenggeli et al., J. Comp. Neurol., 2005), presumably contacting giant cells, multipolar cells and bushy cells. Sp5 stimulation can modify the responses of DCN pyramidal cells to acoustic stimulation but the influence of the Sp5 input on auditory coding in the VCN and deep layers of DCN has not yet been studied. An added complication in the interpretation of these experiments is the bidirectional connection between DCN and VCN via tuberculoventral cells in deep DCN and stellate cells in VCN.

To address these questions we have developed a three-dimensional array composed of 4-shank/32 site silicon probes. One to two 32-site probes target the DCN allowing us to record in multiple cell-layers of the DCN across its mediolateral tonotopic axis. One to three 16-site probes target the VCN across its tonotopic axis, with the addition of 16 adjacent or concentric stimulation sites. This configuration allows for simultaneous recordings in VCN and DCN while stimulating Sp5, with the possibility of stimulating in VCN to explore the connections between DCN and VCN in multisensory processing.

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Somatosensory Modulation of Tinnitus, an FMRI Study

ARO-abstract

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Jaw protrusion may lead to a change of tinnitus. To identify the neural mechanisms that are responsible for this somatic modulation, we measured the fMRI response to jaw protrusion. Thirteen patients with tinnitus and 20 healthy controls were included in an fMRI experiment. All patients were able to modulate their tinnitus by performing jaw protrusion. Experiments were performed on a 3T Philips scanner, using sparse sampling (TR=10s). Experimental conditions consisted of (1) bilateral broadband noise, (2) jaw protrusion, (3) the combination of both and (4) a baseline condition. A region of interest analysis was performed to quantify responses to the experimental stimuli. A group analysis of the response to sound showed activity in the auditory pathway, consisting of the cochlear nucleus (CN), the inferior colliculus (IC), the medial geniculate body, and the primary and secondary auditory cortex. Jaw protrusion activated the following structures: the cerebellum, the ventrolateral nucleus of the thalamus, the putamen, the motor cortex and the somatosensory cortex. In addition, the auditory pathway showed significant responses to jaw protrusion. In contrast, the somatosensory cortex only showed a response to jaw protrusion and not to sound stimuli. A difference between subject groups was found in the CN and the IC, where patients showed a larger response to protrusion than controls. These data show that the brainstem auditory nuclei play a role in the somatic modulation of tinnitus.
X Surgical Treatment

Tumor control and hearing preservation after Gamma Knife radiosurgery for vestibular schwannomas in neurofibromatosis type 2.
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To analyze the effect of Gamma Knife radiosurgery (GKS) on tumor control and hearing preservation rates in patients with vestibular schwannomas (VS) in a setting of neurofibromatosis type 2 (NF 2), a retrospective study was carried out at a tertiary-level referral Gamma Knife unit. Dose plans, pre- and postoperative radiology, and follow-up clinical records of patients with NF 2 who had undergone GKS for VS using a Leksell Gamma Knife (Elekta Instruments AB, Stockholm, Sweden) model B unit from 1997 to 2008 were reviewed. Thirty patients with 54 VS underwent GKS. The average age of the cohort was 29 years (range 10-56 years). Twenty-four patients had bilateral VS. The commonest clinical presentation was hearing loss and tinnitus. Primary GKS was given to 36 tumors, while 18 tumors received it as an adjunct to surgery. Average tumor size was 3.7 cc (range 0.1-13.3 cc). A median 12 Gy prescription dose (range 10-15 Gy) was administered at the 50% isodose (range 42-50%) to cover on average 91.5% of the tumor. Eighteen patients were available for clinical, 14 patients for radiological, and 5 patients (with useful hearing) for audiometric follow-up at an average of 26.6 months. The tumor control rate was 87.5% in this series (33.3% tumor regression), while hearing preservation was noted in 66.7% of cases. One patient developed worsening of facial function. GKS for VS provides satisfactory tumor control and hearing preservation in patients with NF 2. Long-term follow-up will determine future recommendations.

Decision analysis of treatment options for vestibular schwannoma.
J Neurosurg. 2010 Apr 16. [Epub ahead of print]

Whitmore RG, Urban C, Church E, Ruckenstein M, Stein SC, Lee JY.

Departments of Neurosurgery

Object Widespread use of MR imaging has contributed to the more frequent diagnosis of vestibular schwannomas (VSS). These tumors represent 10% of primary adult intracranial neoplasms, and if they are symptomatic, they usually present with hearing loss and tinnitus. Currently, there are 3 treatment options for quality of life (QOL): wait and scan, microsurgery, and radiosurgery. In this paper, the authors’ purpose is to determine which treatment modality yields the highest QOL at 5- and 10-year follow-up, considering the likelihood of recurrence and various complications. Methods The MEDLINE, Embase, and Cochrane online databases were searched for English-language articles published between 1990 and June 2008, containing key words relating to VS. Data were pooled to calculate the prevalence of treatment complications, tumor recurrence, and QOL with various complications. For parameters in which incidence varied with time of follow-up, the authors used meta-regression to determine the mean prevalence rates at a specified length of follow-up. A decision-analytical model was constructed to compare 5- and 10-year outcomes for a patient with a unilateral tumor and partially intact hearing. The 3 treatment options, wait and scan, microsurgery, and radiosurgery, were compared. Results After screening more than 2500 abstracts, the authors ultimately included 113 articles in this analysis. Recurrence, complication rates, and onset of complication varied with the treatment chosen. The relative QOL at the 5-year follow-up was 0.898 of normal for wait and scan, 0.953 for microsurgery, and 0.97 for radiosurgery. These differences are significant (p < 0.0052). Data were too scarce at the 10-year follow-up to calculate significant differences between the microsurgery and radiosurgery strategies. Conclusions At 5 years, patients treated with radiosurgery have an overall better QOL than those treated with either microsurgery or those investigated further with serial imaging.
The authors found that the complications associated with wait-and-scan and microsurgery treatment strategies negatively impacted patient lives more than the complications from radiosurgery. One limitation of this study is that the 10-year follow-up data were too limited to analyze, and more studies are needed to determine if the authors’ results are still consistent at 10 years.

Postoperative complications in patients with cochlear implants and impacts of nursing intervention.

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Abstract Conclusion: This study shows that cochlear implantation is relatively safe surgery with few major complications and within acceptable limits. However, close follow-up observation and effective medical and nursing intervention could alleviate further complications and thus become key elements for promoting recovery of patients undergoing such surgery. Objectives: Cochlear implantation has become an effective method for curing patients disabled by profound hearing loss in China. However, full exploration of the associated complications remains to be completed. The objective of this study was thus to analyse the postoperative complications in patients with cochlear implants (CIs) in order to design improved measures for clinical and nursing interventions. Methods: A retrospective study of 262 patients receiving CIs at the Department of Otorhinolaryngology/Head and Neck Surgery, Chinese People’s Liberation Army General Hospital, Beijing, China from March 1997 to December 2006 was conducted. Results: Among 262 patients, 4 cases (1.5%) had 1 or more major complications requiring substantial medical or nursing interventions, including 1 case of cerebrospinal fluid (CSF) otorrhoea accompanied by meningitis, 2 cases of facial nerve paresis and 1 case of perforation of tympanic membrane. Forty cases (15.3%) had some form of minor complication that settled spontaneously or easily with conventional treatments and nursing, of which dizziness and vomiting was the most frequent (4.2%), followed by CSF gusher without otorrhoea and/or induced meningitis (2.7%), tinnitus (1.9%) and facial nerve partially exposed without paralysis (1.5%). Eleven cases (4.2%) had some symptoms associated with installation of the cochlear device. Except for one patient who had no response after implantation because his auditory nerves were underdeveloped, all the patients who received appropriate treatment and nursing intervention had a favourable prognosis.

Microvascular decompression for tinnitus: significant improvement for tinnitus intensity without improvement for distress. A 4-year limit.


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Objective: Microvascular compressions of the cochlear nerve can lead to tinnitus. The tinnitus initially is related to nonsynchronous signal transmission in the auditory nerve, neurophysiologically characterized by a peak II amplitude decrease. Chronic compression can lead to a focal demyelination, resulting in an increase in interpeak latency I-III with tinnitus and frequency-specific hearing loss as a consequence. Decompressing the cochlear nerve may result in improvement in tinnitus if the auditory nerve is not too damaged for recovery. The aim of the study is to find a cut-off point for this recovery based on clinical data. Materials and methods: Twenty patients undergo a microvascular decompression of the vestibulocochlear nerve for unilateral intractable tinnitus. Pre- and postoperative visual analogue scale for tinnitus intensity and tinnitus questionnaires for tinnitus distress are analyzed before and after microvascular decompression. Results: Of the 20 patients studied, 10 had improvements on their tinnitus visual analogue score intensity postoperatively, 8 were unchanged, and 2 worsened. On the Tinnitus
Questionnaire scores, 7 of 13 patients improved and 6 of the 13 patients worsened. If decompression is performed before the end of the 4th year of tinnitus duration, a significant tinnitus intensity improvement can be obtained (P < .05); after 4 years, improvement cannot be obtained (P = .55). However, the tinnitus distress does not seem to decrease significantly. CONCLUSION: Microvascular decompression of the cochlear nerve can improve tinnitus intensity in selected patients if decompression is performed early, before the end of the 4th year. Tinnitus distress does not seem to change.

