Dear Colleagues,

Together for a cure! The motto of the new TRI brochures is impressively reflected in the fifth TRI newsletter – the first Newsletter of the year 2008. The great number of new literature and of clinical trials shows the continuously increasing interest in Tinnitus Research all over the world. Even though we did not make the breakthrough we believe that the efforts to combine forces and to initialize a network of research will finally be the right way.

As always we do not want to pass up the chance to remind you, that we would be very grateful for your cooperation. So, if you have some news which are worth publishing in this newsletter – please, let us know immediately.

Berthold Langguth  Benjamin Questier  Susanne Staudinger
We would like to introduce our new colleagues, Mrs. Sylvia Dorner-Mitschke and Jean Fugate. As Ulli Soltani has left the TRI at the end of last year, Sylvia will be your contact person for all TRI matters and will be supporting Berthold Langguth, Benjamin Questier and Susanne Staudinger in increasing duties of TRI. Jean will be working with TRI starting April 4th and will be mainly assisting Michael Landgrebe in his various duties and responsibilities concerning the subtyping workgroup. Please, do not hesitate to contact both via e-mail sylvia.dorner-mitschke@tinnitusresearch.org jean.fugate@tinnitusresearch.org or by phone +49 941 941 2096.

The new TRI booklets and folders are now available. Please order via mail info@tinnitusresearch.org, or call +49 (0)941 941 2096.

The American Tinnitus Association (ATA) recently achieved Congressional report language through the Departments of Defenses’s Peer Review Medical Research Program (PRMRP). This language directs the Department of Defense (DoD) to allocate $50 million to research only 21 conditions, including tinnitus.

Pre-announcements are now available online! You may submit letters of intent for one or more of the four funding mechanisms. Both basic and clinical research proposals will be considered. In addition to scientific merit, proposals will be evaluated on their relevance to the war-fighter, military families of combat readiness. This programmatic relevance is crucial to a successful proposal. ATA’s resource center can help you make this connection.

The PRMRP requests for proposals are expected in April 2008. ATA staff will keep you up to date on the release of these announcements
For research-related question, please contact amy@ata.org; or call 800-634-8978 x218
For PRMRP questions, please contact jennifer@ata.org; or call 800-634-8978 x215

RNID Research Grants Call for Proposals
RNID is the largest UK charity representing people with hearing loss and tinnitus. They fund research all around the world to understand the causes of hearing loss and tinnitus, develop new treatments and improve existing technology.

Research proposals are now invited within the following areas:
1) Silencing tinnitus
2) Protecting hearing
3) Restoring hearing
4) Applications may also be considered for proposals outside of these subject areas if the research will benefit people with hearing loss or tinnitus. If applying under this category, applicants must submit a brief summary of the proposed project in advance of the full application to check its suitability.

Applicants may be from any country!
For further details look at RNID website http://www.rnid.org.uk/researchfunding
call +44 (0) 20 72 96 80 13
or write an e-mail research@rnid.org.uk

Deadline for full applications: 2 May 2008
Upcoming Meetings

April 2008

10th International Conference on Cochlear Implants and Other Implantable Auditory Technologies
When: April 10 – 12, 2008
Where: Manchester Grand Hyatt, San Diego, California, USA
E-Mail: ci@ci-2008.com

March 2008

When: April 30 – May 4, 2008
Where: Bonn, Germany
Contact: Deutsche Gesellschaft für Hals- Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie
Geschäftsstelle
Hittorfstr. 7
53129 Bonn
Phone: +49 (0228) 23 17 70
Fax: +49 (0228) 23 93 85
E-Mail: info@hno.org

Internationales Tinnitus-Symposium
10 Jahre Österreichische Tinnitus-Liga (ÖTL)
When: May 1 – 3 2008
Where: Bildungszentrum Raiffeisenhof, Graz – Austria
Contact: Manfred Koller, President ÖTL
Phone: +43 (0)316/68 52 55 11 (Mrs Zettl, Mrs Haingartner)
Fax: +43 (0)316/68 52 55 99
E-mail: koller-oetl@sime.com
Detailed information: http://www.tinnitus.at/53409699a012fd601/index.html

May 2008

2nd International Symposium of the Politzer Society On Otosclerosis & Stapes Surgery
When: May 8 – 10, 2008
Where: Biarritz, France
Contact: Scientific Secretariat Gisèle Bouissou
Service ORL - CHU Purpan, TSA 40031
31059 Toulouse Cedex 9, France
Phone: +33 (0)5 61 77 77 04
Fax: +33 (0)5 61 49 36 44
E-Mail: bouissou.g@chu-toulouse.fr
Symposium “Molecular Medicine of Sensory Systems”
German Academy of Sciences Leopoldina founded 1652
When: May 18 – 20, 2008
Where: University of Tübingen, Germany
Contact: Prof. Dr. Jutta Schnitzer-Ungefug
German Academy of Science Leopoldina
Emil-Abderhalden-Str. 37
06108 Halle / Saale
or Prof. Dr. Hans-Peter Zenner
German Academy of Science Leopoldina
Dept. of Otalaryngology Head and Neck Surgery
Tübingen University
Elfriede-Aulhorn-Str. 5
72076 Tübingen
Phone: +49 (0)345 472 39 12 11
Fax: +49 (0)345 472 39 19
E-Mail: schnitzer@leopoldina-halle.de
hpzenner@med.uni-tuebingen.de
Detailed information: http://thrc.hno.medizin.uni-tuebingen.de/Leopoldina/

ICA 2008 XXIXth International Congress of Audiology
When: June 8 – 12, 2008
Where: Hong Kong
Contact: Ms Kate Kwan/ Ms Rachel Cheng
Room 2704, 27/F, C C Wu Building
302-308 Hennessy Road
Wanchai, Hong Kong
Phone: 852 2372 0090
Fax: 852 2372 0490
E-Mail: enquiry@ica2008.com

From the Ear to the Brain and back – 50th Anniversary of the Eaton Peabody Laboratory of Auditory Physiology
When: June 12 – 13, 2008
Where: Massachusetts Eye and Ear Infirmary, Boston, MA, United States
E-Mail: epl50@meei.harvard.edu
Detailed information: http://research.meei.harvard.edu/EPL/EPL50.html

IXth International Tinnitus Seminars
When: June, 15 – 18, 2008
Where: Göteborg, Sweden
Contact: Congrex Sweden AB, Ref. Tinnitus 2008
P.O.Box 5078
402 22 Göteborg, Sweden
Phone: +46-31-708-6000
Fax: +46-31-708-6025
E-Mail: tinnitus2008@congrex.com
Detailed information: http://www.congrex.se/ITS2008
Acoustics 08: 155th Meeting of the Acoustical Society of America, 5th Forum Acusticum, 9th Congrès Français d’Acoustique
When:    June 29 – July 4, 2008
Where:   Palais de Congrès, Paris, France
Contact:  SFA Acoustical Society of America
          Conference Secretariat: Armelle Guilloux
          23 avenue Brunetière
          75017 Paris, France
Phone: +33 (0)6 37 88 39 79 or +33 (1) 48 88 90 59
Fax: +33 (1) 48 88 90 60
E-Mail: acoustics08@laposte.net
Detailed information: http://www.acoustics08-paris.org/

CHHA-AMEC IFHOH Congress 2008 – A Global Community of Communication
When:    July 2 – 6, 2008
Where:   Sheraton Vancouver Wall Center
Contact:  Congress Secretariat
          205 –2415 Holly Lane
          Ottawa, Ontario, CA, K1V 7P2
Phone: 1-800-263-8068 (in Canada) or 613-526-1584 (outside Canada)
Fax: 613-526-4718
E-Mail: congress2008@chha.ca

The 10th International Workshop on the Mechanism of Hearing
When:    July 27 – 31, 2008
Where:   Keele University, UK
Contact:  Dr. N.P. Cooper
          School of Life Sciences
          Keele University
          Keele, Staffordshire
          ST5 5BG
          UK
Phone: +44-1782-583056
Fax: +44-1782-583055
E-Mail: secretary@mechanicsofhearing.com
Detailed information: http://www.mechanicsofhearing.com
International Hearing Aid Research Conference 2008
When: August 13 – 17, 2008
Where: Granlibakken Conference Center, Lake Tahoe, California
Contact: IHCON
House Ear Institute
2100 W. 3rd St
Los Angeles, CA 90057
Phone: 213-989-6772
Fax: 213-413-0950
E-Mail: IHCON@hei.org
Detailed information: http://www.hei.org/ihcon/

Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum
When: August 24 – 27, 2008
Where: Langenbeck-Virchow House of the Medical Society of Berlin, Germany
Contact: ENT Department of the Charité, Mrs. Arndt
Hindenburgdamm 30
12200 Berlin, Germany
Phone: +49 30 84 45 24 31
Fax: +49 30 84 45 44 60 or +49 03450 555 902
Detailed information: http://www.corlas.net/Berlin2008.htm

BTA Conference 2008 – „The Future Pathway for Tinnitus“
When: September 4, 2008
Where: Sheffield Hallam University, Sheffield, UK
Contact: The British Tinnitus Association
Ground Floor, Unit 5, Acorn Business Park
Woodseats Close Sheffield, S8 0TB, UK
Phone: +44 (0)114 250 9922
Fax: +44 (0)114 258 2279
E-Mail: info@tinnitus.org.uk

Sixteenth Annual Management of the Tinnitus Patient Conference
When: September 18 – 20, 2008
Where: University of Iowa, Iowa, USA
Contact: Gareth Smith, University of Iowa, USA
Phone: 319-356-2471
E-Mail: gareth-smith@uiowa.edu
53rd International Congress of Hearing Aid Acousticians
When: October 15 – 17, 2008
Where: Leipzig, Germany
Contact: EUHA
PO Box 40 06
55030 Mainz, Germany
Phone: +49 (0) 61 31/ 28 30-0
Fax: +49 (0) 61 31/ 28 30-30
E-Mail: info@euha.org
Detailed information: http://www.euha.org

European Academy of Otology and Neuro-Otology – 4th Instructional Workshop
When: November 13 – 16, 2008
Where: Pueblo Español Congress Palace, Palma de Mallorca, Spain
E-Mail: orlcongresos@seorl.net
or Erwin.offeciers@gza.be

32nd MidWinter Meeting of the Association for Research in Otolaryngology (ARO)
When: February 14 – 19, 2009
Where: Baltimore, MD, USA
Detailed information: http://www.aro.org/mwm/mwm.html

12. Jahrestagung der Deutschen Gesellschaft für Audiology e.V.
When: March 11 – 14, 2009
Where: Innsbruck, Austria
Contact: Dt. Gesellschaft für Audiologie e.V. Geschäftsstelle
c/o Haus des Hörens
Marie-Curie-Str. 2
26129 Oldenburg
Phone: +49 (0)4 41/2172-500
Fax: +49 (0)4 41/2172-550
E-Mail: info@dga-ev.com
Detailed information: http://www.dga-ev.com
Recently published literature
I Epidemiology

Spontaneous Brief Unilateral Tinnitus (Sbuts) – Prevalence and Properties

Abstract ARO-Meeting

Robert Levine1, Yahav Oron2, Eui-Cheol Nam3, Yehudah Roth2, Jennifer Melcher1
1Massachusetts Eye & Ear Infirmary, 2The Edith Wolfson Medical Center, 3Kangwon National University College of Medicine

Tinnitus refers to a diverse set of phenomena. To understand tinnitus requires an understanding of each of the various types of tinnitus. Progress made in understanding one type of tinnitus may provide further insights into other types of tinnitus. SBUtS appears to be “a blind spot” in tinnitus research. Despite being the most common form of tinnitus, there are no systematic reports of SBUtS. Previously, we had found that about 76% of normal hearing adults have had SBUtS. There was no obvious association between experiencing SBUtS and age, handedness, or chronic tinnitus. Subjects who had previously experienced tinnitus after a loud sound were more likely to have SBUtS than those who had not. From logging the SBUtS of 5 subjects we tentatively concluded that the rate of occurrence of SBUtS varied from less than 1 per year to over 100 per year. Twice as many SBUtS occur in the right ear than the left ear. the dominant pitch of SBUtS ranges from 100 to 1000 Hz. a pressure feeling usually accompanies SBUtS. From obtaining four month SBUt logs for another 69 adults, we now conclude that SBUtS are twice as frequent in tinnitus subjects than non-tinnitus subjects. the rate of occurrence of SBUtS varies from less than 1 per year to over 130 per year. SBUtS more commonly occur in the right than the left ear. the dominant pitch of SBUtS ranges from 100 to 4400 Hz. in about 25% of subjects an ipsilateral ear pressure accompanies all SBUtS, whereas less than 5% of subjects experience an ipsilateral ear pressure with some SBUtS but not with others.

Tinnitus with or without hearing loss: are its characteristics different?

Eur Arch Otorhinolaryngol. 2008 Mar 4 [Epub ahead of print]

Savastano M.
Department of Medical–Surgical Specialities, ENT Section, University of Padova, Via Giustinianini 2, 35128, Padova, Italy, marina.savastano@unipd.it.

The present study was carried out in order to analyze the clinical characteristics of tinnitus both in normal hearing subjects and in patients with hearing loss. The study considered 520 consecutive tinnitus sufferers. The following parameters were considered: age, sex, subjective disturbance caused by tinnitus, subjective judgment of tinnitus intensity, tinnitus laterality, tinnitus duration, tinnitus measurements, normal hearing or associated hearing loss. Among the patients considered, 223 have normal hearing while 297 have a hearing deficit. The hearing impairment was found to be in most cases of sensorineural type. The subjective discomfort is higher in presence of hearing loss. Subjects with hearing loss needed significantly higher masking levels. No evident differences in the residual inhibition (RI) result between the two groups were found. The present study confirms that tinnitus is most frequently associated with hearing loss. The characteristics of tinnitus in normal hearing subjects, except for the subjective judgment of tinnitus intensity, the pitch and the RI, are significantly different for those observed in subjects with hearing loss. The association of tinnitus and hearing deficit seems to increase the perceived severity of the symptom.

The risk of tinnitus following occupational noise exposure in workers with hearing loss or normal hearing.


Rubak T, Kock S, Koefoed-Nielsen B, Lund SP, Bonde JP, Kolstad HA.
Department of Occupational Medicine, Aarhus University Hospital, Denmark.

The purpose was to investigate the relationship between noise exposure and tinnitus among workers with normal hearing and hearing loss, respectively. We conducted a cross-sectional survey of 752
workers employed at 91 workplaces, that were investigated by means of full work-shift noise levels, questionnaire data, and bilateral pure-tone audiometry. Tinnitus was not associated with the present noise level, the duration of noise exposure, or the cumulative noise exposure if participants had normal hearing. As expected, such trends were demonstrated if participants had a hearing handicap. Based on these data, we will be cautious in ascribing tinnitus to noise exposure in our patients’ workplaces if they have a normal audiogram. Furthermore, our data indicates no risk of noise-induced tinnitus at exposure levels where no hearing loss would be expected, e.g. as usually encountered in non-industrial workplaces.

**Auditory lifestyles and beliefs related to hearing loss among college students in the USA.**

**Rawool VW, Colligon-Wayne LA.**
Department of Speech Pathology and Audiology, West Virginia University, Morgantown WV 26505, USA. vwrawool@mail.wvu.edu.

The purpose of this study was to evaluate the auditory life styles and beliefs of college students with reference to exposure to loud sounds in the context of the health belief model. A survey was administered to 238 (40 men, 198 women) students in the USA. Results suggest that 44% of the students use noisy equipment without ear protection and 29% (69/238) of the students work in noisy environments. Of the 69 who worked in noisy surroundings, only ten reported using hearing protection devices although 50 (72.46%) reported tinnitus. The use of hearing protection devices (HPDs) was associated with previous experience with hearing loss and tinnitus. Although 75% of the students were aware that exposure to loud sounds could cause hearing loss, 50% of the students appeared to be exposing themselves to potentially harmful loud music. Furthermore, 46% of the students reported not using HPDs during loud musical activities because they felt that the music was difficult to hear with HPDs. Most students in this study considered hearing loss to be serious but 76% of the students believed that they would not lose their hearing until a greater age. Although 66% of the students had experienced tinnitus, 58% of these students reported not being concerned about it. These results suggest a critical need for promoting healthy hearing behavior among college students. Possible strategies could include improved education, experience with simulated hearing loss for extended periods and availability of cosmetically appealing or invisible HPDs with uniform attenuation across the frequency range.

**Prevalence of tinnitus and audiometric shape.**
B-ENT. 2007;3 Suppl 7:37-49.

Department of Otolaryngology, University (UA) and University Hospital of Antwerp, Belgium. kelly.demeester@ua.ac.be

Objectives: Studies of tinnitus are often conducted on patient populations presenting for treatment. It is, however, difficult to generalise prevalence numbers and aetiological results from these studies to a healthy, elderly population. The first aim of our study was to determine the prevalence of tinnitus in an otologically screened population between 55 and 65 years old. Secondly, both prevalence and the specific characteristics of tinnitus were compared in subjects with either a flat audiogram, a high-frequency gently sloping audiogram or a high-frequency steeply sloping audiogram.

Methods: 1147 subjects (549 males and 598 females) were recruited through population registers and underwent thorough clinical and audiological examinations. Subjects who reported tinnitus in the general questionnaire about medical history and environmental exposure were invited to complete an additional questionnaire on tinnitus history.