A novel surgical technique for management of tinnitus due to high dehiscent jugular bulb.

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OBJECTIVES: To assess the effectiveness of middle ear floor reconstruction in management of vascular tinnitus due to high jugular bulb with dehiscent middle ear floor. STUDY DESIGN: Case series with chart review. SETTING: Tertiary academic medical center. SUBJECTS AND METHODS: We reviewed the medical records of seven patients with high dehiscent jugular bulb, presenting with incapacitating pulsatile roaring tinnitus that was abolished by digital compression of the ipsilateral jugular vein, from January 2002 to December 2006. The diagnosis was confirmed by CT scan of the temporal bone (bone window, coronal views). The seven patients were surgically explored, five under local anesthesia (to monitor the results with possible intraoperative revision) and two under general endotracheal anesthesia, for middle ear floor reconstruction that was done using bone dust, perichondrium, and tragal cartilage (mean follow-up 28 months). RESULTS: Of the seven patients, tinnitus disappeared in four (57%) and decreased in one. The overall improvement was five of seven (71%). One patient had postoperative increased intracranial pressure. CONCLUSION: The preliminary results suggest that surgical reconstruction of the middle ear floor under local anesthesia offers valuable treatment for patients with incapacitating tinnitus due to dehiscent middle ear floor. However, the risk of sigmoid sinus thrombosis should be considered. To our knowledge, this is the first trial of multilayer reconstruction of the middle ear floor dehiscence to manage high jugular bulb causing tinnitus. Copyright 2010 American Academy of Otolaryngology-Head and Neck Surgery Foundation. Published by Mosby, Inc. All rights reserved.

Superior semicircular canal dehiscence syndrome by the superior petrosal sinus.

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Thinning or dehiscence of the superior semicircular canal may occur on the middle cranial fossa floor or adjacent to the superior petrosal sinus (SPS). However, no symptomatic cases of superior canal dehiscence by SPS have been previously described. A 45-year-old woman presented with left-side pulsating tinnitus, autophony and disequilibrium. Examination showed conductive hearing loss and decreased threshold of vestibular evoked myogenic potential in the left side. Sound and vibration stimuli and positive pressure insufflations into the left ear evoked mainly torsional nystagmus instead of vertical-torsional nystagmus. High-resolution temporal bone CT revealed a dehiscence of the superior canal close to the common crus, which was encased by SPS. Symptoms and signs resolved after plugging the dehiscence through a middle fossa approach. Deep groove of SPS may cause superior canal dehiscence close to the common crus, and costimulation of the superior and posterior canals may explain the mainly torsional nystagmus induced by sound and vibration stimuli.
Intralabyrinthine schwannoma of the vestibulocochlear nerve


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AIM: Presenting and discussing the patient with intravestibular schwannoma of the vestibulocochlear nerve, the course of disease, audiologic and radiologic examination and treatment possibilities.

METHODS: Analysis of clinical presentation and treatment of the patient with intravestibular schwannoma and review of available literature on intralabyrinthine schwannomas. RESULTS: A 34-year-old male was diagnosed with a tumor localized in the left vestibule and semicircular canals without accompanying vertigo at any time of the disease but with tinnitus and total deafness of the left ear. Preoperative diagnosis was established on the basis of MRI with contrast. Localization of the tumor laterally to the fundus of internal auditory canal was essential for the diagnosis. Surgical treatment was chosen via translabyrinthine approach. Postoperative course was uneventful. DISCUSSION: Intralabyrinthine schwannoma are rare pathology. Their occurrence implies that schwannomas can originate at any segment of vestibulocochlear nerve. Most commonly intralabyrinthine schwannomas are observed at intracochlear or intravestibular localization. Present trials of these tumors classification were presented. The symptoms emerging in the course of disease are hearing loss, tinnitus, and vertigo, thus there were described patients with intralabyrinthine schwannomas diagnosed and treated as Meniere disease. Treatment depends on the intensity of symptoms and tumor expansion, while approach is dependant on its localization. CONCLUSION: Elaborate radiologic examination including MRI with contrast is essential in case of atypical course of disease with hearing loss, tinnitus and vertigo, or with early diagnosis of Meniere disease.

An unusual tumour of the cerebellopontine angle.


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An unusual tumour of the cerebellopontine angle. Objective: To report an extremely rare case of lipoma of the cerebellopontine angle (CPA). CASE REPORT: A 33-year-old woman presented with vertigo and tinnitus in the left ear. Her physical examination was unremarkable. Audiometric evaluation was normal in both ears. T1-weighted magnetic resonance imaging (MRI) without fat signal suppression revealed a hyperintense lesion of the left CPA. Based on the neuroimaging findings, the diagnosis was left CPA lipoma. The patient was managed conservatively. After 48 months, follow-up MRI revealed no further growth of the lesion and the patient was symptom free. CONCLUSION: Lipomas of the CPA should be considered in the differential diagnosis of vertigo and tinnitus. Accurate diagnosis by MRI is critical.

Suppurative chronic otitis media: etiology, diagnosis and therapy


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The chronic otitis media is defined as a permanent perforation of the drum membrane, which does not close by itself, and an inflammatory reaction in the mucosa (mucositis) of the middle ear. Two main forms of the chronic otitis media are distinct: the suppurative otitis media and the cholesteatoma. The suppurative otitis media is often accompanied by secretion into the external ear canal (otorrhoe), but „dry
ears" are also common. Other frequent, but not obligatory symptoms are hearing impairment, tinnitus, and aural pain or pressure. Although genetically determined microbial and immunological factors, as well as Eustachian tube characteristics, are supposed to be involved in the pathogenesis of chronic suppurative otitis media, many aspects of the pathogenesis still need to be clarified. Ear microscopy will show the perforation in the drum membrane. Further diagnostic tools are audiometry, vestibular testing, radiological examination (high-resolution computed tomography) and microbiological investigation. The curative treatment for chronic suppurative otitis media is surgery (tymanoplasty, i.e. closure of the perforation in the drum membrane and also—if necessary—the reconstruction of the ossicular chain), not conservative antimicrobial therapy.

**Surgery for Ménière's disease.**

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BACKGROUND: Ménière's disease is characterised by three major symptoms: vertigo, deafness, and tinnitus or aural fullness, all of which are discontinuous and variable in intensity. A number of surgical modalities, of varying levels of invasiveness, have been developed to reduce the symptoms of Ménière’s disease, but it is not clear whether or not these are effective. OBJECTIVES: To assess the effectiveness of surgical options for the treatment of Ménière’s disease. All surgical interventions used in the treatment of Ménière’s disease, either to alter the natural history of the disease or to abolish vestibular function, were considered for this review. SEARCH STRATEGY: We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. The date of the most recent search was 25 February 2009. SELECTION CRITERIA: Randomised or quasi-randomised controlled studies of a surgical modality versus a placebo therapy in Ménière’s disease. DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial quality and extracted data. Study authors were contacted for further information. MAIN RESULTS: The only surgical intervention which has been evaluated in randomised controlled trials and met the inclusion criteria was endolymphatic sac surgery. We identified two randomised trials, involving a total of 59 patients; one comparing endolymphatic sac surgery with ventilation tubes and one with simple mastoidectomy. Neither study reported any beneficial effect of surgery either in comparison to placebo surgery or grommet insertion. AUTHORS’ CONCLUSIONS: The two trials included in this review provide insufficient evidence of the beneficial effect of endolymphatic sac surgery in Ménière’s disease.

**Complications in retrosigmoid cranial nerve surgery.**

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CONCLUSIONS: Although microvascular decompression (MVD), facial nerve splitting (FNS) and neurectomy procedures were safe treatments for hemifacial spasm (HFS), trigeminal neuralgia (TN) and glossopharyngeal neuralgia (GPN) in retrosigmoid cranial nerve surgery, fatal and severe complications may occur. It is essential to pay great attention to the entire procedure to avoid these complications. OBJECTIVE: To report the complications of cranial nerve surgery via the retrosigmoid approach. PATIENTS AND METHODS: We reviewed 516 cases of cranial nerve surgery via the retrosigmoid approach for HFS, TN and GPN. There were 208 cases of HFS, of which 117 cases underwent FNS alone and 91 cases underwent combined MVD and FNS. There were 273 cases of TN treated by MVD and selective neurectomy. There were 35 cases of GPN treated by neurectomy.
RESULTS: Of the cases with complications, two (0.4%) died. Hearing impairment ranging from mild to severe occurred in 31 (6.0%) patients; 4 of these (0.8%) presented total hearing loss. Postoperative cerebrospinal fluid leakage occurred in 29 (5.6%) cases.

**Tinnitus and otosclerosis.**

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OBJECTIVE: To establish the origin of tinnitus in patients with otosclerosis. METHODOLOGY: We performed a literature review to identify the characteristics of tinnitus in the general population and among patients with otosclerosis. RESULTS: Characteristics of tinnitus among patients with otosclerosis differ from those among the general population, suggesting mechanisms other than those implicated in presbycusis. Considerable improvements in the prevalence of tinnitus following corrective surgery demonstrate the limited contribution of diffuse labyrinth lesions. Middle ear and possibly secondary inner ear dysfunction produced by stapes blockage appear to be major etiopathogenic factors in the development of tinnitus in patients with otosclerosis. CONCLUSION: The conductive hearing deprivation produced by otosclerosis is associated with limited and reversible modifications in the central auditory pathway that are linked to tinnitus.

**XI Holistics**

**Energy psychology and thought field therapy in the treatment of tinnitus.**

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Numerous treatment modalities for decompensated tinnitus incorporate psychological principles. Procedures of energy psychology and thought field therapy are introduced in two case studies. Data were collected from psychotherapy sessions and psychological tests. Two case studies demonstrated that thought field therapy reduces symptoms of depression and anxiety in decompensated tinnitus patients. The methods of thought field therapy can be taught to non-mental health professionals. Audiologists and psychotherapists should collaborate to develop more efficacious treatments.

**[The implications of cervical spine degenerative and traumatic diseases in the genese of cervical vertigo and hearingloss]**
[Article in Romanian]


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AIM: Cervical spine together with vestibular system,visual system and proprioceptive afferents plays an important role in mentaining balance. Spine damage causes distortions in transmitting informations to the brain,favoring vertigo. MATERIAL AND METHOD: The authors point out the occurrence of positional vertigo on 23 patients (20 patients with cervical spondylisis and 3 patients with cervical spine injury) due to blood flow disturbance through vertebral artery. RESULTS: The mechano-receptors located in intervertebral disks and cervical spine muscles are activated by column movement. Changes of blood flow in the vertebral and basilar arteries are showed up by cervical X-Rays, intracranial Doppler
ultrasound or angio-MRI, an audiogram marking out the degree of hearing loss or tinnitus occurrence. ENT complex treatment outcomes are analyzed and balneo-physio-therapy performed in order to improve vertigo and hearing loss. CONCLUSIONS: Stress beside muscle overload and cervical spine injures causes alteration in the ear blood-flow circulation that leads to hearing loss, vertigo and tinnitus. It emphasises the need for collaboration between balneologist and ENT specialist in solving balance and hearing disorders with cervicogenic cause.

**Eye movement abnormalities in somatic tinnitus: fixation, smooth pursuit and optokinetic nystagmus.**


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OBJECTIVE: Smooth pursuit (SP), optokinetic nystagmus (OKN) and fixation were investigated in five subjects with somatic tinnitus modulated by eye movements, jaw or neck. METHODS: Eye movements were recorded with the EyeLink II video system. RESULTS: (1) Fixation was characterized by high frequency and amplitude of saccade intrusions; (2) SP had low gain particularly in the vertical direction, and it was characterized by high frequency of catch-up saccades with high amplitude, including predictive saccades; (3) OKN also had low gain particularly in the vertical direction. Each subject showed abnormality for more than one type of eye movement, and for specific directions. CONCLUSIONS AND SIGNIFICANCE: The results suggest mild dysfunction of cortical-subcortical and cerebellar structures involved in the control of these eye movements. Particularly deficits for vertical pursuit eye movements and fixation instability in line with cerebellar signs. Further studies of more patients with or without modulated tinnitus are in progress. Copyright (c) 2009 Elsevier Ireland Ltd. All rights reserved.

**Stomatognathic adaptive motor syndrome is the correct diagnosis for temporomandibular disorders.**


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Temporomandibular disorder is a generic and inadequate conception to be used as a diagnosis. It fails to express the etiology or the pathophysiology and it is mainly associated with the anatomical site. Moreover, the clinical condition presents a mandibular motor problem and not a joint problem. The hypothesis presents the new diagnosis stomatognathic motor adaptive syndrome, which comprehend a motor response and the adaptive processes it induces. Inadequate occlusal contacts cause the mandible to shift in order to reach an ideal intercuspal position. The condylar displacements are proportional to such movements. Temporomandibular joint (TMJ) receptors respond to the capsular mechanical stress and the information reaches the trigeminal sensory nuclei. The mandibular modified position seems to be relevant information and may interfere with catecholaminergic neurotransmission in basal ganglia. The main motor responses comprise increased jaw muscle tone, decreased velocity of movements and incoordination. The overload of muscle function will produce adaptive responses on many stomatognathic structures. The muscle adaptive responses are hypertonia, pain, fatigue and weakness. Temporomandibular joint presents tissue modification, disc alteration and cracking noise. Periodontium show increased periodontal membrane, bone height loss and gingival recession. Teeth manifest increased wear facets, abfraction and non-accidental fractures. The periodontal and teeth adaptive processes are usually identified as occlusal trauma. The altered stomatognathic functions will show loss of velocity during mastication and speech. Fatigue, weakness in jaw muscle and difficulties to chew hard food are related to hypertonia. Incoordination between stomatognathic muscles groups is found, causing involuntary tongue/cheek biting and lateral jaw movements on speech. Otologic complaints, as aural fullness and tinnitus, are related to the tensor tympani muscle, innervated by the trigeminal nerve. © 2009 Elsevier Ltd. All rights reserved.
XII Review

Sudden sensorineural hearing loss.
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Schreiber BE, Agrup C, Haskard DO, Luxon LM.
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Sudden sensorineural hearing loss is usually unilateral and can be associated with tinnitus and vertigo. In most cases the cause is not identified, although various infective, vascular, and immune causes have been proposed. A careful examination is needed to exclude life threatening or treatable causes such as vascular events and malignant diseases, and patients should be referred urgently for further assessment. About half of patients completely recover, usually in about 2 weeks. Many treatments are used, including corticosteroids, antiviral drugs, and vasoactive and oxygen-based treatments. Although no treatment is proven, we recommend a short course of oral high-dose corticosteroids. There is much to learn about pathogenesis of sudden sensorineural hearing loss, and more clinical trials are needed to establish evidence-based management. Copyright 2010 Elsevier Ltd. All rights reserved

XIII Others

Discotheques and the risk of hearing loss among youth: risky listening behavior and its psychosocial correlates.
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There is an increasing population at risk of hearing loss and tinnitus due to increasing high-volume music listening. To inform prevention strategies and interventions, this study aimed to identify important protection motivation theory-based constructs as well as the constructs ‘consideration of future consequences’ and ‘habit strength’ as correlates of adolescents’ unsafe discotheque-visiting behavior. We invited 1687 adolescents (12-19 years old) at Dutch secondary schools to complete questionnaires about music-listening behaviors, sociodemographic characteristics and psychosocial determinants of behavior. Over 70% of participants reported to have visited discotheques; 24.6% of them were categorized as visitors at risk for hearing loss due to estimated exposure of 100 dBA for 1.25 hours per week or more without the use of hearing protection. Compared with visitors not at risk for hearing loss, those at risk were more likely not to live with both parents and less likely to consider future consequences and for them visiting high-volume music discotheques was more habitual. Risky exposure to high-volume music in discotheques is associated with several sociodemographic and psychosocial factors, with habit strength being the strongest correlate. Voluntary behavior change among adolescents might be difficult to achieve, because visiting discotheques seems to be strongly linked to current adolescent lifestyle.
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Introduction and aims: The School of Salerno stood as a landmark in the teaching and practice of medicine in the Western mediaeval world. Women could be both teachers and students and made significant contributions to its abundant scientific production. One of the most important of such women was Trotula of Salerno, the 12th century author of the Passionibus mulierum curandorum. De secretis mulierum, de chirurgia et de modo medendi libri septem is an anonymous medical poem from the School of Salerno, which was discovered in a manuscript from the 13th century. It consists of seven books and 7280 dactylic hexameters. The first book is specifically devoted to women's diseases and the second is a treaty on cosmetics. Books III and IV deal with surgery and follow the classical a capite ad calcem formula. The seventh book, De modo medendi, deals with therapeutics. We review the references to neurological diseases, using a critical translation of this text to carry out our study. Development: The poem proposes therapies to treat epilepsy, headache or tinnitus. The treatment to be prescribed for headache differs depending on its origin. It puts forward pathophysiological explanations for the different types of headache, it relates engorged blood vessels with hemicranial headache, and suggests an excess of phlegm as the origin of mild occipital headache. Conclusions: Neurological pathology is well represented in this mediaeval monograph on women’s diseases. Furthermore, it also shows us the vision that the Salerno physician has of these conditions and the therapeutic arsenal (based mainly on medicinal plants) that was available for use

Long-term prognosis of low-frequency hearing loss and predictive factors for the 10-year outcome.


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OBJECTIVES: To determine the long-term prognosis of low-frequency hearing loss and predictive factors for the 10-year outcome of low-frequency hearing loss. STUDY DESIGN: Case series with chart review. SETTING: Tertiary referral center. SUBJECTS AND METHODS: From 1979 to 1998, 466 consecutive patients with low-frequency hearing loss received initial treatment at the Hearing and Tinnitus Clinic of Keio University Hospital. Of the 49 eligible patients, pure-tone threshold data obtained over a period of 10 years after onset of low-frequency hearing loss were available for analysis. To determine the progression of hearing loss, we analyzed audiometric pattern changes. We also examined how the following factors affected 10-year prognosis: sex, age, side of hearing loss, accompanying dizziness, pre-therapeutic hearing thresholds at low frequencies, initial therapy results, and fluctuation of hearing during the first year after onset. RESULTS: High- and pan-frequency hearing loss increased as time progressed. About half of the cases developed high- or pan-frequency hearing loss within 10 years of onset. Audiometric patterns measured at 10 years significantly correlated with those measured at one (r = 0.57), three (r = 0.73), and five years (r = 0.85). The 10-year prognosis significantly correlated with only two factors: initial therapy results (r = 0.49) and fluctuation of hearing during the first year (r = 0.43). CONCLUSIONS: About half of the cases in our study developed high- or pan-frequency hearing loss within 10 years of onset of low-frequency hearing loss. The initial therapy results and fluctuation of hearing during the first year may indicate the long-term prognosis of patients presenting with low-frequency hearing loss. Copyright 2010 American Academy of Otolaryngology-Head and Neck Surgery Foundation. Published by Mosby, Inc. All rights reserved
Long-Term Outcome after Coil Embolization of Cavernous Sinus Arteriovenous Fistulas.