Results: The prevalence of tinnitus was 19.3% according to the general questionnaire on medical health and environmental exposure and 11.8% according to the additional detailed tinnitus-specific questionnaire. Furthermore, our results indicate that gender has a significant effect (tinnitus is more common in males than in females), as does audiometric configuration (tinnitus is more common in subjects with a high-frequency steeply sloping audiogram than in subjects with a flat audiogram).
Both effects were significant in noise-/solvent-exposed subjects, as well as in non-exposed subjects. Finally, comparison of “tinnitus characteristics” in subjects categorised by audiogram configuration revealed significant differences in loudness, pitch, temporal variability and family history of tinnitus.

**Perceived hearing status and attitudes toward noise in young adults.**

**Holmes AE, Widén SE, Erlandsson S, Carver CL, White LL.**
University of Florida, Gainesville, FL, USA. aholmes@phhp.ufl.edu

Purpose: To estimate the prevalence of perceived hearing loss, tinnitus, and temporary threshold shift (TTS) in community college students and to see whether those students’ attitudes toward noise affected their perception of their own possible hearing loss, tinnitus, and TTS.

Method: Young adults (N = 245; age 18-27) completed 3 questionnaires: the Hearing Symptom Description, Youth Attitude to Noise Scale, and Adolescents’ Habits and Hearing Protection Use.

Results: Perceived TTS and pain associated with loud noise were the most common hearing related factors, followed by perceived tinnitus and hearing loss. The students’ attitudes toward noise in their daily environment showed the most negative response, whereas attitudes toward noise and concentration indicated a more positive, or less harmful, response. Chi-square analysis indicated a significant correlation between perceived hearing loss and respondents’ overall attitudes toward noise exposure. Hearing protection use was limited for all participants, with the majority reporting never having used hearing protection.

Conclusion: Approximately 6% of respondents reported perceived hearing loss, and 13.5% reported prolonged tinnitus. In general, participants had neutral attitudes toward noise. Over 20% of participants reported ear pain, tinnitus, and/or TTS after noise exposure at least sometimes. Coincidentally, few participants reported consistent use of hearing protection.

**Risk behaviour and noise exposure among adolescents.**

**Bohlin MC, Erlandsson SI.**
Department of Social and Behavioral Sciences, University West, Sweden. margareta.bohlin@hv.se

Adolescents in Western society often expose themselves to high levels of sound in gyms, rock concerts, discotheques etc. As these behaviours are as threatening to young people’s health as more traditional risk behaviours are, our aim in the present study was to analyze the relationship between self-exposure to noise, risk behaviours and risk judgements among 310 Swedish adolescents aged 15-20 (167 men; 143 women). Adolescents’ behaviour in different traditional risk situations correlated with behaviour in noisy environments, while judgements about traditional risks correlated with judgements regarding noise exposure. It is an interesting finding that although young women judge risk situations as generally more dangerous than young men do, they nevertheless behave in the same way. We suggest that this difference is a social and cultural phenomenon which underscores the importance of adopting a gender perspective in the analysis of risk factors. Adolescents reporting permanent tinnitus judged loud music as more risky than adolescents with no symptoms and they did not listen to loud music as often as those with occasional tinnitus. Research on hearing prevention for young people needs to acknowledge and make use of theories on risk behaviour, especially due to the existence of a relationship between adolescents’ risk-taking in noisy environments and other types of risk-taking. Similarly, theories on risk behaviour should acknowledge noise as a risk factor.

**Hearing-Loss Prevention Practices Should Be Taught in Schools**
Semin Hear 2008; 29: 067-080

**Robert L. Folmer**
Department of Otolaryngology, Oregon Health & Science University, Portland, Oregon, and Research Investigator, the National Center for Rehabilitative Audiology Research, Veterans Administration Medical Center, Portland, Oregon

Children are often exposed to excessive levels of sound, such as loud music, firearms, power tools, and noisy toys.
Such exposure puts children at risk for developing noise-induced hearing loss (NIHL) and tinnitus. For more than 30 years, health policy agencies and numerous experts in hearing science have recommended teaching hearing-loss prevention practices to children in schools as a way to reduce the prevalence of NIHL. Despite these recommendations, basic hearing-loss prevention information that could prevent countless cases of NIHL remains conspicuously absent from most school curricula. At least 10 organizations produce or use a variety of materials in a comprehensive hearing-loss prevention curriculum for school-age children. At least 18 additional organizations produce or disseminate materials (Web-based, video, or printed matter) that could be used to teach hearing-loss prevention in classrooms. Therefore, adequate materials and curricula are available for presenting this information to school-age children. It is time to implement the repeated recommendations of experts by providing hearing-loss prevention instruction in all of our nation’s schools on a regular basis. These educational efforts should eventually help to reduce the prevalence of NIHL, which is a fully preventable condition.

Dangerous Decibels: Partnership for Preventing Noise-Induced Hearing Loss and Tinnitus in Children
Semin Hear 2008; 29: 102-110

William Hal Martin
Oregon Hearing Research Center, Department of Otolaryngology/Head & Neck Surgery, Oregon Health & Science University, Portland, Oregon

Oregon Health & Science University’s Oregon Hearing Research Center, in conjunction with the Oregon Museum of Science and Industry, the Portland State University School of Community Health, the Veterans Affairs National Center for Rehabilitative Auditory Research, and the American Tinnitus Association, formed a public health partnership to address the problem of noise-induced hearing loss and tinnitus. The Dangerous Decibels partnership has received funding from several private foundations and public sources. This support enabled the development of a wide range of activities including exhibits, educational outreach, educator training, and research. All of the Dangerous Decibels activities communicate three educational messages: What are sources of dangerous sounds? What are the consequences of being exposed to dangerous sounds? How can I protect myself from dangerous sounds? The Dangerous Decibels program has been adopted by the Marion Downs National Center for Infant Hearing and is supported by the National Hearing Conservation Association Taskforce for Noise Induced Hearing Loss Prevention in Children.

Auditory dysfunction in traumatic brain injury.

Lew HL, Jerger JF, Guillory SB, Henry JA.
Physical Medicine and Rehabilitation Service, VA Palo Alto Health Care System, 3801 Miranda Ave, B117, Palo Alto, CA 94304. henry.lew@va.gov.

Effective communication is essential for successful rehabilitation, especially in patients with traumatic brain injury (TBI). The authors examined the prevalence and characteristics of auditory dysfunction in patients with TBI who were admitted to a Department of Veterans Affairs TBI inpatient unit before and after the onset of Operation Iraqi Freedom (OIF). In order to delineate the characteristics of the auditory manifestations of patients who had sustained blast-related (BR) TBI, we reviewed the medical records of 252 patients with TBI and categorized them according to admission date, either before (Group I, n = 102) or after (Group II, n = 150) the onset of OIF. We subdivided Group II into non-blast-related (NBR) and BR TBI; no subjects in Group I had BR TBI. We found that admissions for TBI have increased 47% since the onset of OIF. In Group I, 28% of patients with TBI complained of hearing loss and 11% reported tinnitus. In Group II-NBR (n = 108), 44% complained of hearing loss and 18% reported tinnitus. In Group II-BR (n = 42), 62% complained of hearing loss and 38% reported tinnitus. Sensorineural loss was the most prevalent type of hearing loss in Group II-BR patients. In light of the high prevalence of hearing loss and tinnitus in this growing population of returning soldiers, we need to develop and implement strategies for diagnosis and management of these conditions.
II Pathophysiology

Arachidonic Acid Depolarizes Guinea Pig Outer Hair Cells Through Inhibiting KCNQ4
Abstract ARO-Meeting

Tao Wu, Alfred Nuttall
Oregon Health and Science University

KCNQ4 is associated with IK\textsubscript{n}, which is activated at hyperpolarization and dominates the membrane conductance at the resting potential of outer hair cell (OHCs). Genetic mutations in the gene for KCNQ4 resulted in non-syndromic hereditary hearing loss. Arachidonic acid (AA) is usually stored within phospholipids of the cell membrane and released into intracellular medium by stimulation of G protein coupled receptors. As second messengers, AA and its active metabolites, such as hydroperoxyeicosatetraenoic acid (HPETE), prostaglandins (PGs), leukotrienes (LTs), etc, interact with protein kinases and ion channels within the cell. The disturbed AA cascade of OHCs has been thought to mediate the tinnitus induced by salicylate, a cyclooxygenase inhibitor. Surprisingly, in the current study with whole cell recordings, extracellular application of AA (100 μM) led to substantial depolarization of OHCs by 7.8 ± 0.9 mV (from –69.0 to –61.3 mV, n=7), which was completely blocked by linopirdine (100 μM), a KCNQ4 channel blocker, in gap-free recordings of current clamp. The depolarized membrane potential recovered to ist original with a delay of 3-5 minutes' washing. In gap free recordings of voltage-clamp, AA (100 μM) led to a reversible reduction (negatively shift) of 99.6 ± 15.6 pA (70%) in the outward current at the holding voltage (Vh) of –49 mV, which was also completely blocked by linopirdine (100 μM). In voltage-step recordings for the IV curve, AA (100 μM) significantly reduced both the inward current and the outward current by 36.4% at –100 mV and 57.1% at 0 mV respectively without a marked change in the kinetics of outward IK. The reverse potential of AA sensitive currents, was -87.1 ± 3.0 mV, indicating a high K+ selectivity when compared to the theoretical value of –88 mV. In conclusion, Arachidonic acid depolarizes guinea pig outer hair cells through inhibiting KCNQ4.

Specific Autoimmune Antibodies in Acute Inner Ear Disorders
Abstract ARO-Meeting

Kerstin Ratzlaff, Mark Praetorius, Christina Schlecker, Reinhild Klein, Peter K Plinkert
1University of Heidelberg, 2University of Tuebingen

Introduction: By now the exact pathogenesis of the different forms of acute inner ear disorders like sensorineural hearing loss, sudden deafness, tinnitus and Meniere’s disease is still unknown. Disorders of inner ear blood circulation are widely discussed just like viral infections and autoimmune processes. The aim of this study is to examine specific autoimmune antibodies and their function in occurrence, therapy and prognosis of acute inner ear disorder.

Material and Methods: By now n=70 patients were examined, 32 female and 38 male, suffering from acute inner ear disorder. The average age was about 45.2 years. A general autoimmune disease was not known. Patients underwent a therapy consisting of Prednisone according to Stennert’s scheme and Pentoxifylline 3x 400 mg daily. Hearing was examined using pure-tone audiometry at the beginning and 6 weeks after the beginning of therapy. Specific autoimmune antibodies were examined at the beginning and at the end of the therapy using ELISA and immunofluorescence-test (IFL).

Results: Among 70 patients, there were 34 detected with tinnitus (48.57%), 27 with sensorineural hearing loss (38.57%) and 9 with Meniere’s disease (12.86%). In about 64% of all patients there was an occurrence of autoimmune antibodies. Antibodies against sarcolemma (ASA) and sinusoids were mostly detected (23%), followed by anti-nuclei-antibodies (ANA; 15.9%). Antibodies against Microsomes, Phospholipids and Laminin were detected each by about 6.5%, and antibodies against anti-Endothelium and smooth muscle (SMA) at about 3% each. Conclusion: In this study we could demonstrate that there is an occurrence of autoimmune antibodies in acute inner ear disorders. As already described before, this should be considered as one possible mechanism in the pathogenesis of inner ear disease. It is our further aim to examine the effects of these findings in regard to the prognosis and therapeutic treatment of disease.
Molecular Approaches to Tinnitus
Abstract ARO-Meeting

Marlies Knipper¹, Rama Panford-Walsh¹, Lukas Ruettiger¹, Wibke Singer¹, HynSoon Geisler¹, Karin Rohbock¹, Holger Schulze², Ulrike Zimmermann¹
¹Hearing Research Center Tuebingen, ²University Erlangen

Aberrant neuronal activity is known to lead to changes in neuronal plasticity. However, the molecular changes following sensory trauma and the subsequent response of the central nervous system are only poorly understood. We focused on finding a molecular tool for monitoring the features of excitability which occur following acoustic and ototoxic trauma to the auditory system. of particular interest are genes that alter their expression pattern during activity-induced changes in synaptic efficacy and plasticity. The expression of brain-derived neurotrophic factor (BDNF) and the activity-dependent cytoskeletal protein (Arg3.1/arc) were monitored in the peripheral and central auditory system hours and days following tinnitus-inducing traumatic stimuli or salicylate treatment. Tinnitus induction was monitored in a rodent animal behavior model (Rüttiger et al., 2003, Hear Res). Excitatory input to the rat AI were investigated by local field potential (LFP) post pure-tone acoustic trauma using chronic implantion of multi-channel microelectrode arrays. BDNF and Arg3, were monitored at the mRNA and protein level in the cochlea and subcortical and cortical areas. We present here a summary of recent findings comparing and correlating the expression of activity dependent genes with tinnitus-behavior. the data are discussed in the context of using the monitoring of activity-dependent genes to screen for the pharmacological reversal of tinnitus.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft Kni 316/3-2 and Fortüne 816-0-0.

Altered Markers of Glycinergic Function in the Dorsal Cochlear Nucleus (DCN) of a Rat Model of Chronic Tinnitus
Abstract ARO-Meeting

Hongning Wang, Lynne Ling, Thomas J. Brozoski, Jeremy G. Turner, Jennifer L. Parrish, Larry F. Hughes, Donald M. Caspary
Southern Illinois University School of Medicine

Fifteen to 35% of the population in the United States experience tinnitus, a subjective “ringing in the ears”. Up to 10% of tinnitus patients report their symptoms are severe and disabling. Tinnitus was induced in FBN rats using one hour, 116 dB (SPL) unilateral octave-band noise exposure centered at 16 KHz via an anesthetized preparation and assessed behaviorally by an operant conditioning paradigm and GAP detection method. Sixteen weeks following noise exposure, young adult (7mos.) rats showed evidence of tinnitus in the 24-32 kHz range while aged (30 mos.) animals showed the greatest evidence of tinnitus at 10 kHz. These results suggest that the frequency characteristics of tinnitus produced by acoustic exposure may be age-dependent. Protein levels of á1-3 glycine receptor subunits (GlyRs), gephyrin, BDNF and ist receptor TrkB were measured in dorsal cochlear nucleus (DCN) fusiform cells 4 months after exposure using quantitative immunocytochemistry. Young exposed rats showed decreases of GlyRá1 protein at middle and high frequency regions in DCN while aged exposed rats showed higher á1 subunit protein levels in the same DCN regions. the GlyR anchoring protein, gephyrin, was significantly increased in both young and aged exposed rats, suggesting an intracellular receptor trafficking change following acoustic trauma. BDNF and TrkB were also increased over fusiform cells for young and aged exposed rats. [3H] strychnine binding was used to assess DCN GlyR function following noise exposure. an age-related decrease in GlyRá1 protein was reflected in a significant age-related down-regulation of Bmax. Young trauma animals showed a significant decrease in Bmax further suggesting a post-exposure reduction of normal adult GlyR function. These findings suggest that both noise-induced tinnitus and aging are associated with functional GlyR changes in DCN fusiform cells. Identification of the mechanisms could further the development of novel selective drugs for tinnitus.
Molecular Components and Synaptic Functions of the Endocannabinoid System in the Dorsal Cochlear Nucleus (DCN)  
Abstract ARO-Meeting  
Yanjun Zhao¹, Maria Rubio², Thanos Tzounopoulos¹  
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Molecular Components and Synaptic Functions of the Endocannabinoid System in the Dorsal Cochlear Nucleus (DCN). Endocannabinoid (EC) signaling has emerged as one of the most important neuromodulatory systems in the brain. However, the cellular and molecular components of this system have not been determined in the auditory system. Previous studies from our lab have revealed that cellspecific EC signaling in the DCN determines cell-specific synaptic plasticity. the DCN, an auditory brainstem nucleus, integrates acoustic with multimodal sensory inputs from diverse areas of the brain. Excitatory parallel fibers (PFs) carry these diverse signals to the apical, spiny dendrites of fusiform cells (FCs) and cartwheel cells (CWCs), while auditory nerve (AN) fibers carry acoustic inputs to the basal dendrites of FCs. Here, by using electron microscopy and electrophysiological assays we found that key proteins involved in EC signaling are expressed in the molecular layer, but not in the deep layer of the DCN. Presynaptic CB1 receptors (CB1Rs) are expressed in PFs and in inhibitory terminals synapsing onto CWCs and FCs, while they are absent in AN fibers. 2-arachidonoyl-glycerol (2-AG) and anandamide have been identified as ECs. Diacylglycerol lipase a (DGL-a), one of the enzymes synthesizing 2-AG was expressed on dendrites and spines of FC and CWC respectively. By blocking the synthesis of 2-AG with Tetrahydrolipstatin (THL, 20 μM) or RHC80267 (50 μM) depolarizationinduced suppression of excitation (DSE), a form of shortterm plasticity, was blocked in PF inputs to CWCs, further indicating that 2-AG is the endocannabinoid mediating neuromodulation in the DCN. Depolarization-induced suppression of glycinergic inhibition (DSI) was absent in CWC and FC. However, application of the CB1 receptor agonist WIN 55,212-2 (1μM) resulted in a suppression of glycinergic IPSCs in CWCs. These data suggest that glycinergic terminals in the molecular layer express CB1Rs. Subsequently, EM studies confirmed expression of CB1Rs in glycinergic inhibitory terminals to CWC and FCs. Determining the anatomical and functional properties of EC signaling in the DCN should not only contribute to an understanding of the generation of auditory neural responses, but will also have a significant impact on our understanding and cures for disorders caused by neural plasticity-like mechanisms, including tinnitus.