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BACKGROUND AND PURPOSE: Cranial nerve palsies are regularly observed in patients with arteriovenous fistulas of the cavernous sinus. The purpose of our study was to determine the long-term clinical outcome-with a special focus on extra-ocular muscular dysfunctions-in patients who had undergone endovascular treatment of a cavernous sinus fistula with detachable coils. MATERIALS AND METHODS: Sixteen patients were recalled for an ophthalmoneurologic control examination (mean interval of 4.4 years). The mRS and the EQ-5D questionnaire were used for the description of general outcome. Age, duration of symptoms, character of the fistula (direct, dural), and coil volume were tested to assess their relevance for persistent symptoms. RESULTS: All patients displayed complete regression of chemosis, exophthalmus, and pulsating tinnitus with no evidence of recurrences. Oculomotor disturbances persisted in 9 of 13 patients and caused permanent diplopia in 7 patients. In 15 patients a mRS score of 1 or 2 was achieved; however, 7 patients reported some limitations in life quality (EQ-5D). A significant correlation was found between coil volume and persistent diplopia (P = .032) and persistent cranial nerve VI paresis (P = .037). CONCLUSIONS: Coil embolization of the cavernous sinus led to durable closure of AVF and reliable regression of acute symptoms. However, long-term follow-up showed a 44% rate of persistent cranial nerve deficits with disturbances of oculomotor and visual functions. This may be explained by the underlying fistula size itself and/or the space-occupying effect of the coils. As neuro-ophthalmologic outcome is crucial for control of therapeutic success, patients should be routinely examined by ophthalmologists

A systematic review of telehealth applications in audiology.

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Abstract Hearing loss is a pervasive global healthcare concern with an estimated 10% of the global population affected to a mild or greater degree. In the absence of appropriate diagnosis and intervention it can become a lifelong disability with serious consequences on the quality of life and societal integration and participation of the affected persons. Unfortunately, there is a major dearth of hearing healthcare services globally, which highlights the possible role of telehealth in penetrating the underserved communities. This study systematically reviews peer-reviewed publications on audiology-related telehealth services and patient/clinician perceptions regarding their use. Several databases were sourced (Medline, SCOPUS, and CHINAL) using different search strategies for optimal coverage. Though the number of studies in this field are limited available reports span audiological services such as screening, diagnosis, and intervention. Several screening applications for populations consisting of infants, children, and adults have demonstrated the feasibility and reliability of telehealth using both synchronous and asynchronous models. The diagnostic procedures reported, including audiometry, video-otoscopy, oto-acoustic emissions, and auditory brainstem response, confirm clinically equivalent results for remote telehealth-enabled tests and conventional face-to-face versions. Intervention studies, including hearing aid verification, counseling, and Internet-based treatment for tinnitus, demonstrate reliability and effectiveness of telehealth applications compared to conventional methods. The limited information on patient perceptions reveal mixed findings and require more specific investigations, especially post facto surveys of patient experiences. Tele-audiology holds significant promise in extending services to the underserved communities but require considerable empirical research to inform future implementation.
A critical evaluation of Web sites offering patient information on tinnitus.

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The Internet is a vast information resource for both patients and healthcare professionals. However, the quality and content often lack formal scrutiny, so we examined the quality of patient information regarding tinnitus on the Internet. Using the three most popular search engines (google.com, yahoo.com, and msn.com), we found pertinent Web sites using the search term tinnitus. Web sites’ accountability and authorship were evaluated using previously published criteria. The quality of patient information about tinnitus was assessed using a new 10-point scale, the Tinnitus Information Value (TIV). Statistical analysis was performed using the independent sample t-test (p <or= 0.05). An electronic database of 90 Web sites was constructed using the first 30 English-language Web sites identified by each search engine. After duplicates and sites only containing links to other Web sites were eliminated, 39 remained. The mean score for accountability was 2.13 on scale of 0 to 7. The mean TIV was 5.0 on a scale of 0 to 10. Only 12 sites (30.8%) had their authors clearly identified. Twenty-two (56.4%) sites were sponsored by commercial interests or represented private practices. The mean TIV was significantly higher (p = 0.037) for noncommercial (personal, academic institution, or charity) sites (5.88 +/- 2.39 SD) than those representing commercial interests (4.32 +/- 2.10 SD). Tinnitus information available on the Internet is indeed variable, and care should be taken in recommending tinnitus Web sites to patients.

[Expert opinion of ORL for private accident insurance]
[Article in German]

Michel O, Brusis T.

Dienst KNO, Universitair Ziekenhuis - Vrije Universiteit Brussel UZ-VUB, Belgien. OMichel@uzbrussel.be

The provisions and the aims of private accident insurance are not comparable to those of the statutory accident insurance. The ear nose throat- (ENT-)specialist is often consulted on the question of a possible causality between an accident and sequelae. Loss of smell, taste disorder and loss of hearing are specified in a table with a fixed percentage for compensation. The individual invalidity for ear ringing, vertigo and other disorders have to be determined separately from this table. In private accident insurance a probability bordering on absolute certainty must be given when establishing a possible causal connection whereby mental reactions are excluded from compensation and all sequelae have to have continued for at least 3 years. The occupation or specific skills of the injured person are not essential for the judgement. The current jurisdiction and conditions of private accident insurance for tinnitus and vertigo have to be taken into consideration.

How Do We Find a Cure for Tinnitus? Approaches and Challenges for Medical Intervention Research
ARO-abstract

William Martin

Oregon Health & Science University

Although tinnitus management strategies are often successful at reducing the emotional and psychological impact of tinnitus, patients have one common desire – to turn the tinnitus off. The more we understand of the brain’s role in tinnitus, the higher the likelihood of accomplishing this goal. Brain-based strategies come in two main forms: One attempts to change the firing pattern of the brain through variations of electrical stimulation. The other attempts the same goal through modifying the chemistry of the brain. The hope is that abnormal firing patterns, perceived as tinnitus, can be eliminated.
Clinical research evolves in cycles. Clinical observation, exploration, trial and error help build hypotheses. The hypotheses then must be tested in extremely controlled, rigorous experiments designed to demonstrate whether or not an intervention really works, and if so, for whom. This presentation will discuss several brain-based interventions to disrupt tinnitus and also some of the great challenges facing tinnitus researchers conducting clinical trials.

XIV Case Reports

[Autoimmune hypophysitis - a differential diagnosis to pituitary adenomas.]
[Article in Danish]

Krarup T, Hagen C.

Ringkøbinggade 10. 4. th., DK-2100 København Ø. theresekrarup@hotmail.com.

A 66-year-old man with a headache in the left temporal region which had persisted for eight months is presented. The patient developed polydipsia and polyuria and also suffered from tinnitus, impaired hearing and episodes of double vision. The patient was diagnosed with autoimmune hypophysitis (AH) in 2007. This case story displays the importance of knowing AH, as it is an important differential diagnosis to pituitary gland adenomas and to diseases in the hypothalamus because it can be treated medically as opposed to surgically

Carbamazepine responsive typewriter tinnitus from basilar invagination.

Nam EC, Handzel O, Levine RA.

Department of Otolaryngology, College of Medicine, Kangwon National University, Chunchon, Korea.

Comment in:

Basilar invagination due to a congenital skeletal disorder kinked the brainstem at the ponto-medullary junction causing both auditory nerves to make an acute turn at the porus acusticus. The associated bilateral asynchronous clicking tinnitus responded to carbamazepine

Resolution of Pulsatile Tinnitus Following an Upper Mediastinal Lymph Node Resection.

Wang YZ, Boudreaux JP, Campeau RJ, Woltering EA.

From the Department of Surgery, Section of Surgical Oncology and Endocrinology, Louisiana State University, New Orleans; and Ochsner Medical Center-Kenner, Kenner, LA.

External compression of extracranial/mediastinal vessels has not been reported as an etiology of pulsatile tinnitus. We present a case in which compression of extracranial vasculature led to long term pulsatile tinnitus which resolved completely with surgical resection of metastatic lymph nodes. This should be included in the list of differential diagnoses when dealing with any patient with a complaint of pulsatile tinnitus. Patients with advanced carcinoid cancer often present with distant metastases to their left superior mediastinum and supraclavicular lymph node chain. We believe a careful search for nodal metastases compressing vascular structures in such patients is warranted as debilitating pulsatile tinnitus may be cured by a simple surgical procedure.
Gorham-Stout disease of the temporal bone.
Laryngoscope. 2010 Mar;120(3):598-600.