Elevated Sound-Evoked Fmri Activation in the Auditory Midbrain of People with Tinnitus and Hyperacusis  
Abstract ARO-Meeting  
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Melcher et al. (Int. Tinnitus Seminar, 2005) demonstrated elevated sound-evoked activation in the inferior colliculi (IC) of normal hearing tinnitus subjects compared to audiometrically-matched controls without tinnitus. Here, we tested whether the elevated activation is associated with the low tolerance for high-level sound (hyperacusis) experienced by many people with tinnitus. 21 subjects with normal pure tone thresholds underwent behavioral tests followed by fMRI. Subjects were classified according to whether (1) they had tinnitus (10 of 21) and (2) they deemed continuous broadband noise (the stimulus used during fMRI) to be intolerably loud at levels above 90 dB SL. 10 of 21 (8 tinnitus, 2 non-tinnitus) were classified as having “low sound tolerance” by this criterion. 10 slices were imaged in a sparse paradigm to prevent the scanner acoustic noise from contaminating activation measurements. Sound levels were 50, 70, and 80 dB SPL. A comparison of tinnitus and non-tinnitus subjects (regardless of sound tolerance) showed significantly greater activation in the tinnitus group at 70 dB SPL (percent change (p.c.) = 1.3 for tinnitus, 1.0 for non-tinnitus; p < 0.04), and the same trend at 80 dB SPL (p.c. = 1.3 for tinnitus, 1.1 for non-tinnitus; p < 0.1). a comparison of subjects according to sound tolerance (regardless of tinnitus) showed a greater and far more significant difference. At 50, 70, and 80 dB, low
sound tolerance subjects showed significantly greater activation (p.c. = 0.94, 1.4, 1.5, respectively) than subjects with high sound tolerance (p.c. = 0.53, 0.91, 1.1; p < 0.002, 0.00002, 0.007, respectively). A two-way ANOVA indicated a main effect of sound tolerance (50 dB SPL: p<0.004, 70 dB SPL: p<0.0004) with no significant effect of tinnitus or interaction. These results suggest that reduced tolerance of high-level sound is associated with, and may arise from, elevated sound-evoked neural activity.

**Salicylate-Induced Tinnitus: Spectral Changes in Spontaneous Ensemble Activity in Auditory Cortex of Awake Rats**

Abstract ARO-Meeting

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Recent evidence suggests that alpha activity in the EEG directly or indirectly reflects inhibitory processes. When alpha activity is disrupted as a result of reduced thalamocortical afferent inputs such as that caused by peripheral hearing loss, a buildup of synchronous spontaneous neural activity occurs that can give rise to phantom perceptions such as tinnitus. To test this hypothesis, rats were treated with a high dose of salicylate known to produce behavioral evidence of tinnitus. We recorded the ensemble of spontaneous activity (ESA) from a gross electrode chronically implanted on the auditory cortex (AC) of adult rats. To avoid the confounding effects of anesthesia that can disrupt spontaneous and sound evoked neural activity, we recorded the ESA from awake, restrained rats that sat comfortably in a sound attenuating booth. ESA recordings were made before, immediately after and several days following a salicylate treatment (250 mg/kg) that consistently induces tinnitus-like behavior in rats. The ESA data were analyzed offline using wavelet analysis in order to quantify changes in the power spectrum of activity. Preliminary results show that at 1-h post-salicylate, there was a decrease in ESA power from 5-9 Hz (alpha band) and a concomitant increase in power from 15–40 Hz (gamma band). The salicylate-induced change in the ESA spectrum returned to the original baseline levels 1 to 2 days post-salicylate treatment. The changes in the ESA spectrum follow closely the time course for the onset and recovery of salicylate-induced tinnitus measured behaviorally.

**Salicylate Increases the Gain of the Central Auditory System**

Abstract ARO-Meeting

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University at Buffalo

There is growing evidence that the neural generator that gives rise to the phantom sound of tinnitus may reside in the central auditory system; however, the neurophysiological changes associated with tinnitus are not well understood. To investigate the peripheral and central changes, we treated rats with a high-dose of sodium salicylate that reliably induces tinnitus and hypersensitivity to sounds. Systemic injection of salicylate (250 mg/kg) induced a significant decrease in the amplitude and an increase in threshold of the cochlear compound action potential (CAP). Paradoxically, there was a striking increase in the amplitude of the sound-evoked local field potential from the auditory cortex (AC) of awake-rats. However, when rats were anesthetized with isoflurane, which presumably increases GABA activity, salicylate had little or no effect on AC responses. On the other hand, when rats were given ketamine (136 mg/kg), which blocks NMDA receptors, the salicylate-induced enhancement of the AC response was larger than observed with salicylate alone in conscious rats. When salicylate was applied directly to the round window (RW) of the cochlea of ketamine-acepromazine anesthetized rats, salicylate caused an increase in CAP threshold, a reduction in CAP amplitude and a reduction in AC response amplitude. These results suggest that the salicylate-induced enhancement of AC amplitude does not originate in cochlea, but may originate centrally possibly by down regulation of GABA mediated inhibition. To determine if the enhancement of the AC response has a behavioral correlate, we measured pre-pulse inhibition (PPI) of the acoustical startle reflex (ASR). After salicylate injection, pre-pulse inhibition (PPI) of ASR significantly increased. This result link the salicylate-induced AC enhancement to behavioral hypersensitivity to sound (hyperacusis) reported by tinnitus patients.
Acoustic Trauma Induced Auditory Cortex Enhancement and Tinnitus
Abstract ARO-Meeting
Erin Laundrie, Lu Jianzhong, Daniel Stolzberg, Edward Lobarinas, Richard Salvi, Wei Sun
University at Buffalo
There is growing evidence that noise-induced cochlear damage may lead to hyperactivity in the central auditory system (CAS) that may give rise to the phantom sound of tinnitus. However, the correlation between the time of onset of the neurophysiological changes in the CAS and behavioral or perceptual onset of tinnitus are not well understood. To investigate this relationship, we implanted chronic electrodes into the auditory cortex (AC) and measured sound evoked activity from awake-rats before and after acoustic overstimulation. The auditory brainstem response (ABR) was used to assess the degree of noise-induced hearing loss. Tinnitus was evaluated by measuring gap pre-pulse inhibition of the acoustic startle response (GPIAS). Rats were exposed monaurally to a high-intensity narrow band or broad band noise at level of 120 dB SPL. After the noise exposure, all the rats developed either permanent (>2 weeks) or temporary (<3 days) hearing loss in the exposed ear; ABR threshold were essentially unchanged in the non-exposed ear. In the rats that developed permanent hearing loss, AC amplitudes increased significantly 4 h after the noise exposure, whereas AC amplitude remained largely unchanged in rats that exhibited only temporary hearing loss. Most of the exposed rats also developed tinnitus-like behavior on GPIAS (decreased GPIAS) 4 h after the noise exposure. Importantly, the post-exposure AC enhancement showed a positive correlation with the amount of hearing loss. However, the onset of tinnitus-like behavior and the onset of AC enhancement did not show a strong correlation.

Increased Fmri Responses to Sound in the Inferior Colliculus and Medial Geniculate Body in Patients with Unilateral Tinnitus
Abstract ARO-Meeting
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Objective: Determine tinnitus related neural activity in the central auditory system of unilateral tinnitus subjects, using fMRI.
Methods: Twelve patients with unilateral tinnitus (6 leftsided) and 16 controls without tinnitus were subjected to functional MRI of the central auditory system. All subjects had no or minor hearing deficits in both ears. Experiments were performed on a 3T Philips Intera scanner, using sparse sampling (TR=10 s). Data were acquired of the complete auditory pathway (CN, SOC, IC, MG and auditory cortex) using a resolution of 2 x 2 x 2 mm3. Stimuli consisted of right and left ear stimulation with levels of 40 and 70 dB (SPL) of rippled broadband noise. After realignment and normalization to a standard brain template, multiple linear regression was performed using SPM5 in order to identify the response of the brain to the sound stimuli. By a region-of-interest analysis a mean percent signal change was obtained for each stimulus, using the ten percent of the voxels that responded most strongly for each nucleus. In addition, a group analysis was performed on a voxel by voxel basis.
Results: We did not observe a difference between tinnitus patients and controls in the fMRI response of the auditory cortex. However there were differences in the medial geniculate body and the inferior colliculus. The responses to stimuli in these nuclei were higher in patients than controls. There was no significant difference in the superior olivary complex and cochlear nucleus between groups. In addition, a difference was observed in the lateral part of the cerebellum in patients. This area responded to sound in left-sided tinnitus patients and not in control subjects.
Conclusion: Neural correlates of tinnitus were identified and located in the auditory pathway and in the cerebellum. A larger response was measured, which is in agreement with the hypothesis of a loss of inhibition in the auditory pathway of tinnitus patients.
The Effect of Pleasant and Unpleasant Sounding Music in Persons with Hearing Loss and Tinnitus: and fMRI Study

Abstract ARO-Meeting

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NIDCD/NIH

We studied auditory processing in persons with bilateral hearing loss and tinnitus (TIN) and in persons with normal hearing without tinnitus (NV). To examine group differences in the neural bases of auditory processing as related to emotion, we employed music stimuli that could be classified as either pleasant (consonant) or unpleasant (dissonant) (Blood, et al, Nat. Neurosci., 1999). In a preliminary study, 4 TIN and 4 NV subjects were scanned using an EPI clustered acquisition paradigm in a 3T GE scanner. Subjects listened to 6s of the stimulus, followed by a 3s response period during which the stimuli were rated as pleasant/unpleasant, then a 2s single volume acquisition. The task trials were presented in pseudorandom order with rest trials interspersed. Image volumes were realigned, normalized into standard stereotactic space and smoothed. Multisubject fixed effects analysis was performed in SPM5 with a threshold of p<0.001 uncorrected. The 2 groups did not differ in their behavioral responses. The average BOLD response for the processing of consonant stimuli produced greater activation than the processing of dissonant stimuli for both groups. For the NV group the consonant greater than dissonant contrast showed activations in the right insula, middle frontal gyrus and dorsal medial frontal gyrus (DMFG). The opposite contrast showed activation only in the left insula. Previous studies have implicated the insula in music processing. For the TIN group, there was no activation in the insula for either contrast. The consonant greater than dissonant contrast showed activations in the nucleus accumbens/putamen, the temporal pole and DMFG. The nucleus accumbens is part of the limbic system and is involved in emotion processing. These preliminary results suggest that although the NV and TIN groups did not differ behaviorally, they invoked different brain regions when responding to emotional auditory stimuli.

Spontaneous MEG Activity in People with and Without Tinnitus

Abstract ARO-Meeting

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Tinnitus is a common clinical problem for which there are no effective treatments and no proven objective measures. Previously, Weisz et al. (PLoS, 2: e153, 2005) reported abnormalities in the spontaneous cortical activity of tinnitus subjects. Specifically, the power spectrum of spontaneous magnetoencephalographic (MEG) signals was increased at delta frequencies (1.5-4 Hz) and reduced at alpha frequencies (8-12 Hz) in tinnitus subjects compared to non-tinnitus controls. However, the tinnitus subjects had hearing loss whereas the non-tinnitus subjects did not. The present study examines whether the previously reported MEG abnormality is evident when audiometrically matched tinnitus and non-tinnitus subjects are compared. Spontaneous MEG activity was measured in 17 subjects with normal pure tone thresholds from 250 to 8000 Hz. 9 subjects had chronic tinnitus, which was perceived during MEG. Measurements were made using a 306-channel Neuromag Vectorview system housed in an electrically and magnetically shielded room. Signals were recorded for 10 minutes at a sampling rate of 600 Hz while subjects sat with their eyes closed. Eye blinks registered in the concurrently recorded electro-oculogram indicated that subjects were awake throughout the measurement. The Fourier transform of the MEG signal was averaged across overlapping 8.5-second time windows and across sensors to yield a power spectrum for each subject. There was no evidence for the previously reported differential effects on delta and alpha activity. Instead, the spectra of tinnitus subjects differed from non-tinnitus subjects only in a global way that may be related to a slight difference in alertness between groups: power was less in delta (1.5-4 Hz, p=0.01), theta (4-8 Hz, p=0.01), and alpha (8-12 Hz, p=0.02). The results suggest that the spectral abnormalities reported by Weisz et al. (2005) are either unrelated to tinnitus or, are related to tinnitus but only when it is accompanied by hearing loss.
Mechanism by Which High-Dose of Salicylate Induces Tinnitus
Abstract ARO-Meeting

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Currently many millions of people treated for various pains receive high-doses of salicylate. Consequently, understanding the mechanisms by which high-doses of salicylate induce tinnitus is an important issue for the medical research community. Behavioral testing in rats showed that tinnitus induced by salicylate or mfenamate (another cyclooxygenase blocker) are mediated by cochlear N-Methyl-D-Aspartate (NMDA) receptors. Here, we report that auditory nerve endings of cochlear spiral ganglion neurons expressed NMDA receptors. Patchclamp recordings and two-photon calcium imaging on cochlear slices demonstrate that salicylate and arachidonate (a substrate of cyclooxygenase) potentiate NMDA responses of cochlear spiral ganglion neurons. Together with the measurement of cochlear arachidonate content in vivo, single unit recordings of auditory nerve fibers suggest that salicylate-induced neural excitation is due to the activation of cochlear arachidonate-sensitive NMDA receptors. This new pharmacological profile of salicylate provides a molecular mechanism for the generation of tinnitus at the periphery of the auditory system.

Changes in Inferior Colliculus Activity of the Rat Related to Tinnitus
Abstract ARO-Meeting

Didier Depireux, Elizabeth Powell, Yadong Ji, Barak Shechter
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Pharmacological, cognitive, and behavioral approaches are used to treat tinnitus, but all have limited success due to the poor understanding of the etiology of tinnitus and the difficulty in consistently and objectively measuring ist symptoms. We have developed a rat model of noise trauma induced tinnitus, which enables us to measure neurophysiological changes induced by tinnitus and their reversal by treatment (e.g., drug treatment or other manipulations). For instance, lidocaine is known to temporarily suppress tinnitus resulting from noise trauma. We use an awake, behaving rat with a chronic multielectrode array implanted in inferior colliculus with which we measure neural activity before, immediately after, and several weeks after noise trauma-induced tinnitus and after intravenous injection of lidocaine. These animals are also subject to behavioral diagnostics for tinnitus. We perform post-mortem characterization of molecular changes in tinnitus correlated with CREB, phosphorylated-CREB, and GABA immuno-reactivity. Once this model is validated, we will be able to use it to screen other potential drugs for tinnitus treatment, evaluating their effectiveness, best course of treatment as well as potential side-effects.

Neural Tonotopy in CI: an Evaluation in Unilateral CI Patients with Contralateral Normal Hearing
Abstract ARO-Meeting

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Objectives: in actual cochlear implant systems the signal is filtered into different frequency bands and transmitted to electrodes along the cochlea which elicit different pitch perceptions. In this study the frequency-place map for electric hearing was investigated as a means to possibly improve current speech coding strategies by delivering spectral information to the appropriate cochlear place.

Methods: Fourteen subjects with near to normal hearing in the contra-lateral ear have been provided with a MED-EL cochlear implant in the deaf ear in order to reduce intractable tinnitus. Pitch scaling experiments were performed using twelve single-electrode stimuli in the implanted ear and twelve acoustic sinusoids logarithmically spaced between 100 and 8500 Hz in the contra-lateral ear. The frequency-place function was calculated according to the exact electrode position in the cochlea.
obtained by postoperative skull radiographs by means of a cochlear view and were compared to Greenwood’s frequency-place function in normal hearing.

Results: Electrical stimulation with a constant stimulation rate elicited a low pitch perception in the apical region of the cochlea, and shifting the stimulating electrode towards the basal region of the cochlea elicited an increasingly higher pitch perception. The frequency-place function obtained with our subjects did not show a significant shift relative to Greenwood’s frequency-position function.

Conclusions: Electrical stimulation of the cochlea in patients with a unilateral cochlear implant and with near to normal hearing at the non-implanted ear, provided a specific frequency-position function consistent with Greenwood’s function.

**A comparison between the feeling of ear fullness and tinnitus in acute sensorineural hearing loss.**


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The feeling of ear fullness (FEF) occurs frequently in patients with acute sensorineural hearing loss; the same is true for tinnitus (TIN). However, the cause of FEF in these patients is unclear. This study included 171 ears of patients admitted with unilateral sudden deafness to the ENT division of Fukuoka University Hospital between January 2001 and December 2004. The results showed TIN was mainly associated with worse high-frequency hearing thresholds, where hearing loss was relatively severe, and this association became stronger after the hearing threshold stabilized. FEF was associated with the low-frequency region, where hearing loss was relatively mild, and this association disappeared after the hearing threshold stabilized. In conclusion, TIN is thought to originate in the region where hair cells are impaired; in contrast, FEF may originate from some functional factor rather than an organic lesion of the cochlea.

**The risk of tinnitus following occupational noise exposure in workers with hearing loss or normal hearing.**


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The purpose was to investigate the relationship between noise exposure and tinnitus among workers with normal hearing and hearing loss, respectively. We conducted a cross-sectional survey of 752 workers employed at 91 workplaces, that were investigated by means of full work-shift noise levels, questionnaire data, and bilateral pure-tone audiometry. Tinnitus was not associated with the present noise level, the duration of noise exposure, or the cumulative noise exposure if participants had normal hearing. As expected, such trends were demonstrated if participants had a hearing handicap. Based on these data, we will be cautious in ascribing tinnitus to noise exposure in our patients’ workplaces if they have a normal audiogram. Furthermore our data indicates no risk of noise-induced tinnitus at exposure levels where no hearing loss would be expected, e.g. as usually encountered in non-industrial workplaces.