Mowry S, Canalis R.
Division of Otolaryngology-Head and Neck Surgery, University of California at Los Angeles, Los Angeles, California 90033, USA. smowry1978@gmail.com

Gorham-Stout (GS) disease is a rare disease of the bone and is also known as massive osteolysis. Less than 200 cases have been reported in the world literature. A 29-year-old female with a diagnosis of GS disease was identified. She complained of aural fullness and tinnitus bilaterally. Demineralization and moth-eaten changes of the osseous structures of the skull base and posterior fossa were prominent. The left mastoid air cells were opacified and erosion extended to the left jugular foramen, left hypoglossal canal, left stylomastoid process, and left eustachian tube. The radiographic findings and brief literature review are presented

[Tinnitus as a symptom of spontaneous cerebral vein thrombosis.]
[Article in German]
HNO. 2010 Feb 3. [Epub ahead of print]

Happe E, Bonacker M.
Hals-, Nasen- und Ohrenheilkunde, Schlafmedizin, Praxis/Belegabteilung/Schlaflabor, Oskar-Schlemmer-Strasse 14, 22117, Hamburg, Deutschland.

Cerebral venous thrombosis (CVT) is a rare cause of tinnitus and headache. We report the case history, clinical presentation, physical examination, imaging studies, therapy, course and outcome of a young patient with CVT. In addition, we present another case with similar findings and varying causes, which could lead to misdiagnoses. With prompt diagnosis and therapy of CVT, full recovery is possible.

Head rotation evoked tinnitus due to superior semicircular canal dehiscence.

Nam EC, Lewis R, Nakajima HH, Merchant SN, Levine RA.
Department of Otolaryngology, School of Medicine, Kangwon National University, Chunchon, South Korea.

INTRODUCTION: Superior semicircular canal dehiscence affects the auditory and vestibular systems due to a partial defect in the canal's bony wall. In most cases, sound- and pressure-induced vertigo are present, and are sometimes accompanied by pulse-synchronous tinnitus. CASE PRESENTATION: We describe a 50-year-old man with superior semicircular canal dehiscence whose only complaints were head rotation induced tinnitus and autophony. Head rotation in the plane of the right semicircular canal with an angular velocity exceeding 600 degrees/second repeatedly induced a ‘cricket’ sound in the patient’s right ear. High resolution temporal bone computed tomography changes, and an elevated umbo velocity, supported the diagnosis of superior semicircular canal dehiscence. CONCLUSION: In addition to pulse-synchronous or continuous tinnitus, head rotation induced tinnitus can be the only presenting symptom of superior semicircular canal dehiscence without vestibular complaints. We suggest that, in our patient, the bony defect of the superior semicircular canal (‘third window’) might have enhanced the flow of inner ear fluid, possibly producing tinnitus.
Neuro-Behçet's disease with dizziness.  

Sugita-Kitajima A, Koizuka I.  
Dept of Otolaryngology, St. Marianna Univ, School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa, Japan. akemiffy@bk2.so-net.ne.jp

A 30-year-old man had complete-type Behçet's disease since he was 23 years old. Disease signs and symptoms were well controlled. After experiencing no symptoms for some years, however, he experienced dizziness, headache, fever, dysarthria, right facial nerve palsy, and right tinnitus. He showed spontaneous horizontal-rotatory nystagmus directed toward the right side, and upbeat nystagmus. T2-weighted and fluid-attenuated inversion recovery MRI showed slight hyperintense signals in the medulla oblongata, pons, and left midbrain. Neurological involvement in Behçet's disease was diagnosed.

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Parallel transverse-sigmoid sinus harboring dural arteriovenous malformation. How to differentiate the pathological and normal sinus in order to treat and preserve patency and function.  

de Paula Lucas C, Prandini MN, Spelle L, Piotin M, Mounayer C, Moret J.  
Dept of Neurosurgery of the Federal University of São Paulo, São Paulo, Brazil. cesar.lucas@uol.com.br

An unusual case of dural arteriovenous malformation (DAVM) harboring a parallel transverse-sigmoid sinus (TSS) is presented. The patient had a 2-year history of left-sided pulsatile tinnitus in the left ear refractory to medical management. Angiography demonstrated a DAVM involving the left TSS. Super-selective transvenous dural sinus occlusion of the DAVM situated at the pathological compartment of the TSS provided cure. We were able to spare the normal compartment providing anatomical venous drainage from this system.

Vestibulocochlear toxicity in a pair of siblings 15 years apart secondary to aspartame: two case reports.  
Cases J. 2009 Sep 15;2:9237.

Pisarik P, Kai D.  
University of Oklahoma College of Medicine, Tulsa, 1111 S. St. Louis Ave. Tulsa, OK 74120-5440, USA.

INTRODUCTION: Aspartame may have idiosyncratic toxic effects for some people; however, there are few case reports published in the medical literature. We present two case reports in a pair of siblings, one with a vestibular and the other with a cochlear toxicity to aspartame. The cochlear toxicity is the first case to be reported, while the vestibular toxicity is the second case to be reported. CASE PRESENTATION: A 29-year-old white female had a 20-month history of nausea and headache, progressively getting worse with time and eventually to also involve vomiting, vertigo, and ataxia. She was extensively evaluated and diagnosed with a vestibular neuronitis versus a chronic labyrinthitis and treated symptomatically with limited success. In response to a newspaper article, she stopped her aspartame consumption with total cessation of her symptoms. Fifteen years later, her then 47-year-old white brother had a 30-month history of an intermittent, initially 5-10 minute long episode of a mild sensorineural hearing loss in his right ear that progressed over time to several hour episodes of a moderately severe high-frequency sensorineural hearing loss to include tinnitus and a hypoesthetic area in front of his right tragus. After a negative magnetic resonance scan of the brain, he remembered his sister's experience with aspartame and stopped his consumption of aspartame with resolution of his symptoms, although the very high frequency hearing loss took at least 15 months to resolve. For both, subsequent intentional challenges with aspartame and unintentional exposures brought back each of their respective symptoms. CONCLUSION: Aspartame had a vestibulocochlear toxicity in a pair of siblings, suggesting a genetic susceptibility to aspartame toxicity. Even though the yield may be low, asking patients with dizziness, vertigo, tinnitus, or high-frequency hearing loss about their aspartame consumption and suggesting cessation of its use, may prove helpful for some.
Clinical Trials

Source: clinicaltrials.gov (24th April 2010)

Clinical Trial of Transcranial Magnetic Stimulation for Relief of Tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
<th>not yet open for participant recruitment</th>
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</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Department of Veterans Affairs</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01104207</td>
</tr>
<tr>
<td>Purpose</td>
<td>The purpose of this study is to assess the effectiveness of repetitive transcranial magnetic stimulation (rTMS) for reducing the loudness or severity of chronic tinnitus.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
</tbody>
</table>
| Interventions                | Device: repetitive transcranial magnetic stimulation (rTMS)  
                               | Device: placebo rTMS                     |
| Study type and design        | Intervventional; Allocation: Randomized  
                               | Endpoint Classification: Efficacy Study  
                               | Intervention Model: Parallel Assignment  
                               | Masking: Double Blind (Subject, Caregiver, Outcomes Assessor)  
                               | Primary Purpose: Treatment                  |
| Official title               | Clinical Trial of Transcranial Magnetic Stimulation for Relief of Tinnitus |
| Arms                         | 1: Experimental  
                               | For half of the subjects, rTMS will be delivered to one side of the head and placebo rTMS will be delivered to the other side of the head simultaneously.  
                               | 2: Sham Comparator  
                               | For half of the subjects, placebo rTMS will be delivered to both sides of the head simultaneously. |
| Assigned Interventions       | 1: Device: repetitive transcranial magnetic stimulation (rTMS)  
                               | rTMS involves application of electromagnetic pulses through a coil to the subject’s scalp. Some of the electromagnetic energy is transmitted to underlying neural tissue. The goal for this study: 1 Hz rTMS will suppress neural activity responsible for tinnitus perception.  
                               | Device placebo rTMS  
                               | placebo rTMS  
                               | 2: Device: placebo rTMS  
<pre><code>                           | placebo rTMS |
</code></pre>
<p>| Primary Outcomes             | Tinnitus Handicap Inventory score [Time Frame: 1, 2, 4, 13 and 26 weeks post-treatment] [Designated as safety issue: No] |
| Secondary Outcomes:          | Tinnitus loudness [Time Frame: 1, 2, 4, 13 and 26 weeks post-treatment] [Designated as safety issue: No] |
| Expected total Enrollment    | 168                                     |</p>
<table>
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<tr>
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<td>June 2014</td>
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<td>March 2014</td>
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<td>Date (Final data collection date for primary outcome measure)</td>
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<tr>
<td>Participants (age)</td>
<td>18 Years and older</td>
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<tr>
<td>Gender</td>
<td>both</td>
</tr>
<tr>
<td>Accepts health volunteers</td>
<td>yes</td>
</tr>
</tbody>
</table>
| Eligibility Inclusion Criteria      | Diagnosis of chronic tinnitus.  
• Able to provide written informed consent.  
• Subject is naive regarding rTMS.  
• Age/Gender: minimum 18 years old, with an attempt to sample equal numbers of male and female subjects.  
• Other concurrent treatments: A four-week washout from any other tinnitus treatment or management program is required prior to entering this study.  
• Other medications: No restrictions, provided the dosages have been in place for at least 6 months.  
• Psychological status: Stable enough to complete this study per the opinion of the Study Physician.  
• Hearing function: All degrees of hearing function can be included recognizing that profound, bilateral losses will not be able to perform tinnitus evaluations and hearing tests, but will be able to rate subjective tinnitus loudness, annoyance and impact on life. This is an important subpopulation because of the challenges in treating them with acoustic therapy and the need for a medical intervention.  
• Tinnitus characteristics: All forms of tinnitus etiology will be accepted, providing the following criteria are met:  
  o Tinnitus duration: Not less than 1 year. Cases of less than 1 year duration have increased likelihood of resolving spontaneously.  
  o Stability: Constant (not pulsatile, intermittent, varying to a high degree in loudness or changing in location of perception). Fluctuating tinnitus reduces the reliability of test-retest measures for loudness.  
  o Tinnitus Severity: a score of 38 on the Tinnitus Handicap Inventory questionnaire. As with all measures in this study, it is important that the beginning points of severity are high enough to show improvement with treatment.  
  o Self-rated tinnitus loudness: > 6 on a visual numerical scale (VNS: 0 labeled “No Tinnitus”, 10 labeled “Very Loud”). This outcome measure will provide a subjective indication of immediate changes in perceived loudness.  
  o Location of tinnitus perception: Unrestricted. Tinnitus may be unilateral, bilateral, or perceived in the head. |
| Eligibility Exclusion Criteria       | Medical conditions: No active neurologic or otologic disease processes that may impact tinnitus perception. No autoimmune diseases. No pregnancy or planned pregnancy during the study. No women who are lactating or are of child-bearing-age without using contraception. |
Objective Tinnitus - tinnitus that is audible to other people in addition to the patient. This type of tinnitus is rare and is unlikely to respond to rTMS because it is not associated with abnormal neural activity in the central auditory system.