**Objective quantification of the tinnitus decompensation by synchronization measures of auditory evoked single sweeps.**


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Large-scale neural correlates of the tinnitus decompensation might be used for an objective evaluation of therapies and neurofeedback based therapeutic approaches. In this study, we try to identify large-scale neural correlates of the tinnitus decompensation using wavelet phase stability criteria of single sweep sequences of late auditory evoked potentials as synchronization stability measure.
The extracted measure provided an objective quantification of the tinnitus decompensation and allowed for a reliable discrimination between a group of compensated and decompensated tinnitus patients. We provide an interpretation for our results by a neural model of top-down projections based on the Jastreboff tinnitus model combined with the adaptive resonance theory which has not been applied to model tinnitus so far. Using this model, our stability measure of evoked potentials can be linked to the focus of attention on the tinnitus signal. It is concluded that the wavelet phase stability of late auditory evoked potential single sweeps might be used as objective tinnitus decompensation measure and can be interpreted in the framework of the Jastreboff tinnitus model and adaptive resonance theory.

**Otosyphilis in HIV-Coinfected Individuals: A Case Series From Toronto, Canada.**
AIDS Patient Care STDS. 2008 Feb 21 [Epub ahead of print]

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We sought to identify and review the clinical features and treatment outcomes of eight recent cases of otosyphilis in HIV-positive patients seen in Toronto. All patients reported tinnitus, and seven (87.5%) reported subjective hearing loss. Not taking auditory findings into consideration, four patients would be classified as having secondary syphilis, three patients as having early latent syphilis, and one patient as having latent syphilis of unknown duration. The median CD4 cell count was 370 x 10^6/L. All patients were treated with intravenous aqueous penicillin G with regimens recommended for the treatment of neurosyphilis; four patients received adjunctive steroids. All eight patients experienced improvement in tinnitus and four of the seven (57.1%) patients with symptomatic hearing loss also experienced improvement. Otosyphilis can occur in HIV-positive individuals despite high CD4 cell counts, and is potentially reversible. Increased awareness of uncommon manifestations of syphilis in high-risk individuals is warranted to prompt appropriate investigation and treatment.

**Rotational vertebral artery syndrome : 3D kinematics of nystagmus suggest bilateral labyrinthine dysfunction.**
J Neurol. 2008 Feb 18 [Epub ahead of print]

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Whether the rotational vertebral artery syndrome (RVAS), consisting of attacks of vertigo, nystagmus and tinnitus elicited by head-rotation induced compression of the dominant vertebral artery (VA), reflects ischemic dysfunction of uni- or bilateral peripheral or central vestibular structures, is still debated. We report on a patient with bilateral high-grade carotid stenoses, in whom rightward head rotation led to RVAS symptoms including a prominent nystagmus. Three-dimensional kinematic analysis of the nystagmus pattern, recorded with search coils, revealed major downbeat nystagmus with minor horizontal and torsional components. Magnetic resonance angiography demonstrated a hypoplastic right VA terminating in the posterior inferior cerebellar artery, a dominant left VA, and a hypoplastic P1-segment of the left posterior cerebral artery (PCA) that was supplied by the left posterior communicating artery (PCoA). The right PCA and both anterior inferior cerebellar arteries were supplied by the basilar artery. The right PCoA originated from the right internal carotid artery. Color duplex sonography showed severe reduction of diastolic blood flow velocities in the left VA during RVAS attacks. The nystagmus pattern can be best explained by vectorial addition of 3D sensitivity vectors of stimulated right and left anterior and horizontal semicircular canals with slightly stronger stimulation on the left side. We hypothesize that in RVAS, compression of dominant VA leads to acute vertebrobasilar insufficiency with bilateral, but asymmetric ischemia of the superior labyrinth. With regard to RVAS etiology, our case illustrates a type of pure vascular RVAS. Severity of attacks markedly decreased after successful bilateral carotid endarterectomy.
Salivary cortisol levels, subjective stress, and tinnitus intensity in tinnitus sufferers during noise exposure in the laboratory.
Int J Hyg Environ Health. 2008 Feb 1 [Epub ahead of print]

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Tinnitus, a chronic internal noise, is thought to increase in intensity during or following external noise exposure. Yet there is no empirical evidence for this complaint in the extant literature. Recently, cortisol has been advanced as a useful tool for studying the physiological effects of noise on stress, but few, if any, studies have examined the short-term effects of noise on cortisol levels in tinnitus sufferers. This study assesses the effects of noise exposure on cortisol levels and subjective stress in tinnitus participants and controls without tinnitus. Twenty tinnitus participants and 20 controls without tinnitus were exposed to a 20-min broadband noise with amplified low frequencies. Saliva samplings for cortisol analysis and subjective stress and tinnitus intensity ratings (for tinnitus participants) were performed at regular intervals throughout testing. Results show higher cortisol levels for both groups immediately before, immediately after, and 10min after the end of noise than at other time points. The tinnitus group had lower overall cortisol levels than controls. In contrast, subjective stress ratings were higher for the tinnitus group, and higher at midpoint and immediately after the noise ended. Tinnitus subjective intensity increased throughout testing, especially for the group with high tinnitus-related distress. Overall results show that noise exposure influences cortisol response, subjective stress, and tinnitus intensity.

The potential role of joint injury and eustachian tube dysfunction in the genesis of secondary Ménière’s disease.

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Ménière’s disease not only includes the symptom complex consisting of attacks of vertigo, low-frequency hearing loss, and tinnitus but comprises symptoms related to the eustachian tube, the upper cervical spine, the temporomandibular joints, and the autonomic nervous system. Quantifiable experience shows that the insertion of a middle-ear ventilation tube can alleviate Ménière’s disease symptoms, suggesting that eustachian tube dysfunction is a contributing feature. Clinical practice also shows that treating disorders of the upper cervical spine and temporomandibular joints can lessen Ménière’s disease symptoms, suggesting a relationship. Similarly, stellate ganglion blocks can be beneficial in controlling Ménière’s disease symptoms, highlighting the influence of the autonomic nervous system. Thus, contrasting symptoms associated with the eustachian tube, the upper cervical spine, the temporomandibular joints, and the autonomic nervous system relate to Ménière’s disease, but the possible reflex pathway by which a link is established is unclear. We made an attempt in this study to describe a hypothetical reflex pathway that links joint injury and the autonomic nervous system, where eustachian tube function is under their influence and is the critical link. In this hypothetical reflex pathway, irritation of facet joints can first lead to an activated anterior cervical sympathetic system via an independent pathway in the mediolateral cell column; it can simultaneously lead to an axon reflex involving nociceptive neurons, resulting in neurogenic inflammation and the prospect of a eustachian tube dysfunction. The eustachian tube dysfunction is responsible for a disturbed middle ear-inner ear pressure relationship, circumstances that have the potential to develop into secondary Ménière’s disease. This reflex pathway is supported by recent animal experiments.
**The NO/ONOO- cycle as the etiological mechanism of tinnitus.**

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Peripheral tinnitus is a good candidate for inclusion under the NO/ONOO cycle etiological mechanism, fitting each of the five principles of this mechanism. Cases of tinnitus are initiated by at least 11 short-term stressors increasing nitric oxide or other cycle mechanisms. Such cycle elements as N-methyl-D-aspartate activity; oxidative stress; nitric oxide; peroxynitrite; vanilloid activity; NF-kappaB activity; and intracellular calcium levels are all reported to be elevated in tinnitus. Tinnitus is comorbid with some putative NO/ONOO- cycle diseases. Most important, multiple agents that down-regulate NO/ONOO-cycle biochemistry are reported to be helpful in the treatment of tinnitus and related diseases. Previous studies suggested that NO/ONOO cycle diseases may be best treated with complex combinations of agents predicted to lower NO/ONOO- cycle biochemistry, and such combinations may be helpful in tinnitus treatment. Other inner-ear-related defects, such as acute or progressive hearing loss, vertigo, and dizziness, may also be NO/ONOO cycle diseases.

**Viral infection and serum antibodies to heat shock protein 70 in the acute phase of Méníere’s disease.**

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Méníère’s disease (MD) is an idiopathic inner-ear disorder characterized by fluctuating hearing loss, episodic vertigo, and tinnitus. Though MD’s etiology is unknown, growing evidence suggests that autoimmunity may be involved in its development. The aim of this prospective study was to investigate the presence of anti-heat shock protein 70 (anti-HSP70) antibodies during the acute phase of MD and to relate its presence to the antibody pattern. We examined the sera of 13 patients by Western blot immunoassays for reactivity to bovine inner-ear antigen (anti-HSP70) antibodies. The presence of viral antibodies and autoantibodies (herpes simplex, types 1, 2; herpes zoster; cytomegalovirus; Epstein-Barr; IgM; IgG; cardiolipin; thyroglobulin and thyroperoxidase; and antinuclear, antimitochondrial, and anti-smooth-cell antibodies) were also tested. We found reactivity to HSP70 in only 1 of the 13 MD patients (7.7%), and it occurred during herpes zoster reactivation. We found no relationship between the presence of antibodies to HSP70 and immunological or viral testing.

**The role of the parabrachial nucleus in the natural history of tinnitus and its implications.**

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The final common pathway in severe tinnitus is modified to include the parabrachial nucleus, which has been identified by c-fos immunocytochemistry as an active, non-auditory site. The parabrachial nucleus acts in conjunction with the amygdala and insula (part of the medial temporal lobe system) to produce a somatic emotional sense that can result in a “bad” feeling. The activation of the final common pathway is rapid, suggesting that early treatment is prudent to prevent neuroplastic changes that would likely lessen affect.
**Familial aggregation of tinnitus: a European multicentre study.**
B-ENT. 2007;3 Suppl 7:51-60.

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Introduction and aim: Tinnitus is a common condition affecting approximately 20% of the older population. There is increasing evidence that changes in the central auditory system following cochlear malfunctioning are responsible for tinnitus. To date, few investigators have studied the influence of genetic factors on tinnitus. The present report investigates the presence of a familial effect in tinnitus subjects.

Methods: In a European multicentre study, 198 families were recruited in seven European countries. Each family had at least 3 siblings. Subjects were screened for causes of hearing loss other than presbyacusis by clinical examination and a questionnaire. The presence of tinnitus was evaluated with the question “Nowadays, do you ever get noises in your head or ear (tinnitus) which usually last longer than five minutes”. Familial aggregation was tested using three methods: a mixed model approach, calculating familial correlations, and estimating the risk of a subject having tinnitus if the disorder is present in another family member.

Results: All methods demonstrated a significant familial effect for tinnitus. The effect persisted after correction for the effect of other risk factors such as hearing loss, gender and age. The size of the familial effect is smaller than that for age-related hearing impairment, with a familial correlation of 0.15.

Conclusion: The presence of a familial effect for tinnitus opens the door to specific studies that can determine whether this effect is due to a shared familial environment or the involvement of genetic factors. Subsequent association studies may result in the identification of the factors responsible. In addition, more emphasis should be placed on the effect of role models in the treatment of tinnitus.

**Prevalence of tinnitus and audiometric shape.**
B-ENT. 2007;3 Suppl 7:37-49.

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Objectives: Studies of tinnitus are often conducted on patient populations presenting for treatment. It is, however, difficult to generalise prevalence numbers and aetiological results from these studies to a healthy, elderly population. The first aim of our study was to determine the prevalence of tinnitus in an otologically screened population between 55 and 65 years old. Secondly, both prevalence and the specific characteristics of tinnitus were compared in subjects with either a flat audiogram, a high-frequency gently sloping audiogram or a high-frequency steeply sloping audiogram.

Methods: 1147 subjects (549 males and 598 females) were recruited through population registers and underwent thorough clinical and audiological examinations. Subjects who reported tinnitus in the general questionnaire about medical history and environmental exposure were invited to complete an additional questionnaire on tinnitus history.

Results: The prevalence of tinnitus was 19.3% according to the general questionnaire on medical health and environmental exposure and 11.8% according to the additional detailed tinnitus-specific questionnaire. Furthermore, our results indicate that gender has a significant effect (tinnitus is more common in males than in females), as does audiometric configuration (tinnitus is more common in subjects with a high-frequency steeply sloping audiogram than in subjects with a flat audiogram). Both effects were significant in noise-/solvent-exposed subjects, as well as in non-exposed subjects. Finally, comparison of “tinnitus characteristics” in subjects categorised by audiogram configuration revealed significant differences in loudness, pitch, temporal variability and family history of tinnitus.
Cochlear NMDA receptor blockade prevents salicylate-induced tinnitus.
B-ENT. 2007;3 Suppl 7:19-22.

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Large doses of aspirin produce reversible hearing loss and tinnitus. These effects have been attributed to the salicylate ion, the active component of aspirin. Salicylate acts as a competitive antagonist at the anion-binding site of prestin, the motor protein of sensory outer hair cells. This provides an explanation for the hearing loss induced by aspirin. However, the molecular mechanism of salicylate-induced tinnitus remains obscure. One physiological explanation is that salicylate ototoxicity is likely to originate in an alteration to arachidonic acid metabolism. Arachidonic acid potentiates NMDA receptor currents. We therefore tested the involvement of cochlear NMDA receptors in the occurrence of tinnitus. Tinnitus was assessed with a behavioural test based on an active avoidance paradigm. Results showed that the tinnitus induced by salicylate may be suppressed by the introduction of NMDA antagonists into the cochlear fluids. To determine if the activation of NMDA receptors was linked to cyclooxygenase inhibition, we investigated the effect of mefenamate (a potent cyclooxygenase inhibitor). Since NMDA antagonists also blocked mefenamate-induced tinnitus, we suggest that salicylate-induced tinnitus is mediated by cochlear NMDA receptors through the inhibition of cyclooxygenase activity. Target cochlear NMDA receptors may therefore present a therapeutic strategy for the treatment of tinnitus.

Sodium salicylate suppresses serotonin-induced enhancement of GABAergic spontaneous inhibitory postsynaptic currents in rat inferior colliculus in vitro.

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Available evidence suggests that sodium salicylate (SS) may produce tinnitus through altering the balance between inhibition and excitation in the central auditory system. Since serotonin (5-hydroxytryptamine, 5-HT) containing fibers preferentially innervate inhibitory GABA neurons, there exists a possibility that SS causes the imbalance between inhibition and excitation through influencing serotonergic modulation of the GABAergic synaptic transmission. In the present study, we examined the effects of SS on 5-HT-mediated GABAergic spontaneous inhibitory postsynaptic currents (sIPSCs) from neurons of the central nucleus of rat inferior colliculus with whole-cell patch-clamp technique and brain slice preparation. Perfusion of 40μM 5-HT robustly enhanced both frequency and amplitude of GABAergic sIPSCs and this 5-HT-induced enhancement of GABAergic sIPSCs could be suppressed by 1.4mM SS. Tetrodotoxin at 0.5μM produced a similar effect as SS did, suggesting that SS suppresses the 5-HT-induced enhancement of GABAergic sIPSCs through depressing spontaneous action potentials of GABA neurons. Our findings suggest that SS may preferentially target GABA neurons and consequently interrupt a normal level of GABAergic synaptic transmissions maintained by the serotonergic system in SS-induced tinnitus.


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Purpose: Interferon-gamma (IFN-gamma) is a key cytokine in inflammatory disorders. Elevated aqueous and serum levels of IFN-gamma levels have been reported to be elevated in patients with Vogt-Koyanagi-Harada (VKH) disease.
The aim of this study was to determine the IFN-gamma gene polymorphisms in VKH disease. Methods: The study involved 136 VKH patients and 176 healthy controls, who were genotyped for functional single nucleotide polymorphism (SNP; rs2430561; A/T) and functional microsatellite (CA) repeats (rs3138557) in the first intron of the IFN-gamma gene. Moreover, clinical manifestations of the patients were also analyzed.

Results: Diffuse choroiditis/staining of fluorescein angiography was seen in all VKH patients in this study. Sunset glow fundus and nummular chorioretinal depigmented scars were observed in 83.9%, and 36.1% of the patients, respectively. Neurological and auditory disorders were observed in 90.1% of the patients: meningismus (79.8%), tinnitus (53.0%), and cerebrospinal fluid pleocytosis (70.0%). Dermatologic manifestations were observed in 22.9% of the patients, manifesting as alopecia (6.9%), poliosis (17.6%), and vitiligo (13.0%). In addition, 22.1% of the patients were classified as having complete VKH disease, while 65.4% as having incomplete VKH disease, and 12.5% as having probable VKH disease. There were no significant differences in the allele and genotype frequencies between VKH patients and healthy controls. In addition, we found no association between each clinical manifestation and SNP (rs2430561) in the healthy control subject. A strong linkage disequilibrium (LD) was found in the functional SNP T allele and functional microsatellite 12 (CA) repeats (D'=0.96-0.99).

Conclusions: The functional SNP T allele and microsatellite 12 (CA) repeats were found to have a strong LD, although a genetic susceptibility for the IFN-gamma gene could not be demonstrated among the Japanese VKH patients.

Transient reduction of tinnitus intensity is marked by concomitant reductions of delta band power.
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Background. Tinnitus is an auditory phantom phenomenon characterized by the sensation of sounds without objectively identifiable sound sources. To date, its causes are not well understood. Previous research found altered patterns of spontaneous brain activity in chronic tinnitus sufferers compared to healthy controls, yet it is unknown whether these abnormal oscillatory patterns are causally related to the tinnitus sensation. Partial support for this notion comes from a neurofeedback approach developed by our group, in which significant reductions in tinnitus loudness could be achieved in patients who successfully normalized their patterns of spontaneous brain activity. The current work attempts to complement these studies by scrutinizing how modulations of tinnitus intensity alter ongoing oscillatory activity.