- History or evidence of significant brain malformation or neoplasm, head injury, cerebral vascular events (such as strokes), neurodegenerative disorders affecting the brain (such as Parkinson’s Disease, ALS, Huntington’s Disease or Multiple Sclerosis) or prior brain surgery.
- Cardiac pace makers, other electronic implants (including cochlear implants), intracranial or intraocular metallic particles.
- History of seizures or epileptic activity.
- Patients who cannot communicate reliably with the investigator or who are not likely to cope with the requirements of the trial.
- Participation in a clinical trial within the last 30 days before the start of this one.
- Maximum number of previous clinical trials for tinnitus in which subjects may have participated: two.

Contact
Robert Folmer, PhD, phone (503) 220-8262 ext 51868; robert.folmer@va.gov

Locations
VA Medical Center, Portland, Portland, Oregon, United States, 97201

Study chairs or principal investigators
Robert Folmer, PhD, VA Medical Center, Portland

Responsible Party
Department of Veterans Affairs (Robert Folmer - Principal Investigator)

Study ID Numbers
C7448I

Last Updated
April 13, 2010

Record first received
April 13, 2010

ClinicalTrials.gov Identifier
NCT01104207

Health Authority
United States: Federal Government

Resting-State Neural Connectivity in Patients With Subjective Tinnitus Without Bother

Current status
not yet open for participant recruitment

Sponsors and collaborators
Washington University School of Medicine

Information provided by
Washington University School of Medicine

ClinicalTrials.gov Identifier
NCT01049828

Purpose
Tinnitus is the occurrence of an auditory sensation without the presence of an acoustic stimulus. Approximately, 50 million people in the United States experience chronic tinnitus and 15 million of these people have bothersome tinnitus. Several studies have shown that people who are bothered by their tinnitus have difficulty in concentration and focus. Through imaging modalities we have deranged neural networks responsible for attention. Only 20 percent of patients diagnosed with tinnitus are severely bothered. We seek the following:
1. Match a group of non-bothered tinnitus patients on age and hearing status to an existing cohort of bothered tinnitus patients.

2. Assess the resting-state neural connectivity in patients with non-bothersome tinnitus. Findings from the comparison of functional connectivity magnetic resonance imaging (fcMRI) from subjects with bothersome tinnitus in our current rTMS clinical trial to normal age-matched controls without tinnitus demonstrates that subjects with bothersome tinnitus have dramatic alterations in cortical attention and control networks. Our hypothesis is that the fcMRI-defined changes in the attention and control networks reflect the impact of excessive auditory stimulation in patients with bothersome tinnitus and explains the difficulty with concentration, short-term memory, and other common problems. To fully test this hypothesis we need to obtain fcMRI of the attention network among subjects with tinnitus but without bother and compare the status of their neural networks with those of tinnitus subjects with bother and with normal controls.

3. Compare the resting cortical networks in subjects with non-bothersome tinnitus to subjects with bothersome tinnitus and subjects without tinnitus. Our null hypothesis is that there are no differences in the resting-state cortical networks, especially the attention and control networks, between tinnitus patients who do not experience bother, tinnitus patients who do experience bother, and subjects without tinnitus. Through fcMRI, we will examine correlations in blood oxygen level dependent (BOLD) signals in established auditory, attention, control, and other brain regions in the resting brain and compare these findings to already collected fcMRI scans of bothered tinnitus patients, and controls (patients without tinnitus).

<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>Tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Other: No intervention</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Observational; Observational Model: Case-Only Time Perspective: Cross-Sectional</td>
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<tr>
<td>Official title</td>
<td>Resting-State Neural Connectivity in Patients With Subjective Tinnitus Without Bother</td>
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<tr>
<td>Biospecimen Retention</td>
<td>None retained</td>
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<tr>
<td>Groups/Cohorts</td>
<td>Slightly or Non-Bothered Tinnitus Group</td>
</tr>
<tr>
<td>Assigned Interventions</td>
<td>Other: No intervention No treatment for tinnitus will occur in this study</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Recruit 20 participants and have them undergo both neuro-cognitive and neuro-imaging testing. [ Time Frame: 8 months ] [ Designated as safety issue: No ]</td>
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<tr>
<td>Expected total Enrollment</td>
<td>20</td>
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<tr>
<td>Participants (age)</td>
<td>18 Years to 60 Years</td>
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<td>----------------------</td>
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<tr>
<td>Accepts health volunteers</td>
<td>yes</td>
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<tr>
<td>Sampling Method</td>
<td>Non-Probability Sample</td>
</tr>
</tbody>
</table>

**Study Population**

20 adults between the ages of 45 and 60 years, age and hearing level-matched to the bothered tinnitus cohort from the on-going research at Washington University. Subjects will be recruited from an institutional tinnitus database, from Washington University Otolaryngology Clinics, as well as the general public through poster advertisement on the Washington University grounds.

**Eligibility Inclusion Criteria**

- Men and women between the ages of 18 and 60 years
- Subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month’s duration or greater
- A recent audiogram (within 6 months)
- Either “not bothered” or “bothered a little” on the Global Bothersome scale
- Able to give informed consent
- English-speaking

**Eligibility Exclusion Criteria**

- Patients experiencing tinnitus related to cochlear implantation, retrocochlear lesion, or other known anatomic/structural lesions of the ear and temporal bone
- Patients with hyperacusis or misophonia (hyper-sensitivity to loud noises)
- Patients with cardiac pacemakers, intracardiac lines, implanted medication pumps, implanted electrodes in the brain, other intracranial metal objects with the exception of dental fillings, or any other contraindication for MRI scan
- Patients with an acute or chronic unstable medical condition which, in the opinion of the investigator, would require stabilization prior to initiation of magnetic stimulation
- Patients with any active ear disease that, in the opinion of the PI, needs to be further evaluated
- Patients with symptoms of depression as evidenced by a score of 14 or greater on the Beck Depression Inventory or, in the opinion of the psychiatrist sub-investigator demonstrates active mood symptoms that meet DSM-IV-TR criteria for Major Depressive Disorder
- Any psychiatric co-morbidity that, in the opinion of the psychiatrist sub-investigator, may complicate the interpretation of study results
- Patients with tinnitus related to Workman’s Compensation claim or litigation-related event
- Weight over 350 pounds
- A Mini-Mental Status Exam42 score less than 27
- Patients with a history of claustrophobia
- Inability to lay flat for 2 hours
- Active alcohol and/or drug dependence or history of alcohol and/or drug dependence within the last year
- Any medical condition that, in the opinion of the investigators, confounds study results or places the subject at greater risk
- Unable to provide informed consent
- Any exclusions from radiology screening
### Somatosensory Based Treatments for Tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
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<tr>
<td>Sponsors and collaborators</td>
<td>Massachusetts Eye and Ear Infirmary</td>
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<td>Information provided by</td>
<td>Massachusetts Eye and Ear Infirmary</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01066273</td>
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</tbody>
</table>

**Purpose**

Studies have established that the somatosensory system of the upper cervical region and head can be intimately involved in tinnitus. Tinnitus can arise directly from a disorder of the head and upper neck via the somatosensory system. Our clinical experience and review of reports of various types of treatments support the hypothesis that treatment modalities involving the somatosensory system can benefit individuals whose tinnitus is likely on a somatosensory basis, namely people with symmetric hearing thresholds but asymmetric widely fluctuating tinnitus. However, these previous studies did not (a) limit their treatment population to only people with tinnitus on a somatosensory basis and (b) did not assess their results by considering this tinnitus subpopulation separately from the entire group of tinnitus subjects they treated. Hence, the purpose of this study is to re-assess these treatments by targeting people whose audiograms cannot account for their tinnitus, such as individuals with symmetric hearing thresholds but asymmetric widely fluctuating tinnitus.