Results: In the present study the relation between tinnitus sensation and spontaneous brain activity was investigated using residual inhibition (RI) to reduce tinnitus intensity and source-space projected magnetencephalographic (MEG) data to index brain activity. RI is the sustained reduction (criteria: 50% for at least 30 s) in tinnitus loudness after cessation of a tonal tinnitus masker. A pilot study (n = 38) identified 10 patients who showed RI. A significant reduction of power in the delta (1.3-4.0 Hz) frequency band was observed in temporal regions during RI (p ≤ 0.001).

Conclusion: The current results suggest that changes of tinnitus intensity induced by RI are mediated by alterations in the pathological patterns of spontaneous brain activity, specifically a reduction of delta activity. Delta activity is a characteristic oscillatory activity generated by deafferented/deprived neuronal networks. This implies that RI effects might reflect the transient reestablishment of balance between excitatory and inhibitory neuronal assemblies, via reafferentation, that have been perturbed (in most tinnitus individuals) by hearing damage. As enhancements have been reported in the delta frequency band for tinnitus at rest, this result conforms to our assumption that a normalization of oscillatory properties of cortical networks is a prerequisite for attenuating the tinnitus sensation. For RI to have therapeutic significance however, this normalization would have to be stabilized.
Salicylate Alters Expression of Calcium Response Transcription Factor 1 (CaRF1) in the Cochlea: Implications for BDNF Transcriptional Regulation.
Mol Pharmacol. 2008 Jan 15 [Epub ahead of print]
HNO Tuebingen.

Brain-derived neurotrophic factor (BDNF) is a key neurotrophin whose expression is altered in response to neurological activity, influencing both short- and long-term synaptic changes. The BDNF gene consists of eight upstream exons (I-VII), each of which has a distinct promoter, and can be independently spliced to the ninth coding exon (IX). We recently showed that the expression of BDNF exon IV in the cochlea is altered following exposure to salicylate, an ototoxic drug that in high doses is able to induce hearing loss and tinnitus. These changes were a crucial trigger for plasticity changes in the central auditory system. BDNF exon IV expression is regulated via interaction between calcium response elements CaRE1, CaRE2 and CaRE3/Cre (CaREs) that are bound by the transcription factors CaRF1, USF1/2 and CREB, respectively. To determine if the salicylate induced changes in cochlear BDNF exon IV expression include a differential use of the CaRE binding proteins, we studied the level of the corresponding binding-proteins in the spiral ganglion neurons prior to and following systemic application of concentrated salicylate using in situ hybridization and RT-PCR. BDNF exon IV and CaRF1 expression were upregulated following application of salicylate, while USF1/2 and CREB mRNA expression remained unaffected. The changes in BDNF exon IV and CaRF1 expression were also dose-dependent. The data show Ca(2+) and CaRF1 as messengers of trauma (salicylate)-induced altered BDNF levels in the cochlea. Furthermore, they also provide the first evidence that a differential regulation of BDNF transcription factors might participate in BDNF-mediated plasticity changes.

Auditory cortical evoked potentials in tinnitus patients with normal audiological presentation.
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Background/purpose: It is widely assumed that damage to the peripheral hearing system is an essential prerequisite for the occurrence of tinnitus. However, previous studies have failed to target tinnitus patients with normal hearing. This study aims to investigate if tinnitus patients with normal audiological presentation demonstrate increased intensity dependence at the selected frequencies.
Methods: This study applied auditory cortical evoked potential test to investigate nine tinnitus patients with normal audiological presentation and nine age- and sex-matched healthy subjects without tinnitus. Auditory cortical evoked potentials (N1-P2) were elicited from stimuli at four frequencies (4000, 2000, 1000 and 500 Hz) with five intensities (50, 56, 62, 68 and 74 dB nHL). Intensity dependences by latency of N1 and amplitude of N1-P2 were surveyed at midline electrodes.
Results: The results showed that the intensity dependence by latency of N1 to the pooled frequencies at three midline electrodes, e.g. Fz, Cz and Pz, revealed non-significant difference. However, significant differences existed in the intensity dependence of amplitude N1-P2 to the pooled frequencies at the Fz and Cz positions. These differences suggested that tinnitus patients tended to respond less to increased sound intensity and were inclined to weaker intensity dependence.
Conclusion: Increased intensity dependence of N1-P2 component at the selected frequencies cannot be demonstrated in tinnitus patients with normal hearing. Restated, the edge frequency phenomenon fails to present in tinnitus patients with normal hearing, a different characteristic from tinnitus patients with hearing loss.
Dorsal cochlear nucleus responses to somatosensory stimulation are enhanced after noise-induced hearing loss.

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Multisensory neurons in the dorsal cochlear nucleus (DCN) achieve their bimodal response properties [Shore (2005) Eur. J. Neurosci., 21, 3334-3348] by integrating auditory input via VIIIth nerve fibers with somatosensory input via the axons of cochlear nucleus granule cells [Shore et al. (2000) J. Comp. Neurol., 419, 271-285; Zhou & Shore (2004)J. Neurosci. Res., 78, 901-907]. A unique feature of multisensory neurons is their propensity for receiving cross-modal compensation following sensory deprivation. Thus, we investigated the possibility that reduction of VIIIth nerve input to the cochlear nucleus results in trigeminal system compensation for the loss of auditory inputs. Responses of DCN neurons to trigeminal and bimodal (trigeminal plus acoustic) stimulation were compared in normal and noise-damaged guinea pigs. The guinea pigs with noise-induced hearing loss had significantly lower thresholds, shorter latencies and durations, and increased amplitudes of response to trigeminal stimulation than normal animals. Noise-damaged animals also showed a greater proportion of inhibitory and a smaller proportion of excitatory responses compared with normal. The number of cells exhibiting bimodal integration, as well as the degree of integration, was enhanced after noise damage. In accordance with the greater proportion of inhibitory responses, bimodal integration was entirely suppressive in the noise-damaged animals with no indication of the bimodal enhancement observed in a sub-set of normal DCN neurons. These results suggest that projections from the trigeminal system to the cochlear nucleus are increased and/or redistributed after hearing loss. Furthermore, the finding that only neurons activated by trigeminal stimulation showed increased spontaneous rates after cochlear damage suggests that somatosensory neurons may play a role in the pathogenesis of tinnitus.

Relation of Distortion Product Otoacoustic Emission With Tinnitus.
Laryngoscope. 2008 Jan 3 [Epub ahead of print]

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Objective: To investigate cochlear outer hair cell function based on distortion product otoacoustic emission (DPOAE) in patients with tinnitus.

Study design: This is a case control study.

Subject and methods: The subjects are patients who attended the Otorhinolaryngology Clinic in Hospital Universiti Kebangsaan Malaysia over a period of 19 months from April 2005 until October 2006. All patients underwent a full ENT assessment and had tympanometry, pure tone audiometry, and DPOAE tests. The UKM Research and Ethics Committee reviewed and approved the study proposal prior to commencement of this study.

Results: The study population included 49 patients. They consisted of 16 patients (32 ears) with tinnitus and reduced hearing, 13 patients (26 ears) with tinnitus and normal hearing, 7 patients (13 ears) without tinnitus with reduced hearing, and 13 patients (26 ears) without tinnitus with normal hearing. Statistical analysis showed significant differences (P = .00) of mean DPOAE levels between the four groups of patients.

Conclusion: Our results suggest that reduced outer hair cell activity, as detected by reduced DPOAE levels, may manifest as tinnitus even before there is a shift on hearing threshold. We also postulate that further reduction of cochlear outer hair cell activity, as shown by further reduced DPOAE levels, may actually terminate the source of tinnitus.
Influence of silence and attention on tinnitus perception.

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Objective: The purpose of this study was to study the effect of attention and sustained silence on the emergence of auditory phantom perception in normal-hearing adults.
Study design: Cross-sectional survey.
Subjects and methods: While sitting in a sound booth, 66 volunteers (age range, 18-65; mean age, 37.3) performed 3 experiments of 5 minutes each, consecutively and randomly presented. Two deviated attention from auditory system (Hanoi and visual attention experiments), and 1 drove attention to the auditory system (auditory attention). After each experiment, participants were asked about their auditory and visual perception. No sound or light change was given at any moment.
Results: Of the participants, 19.7% experienced tinnitus during Hanoi, 45.5% during visual attention, and 68.2% during auditory attention experiment, with no significant differences for studied variables.
Conclusion: Tinnitus-like perceptions may occur in a nonclinical population in a silent environment. Concomitant auditory attention plays an important role on the emergence of tinnitus.

The association between tinnitus and posttraumatic stress disorder.

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Purpose: Posttraumatic stress disorder (PTSD) affects nearly 10% of the population, a prevalence comparable with that of tinnitus. Similarities between the way PTSD and tinnitus influence auditory behaviors include exaggerated startle responses and decreased loudness tolerance. Tinnitus loudness is often exacerbated by sounds that trigger PTSD-related anxiety. This report addresses physical and psychological relations between PTSD and tinnitus.
Method: A chart review of veterans seen over a 4-year period for tinnitus services was conducted. Case history and self-assessments of tinnitus handicap were examined in all patients. A review of the literature related to triggers and effects of PTSD was conducted to explore potential consequences related to the presence of PTSD in the Veterans Affairs Medical Center (VAMC) tinnitus population.
Results: Chart review confirmed that 34% of the first 300 patients enrolled in the VAMC Tinnitus Clinic also carried a diagnosis of PTSD. Patient reports citing tinnitus severity, suddenness of tinnitus onset, sound-tolerance problems, and sound-triggered exacerbation of tinnitus were more common for patients with a PTSD diagnosis than patients with tinnitus only.
Conclusions: Several neural mechanisms linked to both tinnitus and PTSD affect auditory behaviors. Audiologists should be aware that patients with tinnitus and PTSD will require test protocols and referrals that address these powerful responses.

Assessment of psychopathological aspects and psychiatric comorbidities in patients affected by tinnitus.

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The aim of present study was to determine the psychiatric symptoms and comorbidities in patients affected by tinnitus. The study sample, between June 2004 and September 2005, consisted of 180 Turkish adults living in Elazig. Ninety consecutive tinnitus patients were enrolled on their first visit to the outpatients clinic. Control subjects were recruited partly from the social surroundings of the authors. All subjects with significant medical and/or psychiatric pathologies, such as schizophrenia, manic-depressive psychosis, dementia, and behavioural disorders with social withdrawal or suicidal risk, were excluded, as were those unwilling to take part in the study.
For the psychopathological examination, patients underwent the Structured Clinical Interview for DSM-III-R (SCID-I, SCID-II). Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Symptom Check list-90 (Revised) (SCL-90-R) were also administered to patients with tinnitus and control subjects. SCL-90-R subscales scores, Beck Anxiety Inventory and Beck Depression Inventory scores were significantly higher in tinnitus patients than in normal control subjects. Twenty-four patients (26.70%) with tinnitus had at least one psychiatric diagnosis. Five control subjects (5.60%) had at least one psychiatric diagnosis. There were significant differences between the two groups (P < 0.001). Anxiety disorders and somatoform disorders were significantly higher in tinnitus patients than in normal control subjects. We conclude that psychiatric symptoms (such as symptoms of anxiety, depression or somatization) among patients with tinnitus should alert clinicians for the presence of a chronic and complex psychiatric condition (Axis-I and Axis-II disorders).

**Tinnitus and Coxsackie B infections: a case series.**


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Tinnitus is a frequent and often debilitating condition. There is consensus in the scientific community that there exist various forms of tinnitus, which differ in their pathogenesis. Here we report a series of five cases where the onset of tinnitus was associated with viral infections. In all five patients elevated antibodies against Coxsackie B have been detected. This observation suggests that Coxsackie B Virus infections might be involved in the development of some cases of tinnitus and indicate that further systematic investigations are warranted.

**Acoustic Overstimulation and Noise-Induced Tinnitus Assessed with Gap Prepulse Inhibition of Acoustic Startle in Rats**

Abstract ARO-Meeting

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Humans exposed to high level noise often develop temporary or permanent hearing loss. In some cases the hearing loss is accompanied by an immediate onset tinnitus, but in other cases tinnitus onset may begin days or weeks later. The percentage of animals that develop tinnitus following acoustic trauma is poorly understood, but preliminary results suggest that the percentage increases with the duration and intensity of the exposure and that tinnitus begins shortly after exposure. To address these issues, we used gap prepulse inhibition of acoustic startle (GPIAS) to determine the percentage of rats that develop noise-induced tinnitus and the time of tinnitus onset. Rats were unilaterally exposed to a narrow band noise (12 kHz, 1000 Hz BW) at 123 or 126 dB SPL for 2 h and allowed to recover from anesthesia for 2 h. Each rat was then tested for tinnitus and tinnitus pitch at several post-exposure times. GPIAS testing consisted of 40 trials containing a 115 dB SPL noise burst (20 ms) presented in a 60 dB SPL background noise centered at 6, 12, 16, 20 or 24 kHz (100 Hz BW). On 20 trials the background noise was on continuously (no-gap) and on 20 trials a 50ms silent gap (pre-pulse) was inserted in the background noise 100 ms before the startle stimulus. During baseline, detection of the silent gap inhibited startle amplitudes by 20-80% relative to the no-gap condition. Failure of the silent gap to inhibit the startle reflex was interpreted as evidence of tinnitus at the test frequency. When rats were exposed to unilateral 123 dB SPL noise trauma 33% showed results consistent with the presence of tinnitus. Increasing the intensity of the noise exposure to 126 dB SPL increased the percent of animals with tinnitus like behavior to over 70%. GPIAS was impaired at multiple frequencies immediately after the exposure; however, after 48 h tinnitus-like behavior was mainly observed at 12 and 16 kHz. The results suggest that noise-exposure induces tinnitus in a subset of animals and the likelihood of inducing tinnitus increases with exposure level. In some cases, the tinnitus is transient and in other animals it is persistent. When persistent tinnitus is observed after a 12 kHz narrow band exposure, the putative pitch is typically at 12 or 16 kHz.
Can oculomotricity be altered in patients with tinnitus only? A preliminary study.
Int Tinnitus J. 2007;13(2):152-156.

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The study of oculomotricity is performed by evaluating three systems: saccadic ocular movements (SOMs), optokinetic nystagmus (OKN), and smooth pursuit eye movements (SPEMs). Our aim was to study oculomotricity in patients with a complaint of only tinnitus and to compare it with the value of our control group. We studied the SOMs, OKN, and SPEMs in 25 patients complaining only about tinnitus and in 35 normal adults and compared the results. The data analysis showed a significant difference in the value of the SOMs and SPEMs between the two groups. Sensorineural tinnitus can originate in the organ of Corti, in the cochlear nerve, or in the auditory pathways of the central nervous system. The auditory cortex connects with visual areas and with the superior colliculus. The latter structure is involved in the origin of SOMs and OKN. In our study, we found an increased delay in saccadic tests. In the SPEMs, we observed an increase in the degree of distortion, and a reduction in the gain. This outcome is in accordance with the literature. However, we detected a few alterations in the OKN, and this finding is in partial agreement with the studies analyzed. Alterations in oculomotricity can indicate involvement of the central nervous system in patients with a complaint of only tinnitus.

Physiological and psychological stress reactivity in chronic tinnitus
Journal of Behavioral Medicine January 2008

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Several models of tinnitus maintenance emphasize the importance of cognitive, emotional and psychophysiological processes. These factors contribute to distress in patients with decompensated tinnitus symptoms. We investigated whether tinnitus patients show increased physiological levels of arousal, more intense stress reactivity patterns and exaggerated psychological strain compared to healthy controls. Seventy tinnitus patients and 55 healthy controls underwent various stress tests. Muscular reactivity and peripheral arousal as well as strain ratings were assessed. Tinnitus patients reported significantly more strain during stress tests compared to healthy controls. Few physiological reactivity patterns differed significantly between the two groups. The physiological data thus only partly supported a hyperreactivity hypothesis. Strain reports and physiological data were only marginally correlated. Tinnitus patients show maladaptive appraisal processes during stress exposure, yet physiological reactivity is only slightly affected. Treatment programs for patients with decompensated tinnitus symptoms should account for appraisal processes and coping mechanisms in stressful situations.

Abstract ARO-Meeting

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In previous work, 18 investigators highly experienced in evaluating tinnitus were surveyed to develop consensus concerning the item content for a new questionnaire designed to optimize validity for both discriminative (diagnostic) and evaluative (outcomes assessment) purposes. From existing questionnaires (175 items) the group selected 69 items that they judged sensitive to treatment effects while addressing all major components or "dimensions" of tinnitus distress. The number of items was then reduced using objective selection procedures to minimize redundancy and maximize responsiveness, resulting in a total of 43 items for use in Prototype 1 of the TFI. Prototype 1 was tested in a multi-center study (5 clinics in Oregon, Ohio, and Florida). Tinnitus patients' responses to TFI Prototype 1, the Tinnitus Handicap Inventory (THI), the Beck Depression Inventory-FastScreen (BDI-FS), and a Visual Analog Scale (VAS) for tinnitus severity were obtained from 327 subjects. Sixtyfive subjects provided Follow-up data at 3 months and 39 subjects provided test-retest reliability data. Statistical analyses of the TFI revealed excellent test-retest reliability (r=0.92) and internal consistency reliability (alpha=0.99), high intercorrelations for the TFI vs. THI and VAS (0.91 and 0.71 respectively), and expected correlation with BDIFS (0.59). Various factor analysis models were evaluated; the best (Principal Axis Factoring, oblique rotation) yielded 7 easily-identified factors accounting for 80% of the variance. Three-month follow-up data revealed good effect sizes for both the overall TFI (E.S.=0.79, compared to E.S.=0.71 for the THI) and individual items (most E.S.>0.70). In summary, Prototype 1 of the TFI exhibits excellent content and construct validity for both discriminative and evaluative purposes, setting the stage for further work to reduce the number of items while retaining maximal sensitivity to treatment-related change.


Abstract ARO-Meeting

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A prior study (Abstract #611, 2008 ARO Midwinter Meeting) identified 43 questionnaire items that are representative of 7 major dimensions of clinically significant tinnitus. The present research was designed to reduce the number of questionnaire items to the minimum needed for reliable evaluation of those dimensions or subscales. Based on relevant literature, 3-4 items per dimension are required for adequate measurement validity and reliability. Objective selection criteria (to be shown) were therefore applied to the 43-item set, resulting in selection of 23 questions that are well representative of the 7 dimensions or subscales. An additional 7 questions were considered important and had moderate to high factor loadings on more than one factor; these questions were examined using similar criteria, and proved to be interpretable as an eighth factor or subscale characterized as Tinnitus Impact on Quality of Life. Based on data from the prior study, intercorrelations between these eight factors were moderate to high, and all eight showed good or excellent sensitivity to treatment-related change (Effect Sizes of 0.8-1.24 for 6 factors, 0.49 and 0.61 for the other two). The new 30-item TFI will be displayed and responses of over 300 tinnitus patients will be summarized.
Intake data are again being obtained from clinics in Oregon, Ohio and Florida, providing a large, diverse patient group. Treatment follow-up results and test-retest reliability are evaluated in smaller subsets. Responses to the TFI, Tinnitus Handicap Inventory, the Beck-Depression Inventory-FastScreen, and a Visual Analog scale for tinnitus severity are being obtained. In clinic use, the 30-item TFI has proven easy for respondents to complete, with very little missing data. Detailed results will be discussed in relation to both discriminative (diagnostic) and evaluative (outcomes assessment) strengths of the new TFI.

Distortion Product Otoacoustic Emissions (DPOAE) Behavior and Growth Rate in Tinnitus Subjects with Normal Audiograms

Abstract ARO-Meeting

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Tinnitus disrupts the daily life of 1 out of every 200 adults, yet its physiological basis remains largely a mystery. A fundamental, but unanswered, question is whether cochlear pathology is always a prerequisite for developing tinnitus. While tinnitus and hearing loss (as measured by elevated pure tone thresholds) commonly co-occur, they are far from perfectly correlated with one another. The present study took a fresh look at the status of the auditory periphery in people with tinnitus using DPOAEs. We specifically studied people with normal audiograms so any abnormal findings would not be attributable to large-scale hair cell damage. We tested 4 tinnitus and 6 non-tinnitus subjects with normal audiograms (≤25 dB HL at 125 - 8000 Hz) and one tinnitus subject with a slight loss at 8000 Hz (30 - 35 dB HL). DPOAE magnitudes were measured for a set of 52 frequencies (500 Hz ≤ f₂ ≤ 8 kHz, with f₂/f₁=1.2) and nine intensities (20 dB ≤ L₂ ≤ 60 dB, with L₁ = 39 + 0.4*L₂). We found that tinnitus subjects had higher DPOAE levels than control subjects between 1 kHz and 2 kHz at the highest intensity tested (L₂ = 60 dB). Additionally, we found that at both high and moderate intensities (L₂ = 60 and 40 dB), tinnitus subjects had larger DPOAEs than control subjects for frequencies above 4 kHz. Finally, trends indicate that the growth rate of DPOAEs in tinnitus subjects is larger than the growth rate seen in control subjects between 1.5 kHz and 2 kHz. These data suggest peripheral auditory malfunction in tinnitus subjects with normal audiograms.

Vascular loops causing otological symptoms: a systematic review and meta-analysis.

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Objective of review: To determine evidence for a relationship between vascular loops in contact with the vestibulocochlear nerve (CN VIII) and otological symptoms.

Type of review: Systematic review and meta-analysis of observational studies.

Search strategy: Comprehensive search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Clinical Evidence and Cochrane Central Register of Trials. Reference lists cross-referenced and authors contacted for missing data. No language restrictions.

Evaluation methods: Included studies: (1) compared symptoms in subjects with a vascular loop contacting CN VIII to subjects without (inter-subject control); (2) compared the prevalence of vascular loop in contact with CN VIII in symptomatic ears to contra-lateral asymptomatic ears (intra-subject control). Study quality systematically appraised.

Results: Five case-control studies included. A statistically significant association was demonstrated for the prevalence of vascular loops in contact with CN VIII, with unilateral sensorineural hearing loss: pooled odds ratio (OR) 2.0 [95% confidence interval (CI): 1.5-2.6]. No association was demonstrated for non-pulsatile tinnitus. A highly significant association with vascular loops was shown in subjects having pulsatile tinnitus, with pooled OR: 78.8 (95% CI: 10.9-821.8).
Conclusions: Vascular loops in contact with CN VIII are a normal variant. Subjects with unilateral hearing loss were twice as likely to have these vascular loops in the symptomatic ear, than in the asymptomatic ear. Subjects with pulsatile tinnitus were 80 times more likely to have a contacting vascular loop than patients with non-pulsatile tinnitus, suggesting in some cases a causal relationship exists for pulsatile tinnitus, where surgical intervention may be occasionally indicated.

[Arteriovenous dural malformation in ENT]
[Article in Spanish]
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The arteriovenous dural malformation (MAVD) is a rare entity between the vascular cranial anomalies with a not well known ethiology and variability in treatments. We present eleven cases of MAVDs, between them five presented tinnitus as symptom of aparition. The importance of this pathology makes necessary to discard it before a patient consulting because of pulsatile tinnitus with normal otoscopy.

Development and Psychometric Adequacy of the Screening Version of the Tinnitus Handicap Inventory.
Otol Neurotol. 2008 Feb 11 [Epub ahead of print]
Newman CW, Sandridge SA, Bolek L.
*Section of Audiology, Head and Neck Institute, Cleveland Clinic, Cleveland, Ohio; and †Vanderbilt Bill Wilkerson Center, Department of Hearing and Speech Sciences, Vanderbilt University, Nashville, Tennessee, U.S.A.

Objective: To develop a screening version of the Tinnitus Handicap Inventory (THI-S) and establish its psychometric characteristics.

Design: Prospective clinical study to analyze 1) the level of predictability between THI and THI-S; 2) test-retest reliability of the THI-S; 3) 95% confidence intervals (critical difference scores) for the THI-S; and 4) a THI-S cutoff score used for referral purposes.

Setting: Head and Neck Institute at the Cleveland Clinic, a tertiary care medical center.

Patients: Thirty-three patients reporting tinnitus as their primary complaint.

Interventions: There was, on average, a 16-day interval between test-retest administrations of the THI-S.

Main outcome measure: Comparability of scores between the THI and the THI-S and test-retest reliability of the THI-S was assessed using Pearson product-moment correlations. The level of agreement between the 2 administrations of the THI-S was evaluated using Bland-Altman repeatability plots.

Results: Comparability between the THI and THI-S was high (r = 0.90). Test-rest reliability of the THI-S was adequate (r = 0.81), as well as the level of agreement between administrations as demonstrated by the Bland-Altman plot. Based on 95% confidence intervals, pretreatment and posttreatment scores would have to differ by more than 10 points for intervention efforts to be considered significant. A 6-point cutoff score was analyzed as an appropriate fence for referral.

Conclusion: The THI-S is a psychometrically robust screening measure of activity limitation and participation restriction.
In an evolving clinical experience since 1979, the medical significance of the symptom of tinnitus has been identified as a "soft" sign of neurodegeneration (ND) in the central nervous system (CNS) in a particular subset of tinnitus patients diagnosed with a predominantly central-type, severe, disabling, subjective idiopathic tinnitus. To highlight this experience, a retrospective review and analysis of consecutive tinnitus patients (N = 96) was conducted. Ninety-six tinnitus patients (ages 22-90 years) were seen in neurotological consultation from November 1, 2005, to June 30, 2007, all of whom had subjective idiopathic tinnitus of the severe disabling type (SIT). Of these 96 patients, 54 had SIT of the predominantly central type and of these, 18 (ages 39-75 years) were recommended for nuclear medicine imaging (single-photon emission computed tomography [SPECT] and fluorodeoxyglucose-positron emission tomography/computed tomography [FDG-PET/CT]). Patient selection for nuclear medicine imaging fulfilled the criteria of a medical-audiological ND tinnitus profile: completion of a patient protocol that diagnosed a predominantly central-type, severe, disabling, subjective, idiopathic tinnitus lasting in excess of 1 year, and failure of existing modalities of treatment attempting tinnitus relief.

In 16 of the 18 patients, objective evidence of ND was reported in multiple neural substrates of brain obtained with SPECT or FDG-PET/CT of brain. Classification of CNS ND and tinnitus differentiated between (1) ND of nonspecific or unknown etiology; (2) ND manifested by perfusion asymmetries in brain associated with ischemia (n = 11/18); and (3) neurodegenerative CNS disease consistent with nuclear medicine criteria for senile dementia of the Alzheimer’s type (n = 5/18). The diagnosis has been associated with cerebrovascular disease (n = 16/18). The identification of neurodegenerative CNS disease in a selected cohort of patients with subjective idiopathic tinnitus as a soft sign of such CNS disease has implications for diagnosis and treatment.

The identification of neurodegenerative CNS disease in a selected cohort of patients with subjective idiopathic tinnitus as a soft sign of such CNS disease has implications for diagnosis and treatment.

The slow-brainstem syndrome: tinnitus and dyssynchrony in the central nervous system.
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Among older patients we regularly find those who complain of a hazy tinnitus in combination with vertigo, giddiness, and dizziness. They also report a reduced state of alertness. Objectively, these patients exhibit an increase in latencies of experimentally evoked vestibular nystagmus and of auditory brainstem-evoked potentials. This group of patients is affected by the disorder known as slow-brainstem syndrome. By evaluating therapeutic responses, we noted especially in this group that a combination of cocculus (picrotoxin), conium (Coniine), amber, and petroleum (Vertigoheel) has a “tune-up” effect on the brainstem. With regular therapy using this drug regimen, we observed a normalization of the distorted latencies of the statoacoustic pathways, followed by disappearance of the symptoms. Our explanation for this phenomenon suggests an improvement in the vestibular, ocular, and acousticocortical pathway synchronization in such older patients. We present some models.

The Tinnitus Handicap Inventory: a study of validity and reliability.
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Our aim was to compose a Turkish version of the Tinnitus Handicap Inventory (THI). Each of two individuals independently translated and retranslated the English version of the THI, and it was adapted by an expert team. The Turkish version of the THI was completed by 110 tinnitus patients. We assessed the internal consistency and reliability of the Turkish version by Cronbach’s alpha. We assessed test-retest reliability with a second investigation in 21 patients. We assessed construct validity by analyzing the patients according to their age and to tinnitus duration.
Internal validity was tested by multi-item analysis, to assess item convergence and discriminant validity. We obtained high internal consistency and reliability with the Cronbach’s alpha coefficient (0.88) and high intraclass correlation coefficient (ICC, 0.78-0.90). Test-retest correlation coefficient scores were highly significant. The Turkish version of the THI is a highly consistent and reliable measure that can be used in evaluating symptoms in tinnitus patients.

**Validation of the Dutch and the French version of the Tinnitus Questionnaire.**

* B-ENT. 2007;3 Suppl 7:11-17.

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Objectives: To validate the Dutch and the French version of the Tinnitus Questionnaire and characterise the subscales. The original Tinnitus Questionnaire has already proven to be a usable measurement tool to discriminate complaining from non-complaining tinnitus patients and it provides differentiation into 5 dimensions.

Methods: The English version of the TQ was used. The Dutch and the French version were obtained by the process of translation and back-translation. The TQ was assessed in 167 patients whose mother tongue was Dutch and who presented at the ENT department of the Antwerp University Hospital. Internal consistency was evaluated using Cronbach’s alpha coefficient. Factor analysis with Varimax oblique rotation was compared to the results from previous psychometric analysis of the original TQ.

Results: The internal consistency of the Dutch version of the TQ proved to be very high, with a Cronbach’s alpha value of 0.95. Independent factor analysis identified the five subscales in accordance with the Hiller and Goebel’s findings: emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances and somatic complaints.

Conclusion: The Dutch and the French translation of the TQ are included here. The psychometric characters of the Dutch questionnaire are similar to the original English questionnaire. This questionnaire provides appropriate disease-specific health-related quality-of-life outcome measures in tinnitus patients. In addition to the TQ, we advise the incorporation of three equal-appearing interval scales in all tinnitus anamnesis and follow-up.

**MRI in patients with otovestibular complaints of unknown origin.**

* B-ENT. 2007;3 Suppl 7:27-35.

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Objectives: The place of MRI in the diagnostic work-up of patients with bilateral perceptive hearing loss, tinnitus and vertigo is under discussion. The purpose of this study is to investigate the role of MRI in patients with otovestibular and cranial nerve complaints of unknown aetiology.

Methodology: After thorough otologic examination, 430 patients were consecutively referred for an MR examination of the cerebellopontine angle.

Results: The detection rate for essential lesions was 4.9%. Two groups of retrocochlear lesions were frequently observed: central WMLs/atrophy and neurovascular conflict affecting a cranial nerve. Conclusions: MR imaging of the cerebellopontine angle, fossa posterior and petrous bones makes it possible to observe abnormalities of the vestibulocochlear nerve and inner ear. Additional T2-weighted FSE images of the whole brain make it possible to evaluate the occurrence of early central lesions. This imaging protocol can diagnose essential lesions relating directly to the complaint in 4.9% of the patients with hearing loss, subjective tinnitus or vertigo. We frequently observed two groups of lesions of uncertain significance in our study population. WMLs are present in 50% of patients with a mean age of 59 years. In the younger subpopulation aged under 51 years the prevalence of WMLs is 24%. It remains unclear whether these lesions can be accounted for by the diversity of symptoms with which the patients presented. In addition, we found a high number of neurovascular conflicts involving different cranial nerves.
Diagnostic Value of Color-Coded Doppler Sonography in Neuro-Otologic Disorders.

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Purpose: The successful introduction of Doppler and Color-Coded Doppler Sonography (CCDS) in the field of Otorhinolaryngology has improved the diagnostic sonographic value for several diseases of the head and neck region, e.g. in hemangiomas and vascular malformations. The diagnostic value of CCDS for examination of the extracranial brain supplying vessels in combination with neuro-otologic disorders is still under controversial discussion.

Materials and methods: We investigated the diagnostic CCDS findings for 215 patients suffering from different neuro-otologic disorders. All patients were classified into 4 groups according to the different disorder entity (sudden deafness, tinnitus, vestibular neuropathy, combined diagnosis). The frequency of pathologic CCDS findings was correlated with the different groups using sonographic parameters such as atherosclerosis, stenosis and intima-media thickness.

Results: Classification of the disorder entities led to the following distribution: Sudden deafness group (85 patients; 40 %), Tinnitus group (44 patients; 20 %), Vestibular neuropathy group (41 patients; 19 %), Combined diagnosis group (45 patients; 21 %). Sonographic evaluation of atherosclerosis was possible in 76 cases (35 %), changes of the intima-media thickness were observed in 43 cases (20 %) while proof of stenoses was identified in 15 cases (7 %).

The evaluation of plaque formation (atherosclerosis) in the sudden deafness group was significantly higher (p < 0.01) than in all other groups although the combined diagnosis group demonstrated certain tendencies (p < 0.08) without significant correlation.

Conclusion: Our results reinforce the hypothesis of a vascular genesis of sudden deafness and seem to offer the possibility of sonographic differentiation between neuro-otologic disorder entities by use of CCDS. In contrast, it seems that the role of CCDS is negligible for individual diagnostic purposes.

A convenient sonographic technique for diagnosis of pulsatile tinnitus induced by a high jugular bulb.

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Objective: The purpose of this report is to describe our experience with sonography in a case of pulsatile tinnitus (PT) due to a high jugular bulb (HJB).

Methods: A 71-year-old woman came to our hospital with a 1-year history of right PT. A right HJB was shown on cerebral angiography, and enlargement of the right jugular bulb compared with the left side was found. First, the ultrasound probe was placed on the anterior right upper neck at the anterior edge of the sternocleidomastoid muscle to identify the ipsilateral internal jugular vein (IJV) and measure the flow velocity. After the measurement, the ultrasound probe gradually compressed the skin until the flow in the IJV decreased.

Results: The patient reported that her PT decreased after the flow in the IJV decreased. We decided that the PT in this case was induced by the HJB.

Conclusions: This technique is less invasive and convenient for the diagnosis of PT caused by an HJB.
IV Imaging

Imaging of tinnitus.

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From a radiologic workup perspective, tinnitus is classified into pulsatile, which can be objective, and nonpulsatile, which is typically subjective. There is considerable discrepancy within the literature regarding the percentage of positive findings in patients with pulsatile tinnitus. The authors discuss the overlap in the radiographic findings detected in association with tinnitus in both asymptomatic patients and symptomatic patients and the importance for imaging to detect treatable causes. They discuss imaging related to diagnosis and treatment and provide an imaging workup algorithm.