**Condition(s)**

Tinnitus

**Interventions**

Device: P-Stim

**Study type and design**

Interventional; Allocation: Non-Randomized; Control: Historical Control; Endpoint Classification: Efficacy Study
#### Intervention Model: Single Group Assignment

- **Masking:** Open Label
- **Primary Purpose:** Treatment

#### Official title:
Somatosensory Based Treatments for Tinnitus

#### Arms
- **P-Stim device:** Experimental
- Receiving the device that is activated

#### Assigned Interventions

**Device:** P-Stim

The P-Stim is a battery-powered, transcutaneous electrical stimulator that delivers 1 per second bipolar 1 millisecond pulses to three points on the auricle. The device connects via three fine insulated stainless steel wires to three needles (each 0.4 mm diameter, 2 mm long) that have been applied to three different points on the auricle. The device is powered by three zinc air batteries, each with a voltage of 1.4 V. The device is on for 180 minutes, then off for 180 minutes, for a maximum period of up to 96 hours. The battery and electronics are contained in a 6 mm by 2.5 mm pack that has one adhesive surface which is applied to the skin behind the ear. The adhesive is conductive and acts as the return for the device. The battery pack is secured with tape.

#### Detailed description

Until recently our attempts over the years at treatment of patients with such types of tinnitus has met with little or no success. These treatments have included cervical physical therapy and dental treatments for bruxism. A few with such tinnitus responded have had some benefit from acupuncture applied to their periauricular region. A small formal trial with a few patients did not provide any relief. However a literature review (Levine et al., 2007) found a consistent line of evidence for a tinnitus subgroup responsive to somatosensory based treatment modalities, including electrical stimulation in the periauricular region, and acupuncture. Furthermore an electrical stimulation device of the auricle P-Stim was found to be more effective than standard acupuncture for a variety of conditions, including chronic cervical and low back pain. For this convergence of reasons we have initiated an open trial with P-Stim over the past 11 months. In a sense we have used it in an “off-label” capacity; just as many medications have been found to be useful for conditions for which the medications were not developed (see Levine 2006).

The P-Stim is a battery-powered, transcutaneous electrical stimulator that delivers 1 per second bipolar 1 millisecond pulses to three points on the auricle. The device connects via three fine insulated stainless steel wires to three needles (each 0.4 mm diameter, 2 mm long) that have been applied to three different points on the auricle. The device is powered by three zinc air batteries, each with a voltage of 1.4 V. The device is on for 180 minutes, then off for 180 minutes, for a maximum period of up to 96 hours. The battery and electronics are contained in a 6 mm by 2.5 mm pack that has one adhesive surface which is applied to the skin behind the ear. The adhesive is conductive and acts as the return for the device. The battery pack is secured with tape.

We have met with some success using P-Stim for what appear to be two tinnitus subgroups: somatic pulsatile tinnitus syndrome (Levine et al., 2008) and patients with non-pulsatile unilateral fluctuating tinnitus associated with deep ear pain.

#### Primary Outcomes

- Quieter tinnitus [Time Frame: 6 months ] [Designated as safety issue: No]

#### Expected total Enrollment

60
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<tr>
<td>Accepts health volunteers</td>
<td>no</td>
</tr>
<tr>
<td>Eligibility Inclusion Criteria</td>
<td>Age range: above age 18</td>
</tr>
</tbody>
</table>
| Eligibility Exclusion Criteria | • people with a bleeding disorder,  
• and those on coumadin will be excluded |
| Responsible party | Massachusetts Eye and Ear Infirmary (Robert A. Levine) |
| Study ID Numbers | 08-12-056 |
| Last Updated | February 9, 2010 |
| Record first received | February 8, 2010 |
| ClinicalTrials.gov Identifier | NCT01066273 |
| Health Authority | United States: Institutional Review Board |

**Repetitive Transcranial Magnetic Stimulation for Tinnitus Treatment**

<table>
<thead>
<tr>
<th>Current status</th>
<th>currently recruiting participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Singapore General Hospital</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Singapore General Hospital</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01093872</td>
</tr>
<tr>
<td>Purpose</td>
<td>In this study, we perform an open-label rTMS over the left AC on patients with tinnitus. Outcome measures will be evaluated statistically. The results will be instrumental in deciding the efficacy of this technique in a local patient group.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>Device: Repetitive Transcranial Magnetic Stimulation (rTMS)</td>
</tr>
</tbody>
</table>
| Study type and design | Interventional; Intervention Model: Single Group Assignment  
Masking: Open Label  
Primary Purpose: Treatment |
<table>
<thead>
<tr>
<th>Official title:</th>
<th>Repetitive Transcranial Magnetic Stimulation for Tinnitus Treatment</th>
</tr>
</thead>
</table>
| Intervention details | Device: Repetitive Transcranial Magnetic Stimulation (rTMS)  
Upon recruitment, all patients will undergo a 1 week treatment consisting of 5 rTMS sessions  
Repetitive TMS consists of 2000 stimulations/ day at 1 Hz and 110% of the motor threshold, for five consecutive days over the left AC |
| Detailed description | Tinnitus is a subjective auditory perception of sounds or noise not triggered by external auditory stimuli, affecting millions of people worldwide. To date, pharmacological and physical/ behavioural treatments in severe cases are generally unsatisfactory. Functional brain imaging changes associated with tinnitus include hyperactivity of discrete temporoparietal regions, including both the primary auditory cortex (AC) and the secondary, or associative cortex. High-frequency rTMS (10 Hz or more) applied on the scalp overlying the hyperactive left AC produced an intense tinnitus attenuation.  
Repetitive TMS consists of 2000 stimulations/ day at 1 Hz and 110% of the motor threshold, for five consecutive days over the left AC. A high number of stimuli/day were applied because of the previously suggested dose dependency of tinnitus alleviation by rTMS. Furthermore, the use of such relatively high intensity assured the stimulation of most of the target region, even in the case of mismatch between the scalp position and the underlying anatomy, which can be expected using the International EEG system as anatomical reference for TMS stimulation.  
Upon recruitment, all patients will undergo a 1 week treatment consisting of 5 rTMS sessions. Tinnitus rating will be performed weekly.  
Tinnitus is rated by a 0-100 Visual Analogue Scale (VAS), where 0 is wellness and 100 the worst possible tinnitus related discomfort. In addition, our validated Tinnitus Inventory scoring will be administered. Audiometry and otoscopy will be performed at enrolment and at the end of the study. Tinnitus, and acoustic evaluations are then collected by experimenters blind to the type of rTMS applied. Standard statistical methods (SPSS for Windows) will be used to perform comparisons. |
| Primary Outcomes | Tinnitus Inventory Handicap scoring & Visual Analogue Scale (VAS) [Time Frame: Baseline, 1,2,3 & 4weeks after treatment ] [Designated as safety issue: No ]  
THI and VAS is measure before the treatment and weekly for 4 weeks after the treatment |
| Expected total Enrollment | 100 |
| Study start | August 2008 |
| Estimated Study Completion Date: | May 2011 |
| Estimated Primary Completion Date: | May 2011 (Final data collection date for primary outcome measure) |
| Participants (age) | 21 Years to 90 Years |
| Gender | both |
| Accepts health volunteers | no |
Eligibility Inclusion Criteria | All patients with tinnitus
---|---
Eligibility Exclusion Criteria | Patients with contraindications to TMS: pacemaker, intracranial surgery, implants and seizures

**contact**
YL Lo, MD; phone: 63265003; lo.yew.long@sgh.com.sg
Priscilia Cheong; priscila.cheong.w.t@sgh.com.sg

**Location**
Singapore General Hospital, Singapore, Outram Road, Singapore, 169608

**Principal Investigator**
YL Lo, MD, National Neuroscience Institute, Singapore General Hospital

**Responsible party**
Singapore General Hospital campus, National Neuroscience Institute (A/Prof Lo Yew Long)

**Study ID Numbers**
#2008/061/A

**Last Updated**
March 24, 2010

**Record first received**
March 24, 2010

**ClinicalTrials.gov Identifier**
NCT01093872

**Health Authority**
Singapore: Health Sciences Authority

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**OTO-104 for Meniere's Disease**

**Current status**
currently recruiting participants

**Sponsors and collaborators**
Otonomy, Inc.

**Information provided by**
Otonomy, Inc.

**ClinicalTrials.gov Identifier**
NCT01084525

**Purpose**
The purpose of this study is to evaluate the safety of OTO-104 in subjects with unilateral Meniere's disease. The effectiveness of OTO-104 to reduce the symptoms of Meniere's disease will also be evaluated.