V Pharmacotherapy

Sustained Release of Lidocaine into the Cochlea via Biodegradable Materials
Abstract ARO-Meeting

Rie Horie¹, Takayuki Nakagawa¹, Tatsunori Sakamoto¹, Yayoi S Kikkawa¹, Kazuya Ono¹, Yasuhiro Tabata², Jyuichi Ito¹
¹Otolaryngology Head and Neck Surgery, Graduate School of Medicine, Kyoto University, ²Biomaterials, Frontier Medical Sciences, Kyoto University

Effective treatment for tinnitus has not been established. Lidocaine is a non-steroidal, anti-inflammatory local anesthetic and intravenous injection of lidocaine has been shown to transiently suppress tinnitus in several doubleblind studies. However, transtympanic infusion of lidocaine into the tympanic cavity can cause several vestibular side effects such as vertigo and nausea, making it impractical to use in clinics. Therefore, we developed biodegradable sustained-release materials which has longer and localized release profile, and tested this system In Vitro and in vivo. Sustained release of drugs to the inner ear has been achieved by placing these biodegradable materials on the round window membrane (Endo 2005, Tamura 2005, Iwai 2006, Lee 2007). In view of clinical application, we chose gelatin hydrogel and PLGA (poly lactic-co-glycolic acid) as biomaterials for sustained release of lidocaine. In Vitro release studies of lidocaineloaded biomaterials were performed. Results showed no sustained release of lidocaine using gelatin hydrogels. In contrast to hydrogels, PLGA exhibited preferable release profiles of lidocaine In Vitro. PLGA particles of which outer diameter was 5 μm showed sustained release of lidocaione over 2 weeks and 100 μm-PLGA particles achieved over 4 week-release of lidocaine. We thus designed an In Vivo study to examine the potential of PLGA particles for sustained delivery of lidocaine into the cochlea fluids using guinea pigs.

Molecular Approaches to Tinnitus
Abstract ARO-Meeting

Marlies Knipper¹, Rama Panford-Walsh¹, Lukas Ruettiger1, Wibke Singer¹, HynSoon Geisler¹, Karin Rohbock¹, Holger Schulze², Ulrike Zimmermann¹
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Aberrant neuronal activity is known to lead to changes in neuronal plasticity. However, the molecular changes following sensory trauma and the subsequent response of the central nervous system are only poorly understood. We focused on finding a molecular tool for monitoring the features of excitability which occur following acoustic and ototoxic trauma to the auditory system. of particular interest are genes that alter their expression pattern during activity-induced changes in synaptic efficacy and plasticity. The expression of brain-derived neurotrophic factor (BDNF) and the activity-dependent cytoskeletal protein (Arg3.1/arc) were monitored in the peripheral and central auditory system hours and days following tinnitus-inducing traumatic stimuli or salicylate treatment. Tinnitus induction was monitored in a rodent animal behavior model (Rüttiger et al., 2003, Hear Res).
Excitatory input to the rat AI were investigated by local field potential (LFP) post pure-tone acoustic trauma using chronic implantation of multi-channel microelectrode arrays. BDNF and Arg3, were monitored at the mRNA and protein level in the cochlea and subcortical and cortical areas. We present here a summary of recent findings comparing and correlating the expression of activity dependent genes with tinnitus-behavior. the data are discussed in the context of using the monitoring of activity-dependent genes to screen for the pharmacological reversal of tinnitus.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft Kni 316/3-2 and Fortüne 816-0-0.

Molecular Components and Synaptic Functions of the Endocannabinoid System in the Dorsal Cochlear Nucleus (DCN)
Abstract ARO-Meeting

Yanjun Zhao¹, Maria Rubio², Thanos Tzounopoulos¹
¹Chicago Medical School, Rosalind Franklin University, ²University of Connecticut

Molecular Components and Synaptic Functions of the Endocannabinoid System in the Dorsal Cochlear Nucleus (DCN). Endocannabinoid (EC) signaling has emerged as one of the most important neuromodulatory systems in the brain. However, the cellular and molecular components of this system have not been determined in the auditory system. Previous studies from our lab have revealed that cellspecific EC signaling in the DCN determines cell-specific synaptic plasticity. The DCN, an auditory brainstem nucleus, integrates acoustic with multimodal sensory inputs from diverse areas of the brain. Excitatory parallel fibers (PFs) carry these diverse signals to the apical, spiny dendrites of fusiform cells (FCs) and cartwheel cells (CWCs), while auditory nerve (AN) fibers carry acoustic inputs to the basal dendrites of FCs. Here, by using electron microscopy and electrophysiological assays we found that key proteins involved in EC signaling are expressed in the molecular layer, but not in the deep layer of the DCN. Presynaptic CB1 receptors (CB1Rs) are expressed in PFs and in inhibitory terminals synapsing onto CWCs and FCs, while they are absent in AN fibers. 2-arachidonoyl-glycerol (2-AG) and anandamide have been identified as ECs. Diacylglycerol lipase a (DGL-a), one of the enzymes synthesizing 2-AG was expressed on dendrites and spines of FC and CWC respectively. By blocking the synthesis of 2-AG with Tetrahydrolipstatin (THL, 20 μM) or RHC80267 (50 μM) depolarizationinduced suppression of excitation (DSE), a form of shortterm plasticity, was blocked in PF inputs to CWCs, further indicating that 2-AG is the endocannabinoid mediating neuromodulation in the DCN. Depolarization-induced suppression of glycinergic inhibition (DSI) was absent in CWC and FC. However, application of the CB1 receptor agonist WIN 55,212-2 (1μM) resulted in a suppression of glycinergic IPSCs in CWCs. These data suggest that glycinergic terminals in the molecular layer express CB1Rs. Subsequently, EM studies confirmed expression of CB1Rs in glycinergic inhibitory terminals to CWC and FCs. Determining the anatomical and functional properties of EC signaling in the DCN should not only contribute to an understanding of the generation of auditory neural responses, but will also have a significant impact on our understanding and cures for disorders caused by neural plasticity-like mechanisms, including tinnitus.

Effect of MK-801 Treatment On the Induction of Hyperactivity in the Dorsal Cochlear Nucleus by Intense Sound Exposure
Abstract ARO-Meeting

Michael Criddle, James Kaltenbach
Wayne State University

Numerous lines of evidence support the hypothesis that DCN hyperactivity, characterized by an increase in spontaneous activity, is an important neural correlate of some forms of tinnitus. for example, both tinnitus and DCN hyperactivity develop in animals following intense noise exposure and there is a significant relationship between the behavioral evidence of tinnitus and the degree of hyperactivity in the DCN (Kaltenbach et al., 2004). Moreover, the tonotopic profile of activity and numerous features of its behavior correlate with similar features in psychophysically defined tinnitus in human subjects (Kaltenbach, 2006).
The present study was carried out in an effort to explore the mechanism by which hyperactivity emerges in the DCN following intense noise exposure. We hypothesized that hyperactivity involves plasticity in the NMDA receptor pathway, because the NMDA receptor is found in the superficial layer of the DCN where it affects the activity of fusiform cells, which have been shown previously to be generators of hyperactivity. To test this hypothesis, we examined the effect of blocking NMDA receptors on the level of hyperactivity that develops in the DCN. Comparisons of DCN activity were performed in three groups of hamsters. The first group consisted of animals exposed to intense sound (10 kHz, 115 dB SPL, 4 hrs) while a second group served as unexposed controls. A third group of animals was exposed to sound after being pretreated with the NMDA receptor antagonist, MK-801. The control group received a sham injection of 0.9% saline. All groups were allowed a recovery period of 30-40 days following exposure or control treatment. Each was then studied electrophysiologically by recording levels of spontaneous activity as a function of location along the tonotopic axis of the DCN. The results showed that intense tone exposure caused a significant increase in spontaneous activity in the DCN relative to those in control animals, similar to those observed in previous studies. In contrast, the exposed animals treated with MK-801 displayed a consistent decrease in spontaneous activity across the entire DCN. These findings suggest that NMDA receptor blockade may play an important role in the generation of hyperactivity in the DCN. The possible circuit elements involved in the induction of hyperactivity will be discussed. (This work was supported by R01 DC003258).

An unusual case of prolonged tinnitus following low-dose amitriptyline.
J Psychopharmacol. 2008 Feb 28 [Epub ahead of print]

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We report on a case of unilateral tinnitus after a short course of low-dose amitriptyline for neuralgic foot pain. This has been described in the literature previously at much higher doses and is associated with prolonged administration; we present our case with a review of the current literature in-order to raise awareness of this possible complication of anti-depressant therapy. We also propose a novel hypothesis for the pharmacological basis of amitriptyline-induced tinnitus.

Blockade of cochlear NMDA receptors prevents long-term tinnitus during a brief consolidation window after acoustic trauma.

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Tinnitus, the perception of sound in the absence of external acoustic stimulation, is a common and devastating pathology. It is often a consequence of acoustic trauma or drug toxicity. The neuronal mechanisms of tinnitus are neither yet fully understood nor are effective treatments available. Using a novel behavioral paradigm for measuring tinnitus in the rat based on tone-guided navigation, we show here that the development of long-term noise-induced tinnitus, the most prevalent and clinically important form of human tinnitus, can be abated by local administration of the NMDA antagonist “ifenprodil” into the cochlea in the first 4 days following the noise insult but not afterwards. This suggests that long-term tinnitus undergoes a consolidation-like process, resembling the ontogeny of items in long-term memory. Furthermore, this finding paves the way to potential therapeutic strategies for the prevention of chronic tinnitus once the noise insult had taken place.

The slow-brainstem syndrome: tinnitus and dyssynchrony in the central nervous system.

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Among older patients we regularly find those who complain of a hazy tinnitus in combination with vertigo, giddiness, and dizziness. They also report a reduced state of alertness. Objectively, these patients exhibit an increase in latencies of experimentally evoked vestibular nystagmus and of auditory
brainstem-evoked potentials. This group of patients is affected by the disorder known as slow-brainstem syndrome. By evaluating therapeutic responses, we noted especially in this group that a combination of cocculus (picrotoxin), conium (Coniine), amber, and petroleum (Vertigoheel) has a “tune-up” effect on the brainstem. With regular therapy using this drug regimen, we observed a normalization of the distorted latencies of the statoacoustic pathways, followed by disappearance of the symptoms. Our explanation for this phenomenon suggests an improvement in the vestibular, ocular, and acousticocortical pathway synchronization in such older patients. We present some models.

The NO/ONOO- cycle as the etiological mechanism of tinnitus.

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Peripheral tinnitus is a good candidate for inclusion under the NO/ONOO cycle etiological mechanism, fitting each of the five principles of this mechanism. Cases of tinnitus are initiated by at least 11 short-term stressors increasing nitric oxide or other cycle mechanisms. Such cycle elements as N-methyl-D-aspartate activity; oxidative stress; nitric oxide; peroxynitrite; vanilloid activity; NF-kappaB activity; and intracellular calcium levels are all reported to be elevated in tinnitus. Tinnitus is comorbid with some putative NO/ONOO- cycle diseases. Most important, multiple agents that down-regulate NO/ONOO-cycle biochemistry are reported to be helpful in the treatment of tinnitus and related diseases. Previous studies suggested that NO/ONOO cycle diseases may be best treated with complex combinations of agents predicted to lower NO/ONOO- cycle biochemistry, and such combinations may be helpful in tinnitus treatment. Other inner-ear-related defects, such as acute or progressive hearing loss, vertigo, and dizziness, may also be NO/ONOO cycle diseases.

Cochlear NMDA receptor blockade prevents salicylate-induced tinnitus.
B-ENT. 2007;3 Suppl 7:19-22.

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Large doses of aspirin produce reversible hearing loss and tinnitus. These effects have been attributed to the salicylate ion, the active component of aspirin. Salicylate acts as a competitive antagonist at the anion-binding site of prestin, the motor protein of sensory outer hair cells. This provides an explanation for the hearing loss induced by aspirin. However, the molecular mechanism of salicylate-induced tinnitus remains obscure. One physiological explanation is that salicylate ototoxicity is likely to originate in an alteration to arachidonic acid metabolism. Arachidonic acid potentiates NMDA receptor currents. We therefore tested the involvement of cochlear NMDA receptors in the occurrence of tinnitus. Tinnitus was assessed with a behavioural test based on an active avoidance paradigm. Results showed that the tinnitus induced by salicylate may be suppressed by the introduction of NMDA antagonists into the cochlear fluids. To determine if the activation of NMDA receptors was linked to cyclooxygenase inhibition, we investigated the effect of mefenamate (a potent cyclooxygenase inhibitor). Since NMDA antagonists also blocked mefenamate-induced tinnitus, we suggest that salicylate-induced tinnitus is mediated by cochlear NMDA receptors through the inhibition of cyclooxygenase activity. Target cochlear NMDA receptors may therefore present a therapeutic strategy for the treatment of tinnitus.
Multifaceted therapeutic benefits of Ginkgo biloba L.: chemistry, efficacy, safety, and uses.

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The new age of nutraceuticals is now embracing the centuries old herbal extract of Ginkgo biloba (Mantissa Plantarum Altera, 1771, Ginkgoceae). The standardized preparation of the Ginkgo leaf extract (EGb 761) contained 2 main bioactive constituents, flavonoid glycosides (24%) and terpene lactones (6%), along with less than 5 ppm of the allergenic component, ginkgolic acid. The Ginkgo leaf extract has been reported to have neuroprotective, anticancer, cardioprotective, stress alleviating, and memory enhancing effects and possible effects on tinnitus, geriatric complaints, and psychiatric disorders. The therapeutic mechanisms of action of the Ginkgo leaf extract are suggested to be through its antioxidant, antiplatelet, antihypoxic, antiedemic, hemorrhheologic, and microcirculatory actions, where the flavonoid and the terpenoid constituents may act in a complementary manner. Toxicity studies show that the Ginkgo leaf extract is relatively safe for consumption, although a few side effects have been reported, that is, intracerebral hemorrhage, gastrointestinal disturbances, headaches, dizziness, and allergic skin reactions. The use of Ginkgo leaf extract may be promising for treatment of certain conditions, although its long-term use still needs to be evaluated.

Extract of Ginkgo biloba induces glutamate cysteine ligase catalytic subunit (GCLC).

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The extract of Ginkgo biloba (EGb), containing 24% flavone glycosides and 6% terpenoids, is widely used to treat early-stage Alzheimer’s disease, vascular dementia, peripheral claudication and vascular tinnitus. Its marked antioxidant activity has recently been demonstrated in both cell lines and animals. Glutathione (GSH) plays an important role in the antioxidant system by conjugating to xenobiotics to facilitate their export from cells. Glutamate cysteine ligase (GCL) is the rate-limiting enzyme for GSH synthesis and its catalytic subunit (GCLC) determines this de novo synthesis. Thus, induction of GCLC is a strategy to enhance the antioxidant capability in cells. The present study aimed to investigate the induction effect of EGb on GCLC in HepG2 and Hep1c1c7 cell lines. Real-time PCR, Western blot and enzyme activity assay were used to detect induction and it was found that GCLC was induced by EGb in these two cell lines. It is suggested that the antioxidant activity of EGb is (or is partly) through the induction of GCLC. Copyright (c) 2007 John Wiley & Sons, Ltd.

VI Auditive Stimulation
Sound Stimulation During Sleep for the Tinnitus Treatment: Trans-Disciplinary Approach
Abstract ARO-Meeting
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Subjective tinnitus is a sound created by the central nervous system. During wakefulness, different sound stimulation treatments were used (music, white noise, pure tones) with no clear results. Previous research demonstrated that the auditory system processes incoming information during sleep. Then, we may assume that some kind of learning takes place during this stage. It is our tenet that the brain could learn to mask the tinnitus perception with a particular sound stimulation during sleep. Eight patients with subjective idiopathic tinnitus were selected and treated by an otolaryngologist, a psychologist and a sleep medicine expert. The tinnitus was characterized in frequency and intensity and an equivalent sound was recorded in an ipod for night stimulation. In 2 patients, 2 Polysomnography (PSG) studies were
carried out in order to assess the hypnograms characterizing sleep organization previous to the treatment and after 15 nights of sound stimulation. In other 2 patients, 1 PSG was done -half of the night with sound stimulation and the other half with silence- to analyze the electroencephalographic power spectra in each sleep stage with and without sound. Psychological interviews and “Tinnitus Handicap Inventory” (THI) tests were done every two months. Preliminary results: 1) sound stimulation at night did not alter sleep while in some patient improved the insomnia of conciliation. 2) All 8 patients improved tinnitus. Two of them with waking periods of total silence. 3) The THI results are independent of the tinnitus improvement. 4) During sound stimulation there was a significant increment in the delta wave power (2.5-4 c/s) during slow wave sleep. Results suggest that the brain processes auditory information during sleep perhaps learning to mask the tinnitus perception. A trans-disciplinary approach is essential to assess the different tinnitus components: the sound perception alteration, attention processes and affective disorders.

Neural Tonotopy in CI: an Evaluation in Unilateral CI Patients with Contralateral Normal Hearing

Abstract ARO-Meeting

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Objectives: In actual cochlear implant systems the signal is filtered into different frequency bands and transmitted to electrodes along the cochlea which elicit different pitch perceptions. In this study the frequency-place map for electric hearing was investigated as a means to possibly improve current speech coding strategies by delivering spectral information to the appropriate cochlear place. Methods: Fourteen subjects with near to normal hearing in the contra-lateral ear have been provided with a MED-EL cochlear implant in the deaf ear in order to reduce intractable tinnitus. Pitch scaling experiments were performed using twelve single-electrode stimuli in the implanted ear and twelve acoustic sinusoids logarithmically spaced between 100 and 8500 Hz in the contra-lateral ear. The frequency-place function was calculated according to the exact electrode position in the cochlea obtained by postoperative skull radiographs by means of a cochlear view and were compared to Greenwood’s frequency-place function in normal hearing. Results: Electrical stimulation with a constant stimulation rate elicited a low pitch perception in the apical region of the cochlea, and shifting the stimulating electrode towards the basal region of the cochlea elicited an increasingly higher pitch perception. The frequency-place function obtained with our subjects did not show a significant shift relative to Greenwood’s frequency-position function. Conclusions: Electrical stimulation of the cochlea in patients with a unilateral cochlear implant and with near to normal hearing at the non-implanted ear, provided a specific frequency-position function consistent with Greenwood’s function.