**Condition(s)**
Menière's Disease

**Interventions**
Drug: OTO-104 (steroid) 3 mg
Drug: Placebo
Drug: OTO-104 (steroid) 12 mg

**Phase**
I

**Study type and design**
Interventional; Allocation: Randomized Control: Placebo Control Endpoint Classification: Safety Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Official title: A Prospective, Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 1B Study of OTO-104 Given as a Single Intratympanic Injection in Subjects With Unilateral Meniere's Disease

Arms
1) OTO-104 (steroid) 3 mg: Experimental
2) Placebo: Placebo Comparator
3) OTO-104 (steroid) 12 mg: Experimental
   The start of 12 mg dose cohort is contingent on safety data from 3 mg dose cohort.

Assigned Interventions
1) Drug: OTO-104 (steroid) 3 mg
   OTO-104 3 mg dose cohort, single intratympanic injection.
2) Drug: Placebo
   Placebo arm will be conducted in parallel with each OTO-104 dose cohort.
3) Drug: OTO-104 (steroid) 12 mg
   Sequential dose cohort escalation to OTO-104 12 mg dose cohort will occur pending the safety evaluation of 28 day follow up safety data for the OTO-104 3 mg dose cohort. OTO-104 12 mg dose cohort is also a single intratympanic injection.

Detailed description
Meniere's disease is a debilitating disorder of the inner ear which includes symptoms such as vertigo, tinnitus, hearing loss and aural fullness. Meniere's disease may result from an imbalance of fluid in the inner ear. Several studies have shown that corticosteroids may help manage this imbalance yet the effect does not last very long. OTO-104 is a longer lasting corticosteroid which could provide significant benefit to patients with Meniere's disease.

Primary Outcomes
The primary objective of this study is to evaluate the safety and tolerability of two ascending OTO-104 doses relative to placebo. Safety assessments will be performed for 3 months post single intratympanic injection of OTO-104 or placebo. [Time Frame: 3 months] [Designated as safety issue: Yes]

Secondary Outcomes
• The secondary objective of this study is to evaluate the clinical activity of two OTO-104 doses relative to placebo. Change in baseline for vertigo frequency will be evaluated with descriptive statistics. [Time Frame: 3 months] [Designated as safety issue: No]
• The impact of tinnitus on activities of daily living will be measured. [Time Frame: 3 months] [Designated as safety issue: No]
• Hearing loss in the affected ear will be measured by audiometric examination. [Time Frame: 3 months] [Designated as safety issue: No]
• Quality of life will be measured by patient reported questionnaire. [Time Frame: 3 months] [Designated as safety issue: No]
• Severity of vertigo episodes will be measured by the patient reported vertigo score. [Time Frame: 3 months] [Designated as safety issue: No]

Expected total Enrollment
42

Study start
March 2010

Estimated Study Completion Date:
February 2011

Estimated Primary Completion Date:
December 2010 (Final data collection date for primary outcome measure)
<table>
<thead>
<tr>
<th>Participants (age)</th>
<th>18 Years to 60 Years</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>both</td>
</tr>
<tr>
<td>Accepts health volunteers</td>
<td>no</td>
</tr>
</tbody>
</table>

### Eligibility Inclusion Criteria
1. Subject has a diagnosis of unilateral Meniere’s disease by 1995 American Academy of Otolaryngology — Head and Neck Surgery (AAOHNS) criteria and reports active vertigo for the 2 months prior to the study lead-in period.
2. Subject has experienced active vertigo during the lead-in period.
3. Subject has asymmetric low frequency sensorineural hearing loss.
4. Subject agrees to maintain their current treatments for Meniere’s disease while on-study.
5. Subjects not currently on a low-salt diet or diuretic should have a medical history of having used one or both of these treatments for at least 1 month without relief of symptoms.
6. Subjects currently on a low-salt diet and/or diuretic at the time of screening agree to continue this treatment throughout the study.

### Eligibility Exclusion Criteria
1. Subject has an infection in the ear, sinuses, or upper respiratory system.
2. Subject is pregnant or lactating.
3. Subject has a history of immunodeficiency disease.
4. Subject has a history of previous endolymphatic sac surgery.
5. Subject has a history of previous use of intratympanic (IT) gentamicin in the affected ear.
6. Subject has a history of tympanostomy tubes with evidence of perforation or lack of closure.
7. Subject has experienced an adverse reaction to IT injection of steroids.
8. Subject has used an investigational drug or device in the 3 months prior to screening.
9. Subject has had a duration of Meniere’s disease of >20 years.

### Contact
Rebecca Calvert; phone: (423) 478-7474; rcalvert@INCresearch.com
Carl LeBel, PhD; phone: (858) 768-7814; clebel@otonomy.com

### Location
University of California, San Diego; San Diego, California, United States, 92037-0970
contact: Quyen Nguyen, MD; phone: 858-822-3965; q1nguyen@ucsd.edu
Northwestern University, Feinberg School of Medicine, Otolaryngology, Chicago, Illinois, United States, 60611
contact: Alan Micco, MD; phone: 312-695-8182; agm109@northwestern.edu
Piedmont Medical Research, Winston-Salem, North Carolina, United States, 27103
contact: Ken Maxwell, MD; phone: 336-768-3361; kmaxwell@piedmontent.com
Transtympanic Ringer's Lactate for the Prevention of Cisplatin Ototoxicity

Current status currently recruiting participants

Sponsors and collaborators McGill University Health Center

Information provided by McGill University Health Center

ClinicalTrials.gov Identifier NCT01108601

Purpose Cisplatin and carboplatin induce ototoxicity manifested as sensorineural hearing loss, tinnitus, and/or vestibular disturbances. Ototoxicity is induced via damage to inner ear structures by reactive oxygen species. Previous animal studies demonstrated that transtympanic injection of Ringer's Lactate (RL) provided near complete otoprotective effect against cisplatin. The purpose of this study is to determine if transtympanic administration of Ringer's Lactate via a pressure equalising (PE) tube in patients undergoing platinum based chemotherapy treatment will prevent tinnitus, vestibular dysfunction and hearing loss especially at high frequencies. Pre- and post- chemotherapy treatment audiometry will be measured and statistically analysed for significance.

Condition(s) Hearing Loss

Interventions Drug: Ringer's Lactate (0.03% Ciprofloxacin)

Phase I II
| Study type and design | Interventional; Allocation: Randomized  
| Intervention Model: Single Group Assignment  
| Masking: Open Label  
| Primary Purpose: Prevention |
| Official title: | Transtympanic Administration of Lactate: An Innovative Otoprotection for Patients Receiving Cisplatin or Carboplatin Chemotherapy |
| Arms | Ringer’s Lactate  
| Each patient will act as their own control with one ear receiving treatment, and the contralateral ear acting as control. |
| Assigned Interventions | Drug: Ringer’s Lactate (0.03% Ciprofloxacin)  
| For each patient, only one ear will receive the Ringer’s Lactate solution. The other ear will act as a control. To ensure adequate delivery of the solution to the middle ear, a small pressure equalizing tube will be inserted under local anesthesia before commencement of chemotherapy treatment. The patient will be instructed to administer four drops of RL solution to the experimental ear twice a day during their chemotherapy treatment. |
| Primary Outcomes | • Audiogram [Time Frame: Before and after chemotherapy treatment] [Designated as safety issue: No]  
| Pre-, mid-(if available) and post-chemotherapy treatment audiograms will be compared to determine changes in hearing from baseline and between ears. Hearing will also be assessed every six months after chemotherapy treatment for up to four years to determine possible long-term effects.  
| • Otoacoustic Emissions [Time Frame: Before and after chemotherapy treatment] [Designated as safety issue: No]  
| Distortion Product Otoacoustic Emissions will also be measured before and after chemotherapy treatment and compared to determine significance |
| Expected total Enrollment | 20 |
| Study start | April 2008 |
| Estimated Primary Completion Date: | April 2011 (Final data collection date for primary outcome measure) |
| Participants (age) | 15 Years and older |
| Gender | both |
| Accepts health volunteers | no |
| Eligibility Inclusion Criteria | • Patients over the age of 14  
| • Patients undergoing platinum based chemotherapy  
| • Patients who agree to participate in the study |
| Eligibility Exclusion Criteria | • Patients unable to provide consent  
| • Patients with head and neck cancer  
| • Patients undergoing radiation of the head and neck  
| • Patients who develop a tympanic perforation  
<p>| • Patients with persistent otorrhea |
| contact | Victoria Akinpelu; phone: 514-412-4400 ext 22249; <a href="mailto:viktoriakinpelu@gmail.com">viktoriakinpelu@gmail.com</a> |</p>
<table>
<thead>
<tr>
<th><strong>Location</strong></th>
<th>Montreal General Hospital, Montreal, Quebec, Canada, H3G 1A1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator</strong></td>
<td>Sam J Daniel, MD, McGill University Health Center</td>
</tr>
<tr>
<td><strong>Responsible party</strong></td>
<td>McGill University Health Center (Dr. Sam Daniel)</td>
</tr>
<tr>
<td><strong>Study ID Numbers</strong></td>
<td>GEN-07-033</td>
</tr>
<tr>
<td><strong>Last Updated</strong></td>
<td>April 20, 2010</td>
</tr>
<tr>
<td><strong>Record first received</strong></td>
<td>April 1, 2010</td>
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<td><strong>ClinicalTrials.gov Identifier</strong></td>
<td>NCT01108601</td>
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<tr>
<td><strong>Health Authority</strong></td>
<td>Canada: Ethics Review Committee</td>
</tr>
</tbody>
</table>