Phase-shift tinnitus treatment: an open prospective clinical trial.


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We report on a novel treatment for tinnitus using phase-shift pure tone sound treatment in patients with predominantly pure tone tinnitus. Thirty-five patients with pure tone tinnitus unresponsive to all previous treatment were enrolled in the study. All patients were treated three times in one week. If the patient noticed an improvement, the therapy was continued for six weeks with a home device customised to their specific treatment frequency. Twenty-one of the 35 patients (60%) responded positively to the initial therapy sessions. Tinnitus was assessed before treatment, after three in-office Tinnitus Phase-Out System therapy sessions, and after six weeks of home use of the Patient Treatment Device. The assessment instruments were a VAS loudness scale and the quality of life Tinnitus Questionnaire. Significant tinnitus reduction was obtained on VAS after three office Tinnitus Phase-Out System therapy sessions (before treatment: mean VAS = 6.4; after three therapy sessions: mean VAS = 4.9; p = 0.042)
After six weeks of home use of the Patient Treatment Device (mean VAS = 4.9; p = 0.005). When analysing the mean TQ score over treatment, there was a significant improvement in total score from pretreatment (mean TQ score = 41.9) to six weeks after home use of the Patient Treatment Device use (mean TQ score = 36.4) (p = 0.003). In view of the results obtained, the Phase-Out Treatment for tinnitus may provide the majority of patients with a significant improvement in their symptoms. Further evaluation, comparing this specific Phase-Out Treatment with more general noise stimulation treatment, will further specify the indications for this treatment option.

VII Brain Stimulation

Combined Transcranial Magnetic Stimulation (TMS) for the Treatment of Tinnitus

Abstract ARO-Meeting

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Objectives: Low-frequency repetitive transcranial magnetic stimulation (rTMS) of the temporal cortex has been proposed as a new treatment strategy for patients with chronic tinnitus. However functional abnormalities in tinnitus patients also involve brain structures relevant for attentional and emotional processing such as the dorsolateral prefrontal cortex and the anterior cingulate. Therefore we developed a new rTMS treatment strategy for tinnitus patients, consisting of a combination of high-frequency prefrontal and low-frequency temporal rTMS.

Study Design: 40 patients received either low-frequency temporal rTMS (10 sessions, 1Hz, left auditory cortex; 2000 pulses/d, 110% motor threshold) or a combination of high-frequency prefrontal and low-frequency temporal rTMS (10 sessions, at each session 1 Hz rTMS, left auditory cortex, 2000 pulses/d, 110% motor threshold, followed by 20 Hz rTMS, left dorsolateral prefrontal cortex; 2000 pulses/d, 110% motor threshold). Treatment effects were assessed by using a standardized tinnitus questionnaire (TQ).

Results: Both treatment modalities resulted in reduced TQscores. Furthermore there was a remarkable advantage for combined prefrontal and temporal rTMS treatment as compared to temporal treatment alone. Conclusion: These results support recent data suggesting that auditory and non-auditory brain areas are involved in tinnitus pathophysiology.

Repetitive Transcranial Magnetic Stimulation (rTMS) on Persistent Noise Induced Tinnitus in Rats – a pilot study

Abstract ARO-Meeting

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rTMS an innovative method for noninvasive stimulation of the cortex has been proposed as a new treatment option for chronic tinnitus. Here we present first results from a pilot study of rTMS in an animal model of tinnitus During each rTMS session 100 stimuli were administered with a figure-of-eight Magstim coil at a frequency of 0.5 Hz and with an intensity of 30% of the maximal stimulator output. In one rat with electrodes implanted in the right auditory cortex rTMS was performed over the implanted auditory cortex. Compared to Baseline there was a reduction of spontaneous and evoked cortical activity ten minutes after rTMS, which returned to baseline levels thirty minutes after rTMS, indicating a transient suppressing effect of low frequency rTMS. Four rats were exposed to unilateral noise trauma (126 dB SPL, 12,000 Hz NBN, 2h). Subjects were then tested for the presence of persistent tinnitus using gap prepulse inhibition of acoustic startle (GPIAS) at 1, 3, 7, 15, and 30 days post trauma. GPIAS was performed for background noise centered at 6, 12, 16, 20 or 24 kHz. All four subjects tested showed the presence of tinnitus like behavior at 12 and 16 kHz throughout all test sessions. Single sessions of rTMS were performed over the right auditory cortex (contralateral to noise induced hearing loss) and over the left auditory cortex (ipsilateral to noise induced hearing loss).
Two of the test subjects showed a partial reversal of tinnitus-like behavior indexed by enhanced startle inhibition following rTMS. In one of these two subjects, ipsilateral and contralateral stimulation was equally effective at reducing tinnitus at 12 and 16 kHz. In the other subject, contralateral stimulation was more effective at 12 kHz with little effect at 16 kHz. These pilot data demonstrate the feasibility of rTMS in animals with evidence of tinnitus. The demonstration of rTMS effects on auditory cortex activity and on tinnitus-related behavior are in line with clinical data in humans.

Auditory Cortex Stimulation to Suppress Tinnitus Related Activity
Abstract ARO-Meeting
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Auditory cortex stimulation (ACS) through rTMS or direct cortical electrical stimulation has recently been used to treat tinnitus. However, the obtained benefit varies greatly across individual patients and is sometimes short-lived. To improve the efficacy of tinnitus treatment, search has been made for optimal stimulation strategies including selection of effective stimulation sites in the auditory cortex and parameters. However, these efforts are hampered by lack of full understanding of the underlying mechanisms of ACS-induced suppression of tinnitus. We electrically stimulated the primary AC to investigate the modulatory effects of cortical electrical stimulation (CES) on neural activity in the dorsal cochlear nucleus (DCN) and inferior colliculus (IC), where neural correlates of tinnitus have been previously reported. Adult rats and Syrian hamsters previously exposed to a loud sound (16 kHz band noise, 115 dB SPL, 6 hours) were used. Behavioral testing was conducted to evaluate tinnitus and hearing loss. Electrical stimulation and electrophysiology were then performed. A 4-shank, 16-channel probe array was inserted in the right primary AC for electrical stimulation. For recording, two 16-channel probes were inserted into the left DCN and right IC, respectively. The stimuli were single charge-balanced biphasic electrical pulses (40 μs wide), delivered at intensities of 0-50 μA and at a rate of 100 pps. Our preliminary results from behavioral testing showed that sound exposure induced both tinnitus and hearing loss. Electrophysiological results indicated that CES induced both suppression and excitation of spontaneous firing rates in the DCN and IC. Among the induced responses, there were higher proportion and degree of suppressive than excitatory effects. Such effects were found to be more potent in noise-exposed animals than unexposed controls. The results suggest that stimulation of certain areas of the auditory cortex may cause modulatory effects on tinnitus-related neural activity at the brainstem level.

Repetitive transcranial magnetic stimulation in veterans with debilitating tinnitus: A pilot study.
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Objective Available evidence suggests tinnitus arises from excessive spontaneous activity in the left superior temporal gyrus, and repetitive transcranial magnetic stimulation (rTMS) may suppress this activity. Our hypothesis is that rTMS applied to this region would decrease tinnitus complaints in veterans.

Study design Prospective, nonrandomized trial.
Subjects and Methods: Eight patients with tinnitus received 5 consecutive days of rTMS (0.5 Hz, 20 minutes) to the left temporoparietal area. Tinnitus Handicap Inventory (THI) measures before sessions 1 and 3 and after session 5 were used to evaluate efficacy.
Results: Patient 1’s THI decreased 40 to 34 to 26, patient 4 reported a subjective improvement, patient 8 withdrew, and the remaining patients reported no improvement. Adverse effects included temporary soreness, restlessness, and photophobia.
Conclusion: The parameters for this rTMS study are different from those that reported success with its use. With these current parameters, rTMS did not improve tinnitus in veterans. There were no permanent adverse outcomes.

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We compared the effect of different frequencies of repetitive transcranial magnetic stimulation (rTMS) (1 Hz, 10 Hz, 25 Hz and sham (occipital, 1 Hz)), given daily over the left temporoparietal cortex for 2 weeks, on 66 patients with chronic tinnitus randomly divided into four treatment groups. Patients were assessed using the Tinnitus Handicap Inventory, self-ratings of symptoms and audiometric measures of residual inhibition before, immediately after 2 weeks’ treatment and monthly thereafter for 4 consecutive months. RESULTS: There were no significant differences in basal measures between the four groups of patients. A two-factor ANOVA revealed a significant “rTMS” x “time” interaction for all measures. This was because real rTMS produced greater improvement than sham. However, there was no significant difference between the responses to different frequencies of rTMS. The response to rTMS depended on the duration of tinnitus: patients who had tinnitus for the longest period of time were the least likely to respond to treatment. CONCLUSION: Daily sessions of rTMS over the temporoparietal cortex may be a useful potential treatment for tinnitus.

Direct Electrical Stimulation of Heschl’s Gyrus for Tinnitus Treatment.

From the Departments of Otolaryngology–Head and Neck Surgery and Neurology (m.d.s., k.e., s.m.b., i.d., j.d., b.s., q.j., n.t., j.e.), Henry Ford Health System, Detroit, Michigan; Towson University (m.s), Towson, Maryland; the Departments of Otolaryngology–Head and Neck Surgery (j.z.) and Neurology (s.m.b.), Wayne State University, Detroit, Michigan, U.S.A.; and the Department of Neurosurgery (d.d.r.), University Antwerp Hospital, Belgium.

Objectives/hypothesis: The purpose of the study was to determine the effect of electrical stimulation of the auditory cortex in patients with tinnitus.
Study design: Nonrandomized clinical trial.
Methods: Two patients with debilitating tinnitus refractory to conventional therapies were treated. Patients were evaluated with validated questionnaires and psychoacoustic measures to determine the frequency and pitch of their tinnitus. Tones at these frequencies were then presented to the first patient (RP) under magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) to determine the tonotopic map for these frequencies in Heschl’s gyrus. These tonotopic sites were targeted for implant with a quadripolar electrode. In the second patient (MV), only the fMRI tonotopic map was performed. These fMRI results detected an area of increased activity, which was selected as the site for the implanted bipolar electrode.
Results: Patient RP (bilateral tinnitus for 2 years) has experienced a sustained reduction to near elimination of tinnitus with intracerebral implanted electrodes, whereas patient MV (unilateral tinnitus for 7 years) had an unsustained reduction in her tinnitus.
Conclusion: These findings suggest that the perception and annoyance of tinnitus may be modulated or reduced through electrical stimulation of the auditory cortex. These unsustained effects for patient MV may have been influenced by the longstanding nature of her tinnitus or by another reason as yet undetermined.
High-frequency priming stimulation does not enhance the effect of low-frequency rTMS in the treatment of tinnitus.

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Based on its ability to reduce the excitability of the cortex locally, low-frequency repetitive transcranial magnetic stimulation (rTMS) has been investigated for the treatment of hyperexcitability disorders such as auditory hallucinations and tinnitus. Results are promising, but characterized by only moderate improvement and a high inter-individual variability. Experimental data from motor cortex stimulation in healthy subjects indicates that the depressant effect of low-frequency rTMS can be enhanced by high-frequency priming stimulation. Here we will investigate whether high-frequency priming also improves the therapeutic efficacy of low-frequency rTMS in a clinical application. 32 patients with chronic tinnitus were randomly assigned to either a standard protocol of low-frequency rTMS (110% motor threshold, 1 Hz, 2000 stimuli/day) or a stimulation protocol in which priming stimulation with 6 Hz (90% motor threshold, 960 stimuli) preceded low-frequency rTMS (110% motor threshold, 1 Hz, 1040 stimuli/day). Stimulation was applied over the left auditory cortex by using MRI-guided coil positioning. The treatment outcome was assessed with a standardized tinnitus questionnaire. There was no significant difference between the standard protocol and the protocol involving priming stimulation. Both stimulation protocols resulted in significant clinical improvement after 10 days of stimulation, as compared to baseline. Our data does not support an enhancing effect of higher frequency priming on low-frequency rTMS in the treatment of tinnitus.

Otol Neurotol. 2007 Dec;28(8):1005-1012.

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Objectives: To investigate the feasibility and safety of an implantable epidural cortical stimulator for the treatment of severe tinnitus.
Study design: Prospective, controlled, single-blinded study of cortical stimulation for 4 weeks, and then an open-label stimulation period.
Setting: Tertiary care referral center.
Patients: Adults (n = 8) with constant tinnitus of at least 1 year with a tinnitus reaction questionnaire score greater than 33. Tinnitus was predominantly unilateral with a frequency less than 8,000 Hz.
Interventions: Surgical implantation of an investigational epidural electrode over the posterior superior temporal gyrus using functional magnetic resonance imaging targeting. A 2-week stimulation period alternated with a 2-week sham period in random order to which subjects were blinded. This was followed by continuous stimulation with parameter adjustments to maximize tinnitus suppression.
Main outcome measures: Subjective rating of tinnitus severity, loudness, and device efficacy. Objective measures of hearing thresholds, tinnitus frequency, loudness, and minimum masking levels. Outcome measures using the Tinnitus Handicap Questionnaire, Tinnitus Reaction Questionnaire, and Beck Depression Inventory.
Results: There were no effects of stimulation during the 4-week blinded period. With continuous chronic stimulation, 2 patients had persistent reduction of pure-tone tinnitus, and 6 patients had short periods of total tinnitus suppression. Significant improvements in the Beck Depression Inventory and tinnitus questionnaires were found, although objective measures of tinnitus loudness remained fairly stable. No surgical or stimulation-related complications were noted.
Conclusion: Chronic electrical stimulation of the secondary auditory cortex seems safe and warrants further investigation as a potential therapeutic intervention for the suppression of tinnitus.
Visualizing out-of-body experience in the brain.
Comment in:

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An out-of-body experience was repeatedly elicited during stimulation of the posterior part of the superior temporal gyrus on the right side in a patient in whom electrodes had been implanted to suppress tinnitus. Positron-emission tomographic scanning showed brain activation at the temporoparietal junction—more specifically, at the angular-supramarginal gyrus junction and the superior temporal gyrus-sulcus on the right side. Activation was also noted at the right precuneus and posterior thalamus, extending into the superior vermis. We suggest that activation of these regions is the neural correlate of the disembodiment that is part of the out-of-body experience. Copyright 2007 Massachusetts Medical Society.

VIII Behavioral Therapy

Ericksonian hypnosis in tinnitus therapy.
B-ENT. 2007;3 Suppl 7:75-77.

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Objective: To evaluate the effect of Ericksonian therapy on tinnitus.
Study design: Non-randomised, prospective longitudinal study.
Setting: Tertiary referral centre.
Patients: A total of 49 patients underwent hypnosis therapy. Fourteen patients failed to finish the therapy (drop-out rate: 35%). Of the 35 patients who completed the therapy, 20 were male and 15 female. The average age was 46.3 years (range 17-78).
Intervention: The treatment is based on the principles and approaches of Ericksonian hypnosis. The first session was mainly dedicated to the evaluation of the impact of tinnitus on the patient’s life and to an explanation of hypnosis therapy. The next sessions were “learning sessions” based on relaxation and mental imaging. Exercises were first based on all senses other than hearing. Then they focused on hearing, teaching patients how to modulate sound intensity, and finally how to modulate tinnitus intensity. Patients also learnt self-hypnosis.
Main outcome Measure(s): To evaluate the effect of the treatment, tinnitus was assessed with the Tinnitus Handicap Inventory questionnaire before and after the therapy.
Results: After 5 to 10 sessions (mean: 8.09 + -1.92) of Ericksonian hypnosis therapy, the 35 patients were capable of self-hypnosis with the aim of modulating their tinnitus, and the measured THI score fell for all patients. The global score improved significantly from 60:23 before EH therapy to 16.9 at discharge. Within the group, the initial score was distributed as follows: 0% slight, 14% mild, 31% moderate, 31% severe and 23% catastrophic. The t-test for dependent variables revealed significant improvements in all subgroups (p < or = 0.005).
Conclusions: The results of this clinical trial demonstrate that Ericksonian hypnosis, in particular using self-hypnosis, is a promising technique for treating patients with tinnitus.

Case report: A case of intractable Meniere’s disease treated with autogenic training.

Goto F, Nakai K, Kunihiro T, Ogawa K.
Background: Psychological stress plays an important role in the onset and course of Meniereas disease. Surgical therapy and intratympanic gentamicin treatment are options for cases that are intractable to conventional medical therapy. Psychotherapy, however, including autogenic training (AT), which can be used for general relaxation, is not widely accepted.
This paper describes the successful administration of AT in a subject suffering from intractable Meniereas disease.

Case presentation: A 51-year-old male patient has suffered from fluctuating right sensorineural hearing loss with vertigo since 1994. In May 2002, he was first admitted to our hospital due to a severe vertigo attack accompanied by right sensorineural hearing loss. Spontaneous nystagmus toward the right side was observed. Since April 2004, he has experienced vertigo spells with right-sided tinnitus a few times per month that are intractable to conventional medical therapy. After four months, tympanic tube insertion was performed in the right tympanic membrane. Intratympanic injection of dexamethasone was ineffective. He refused Meniett therapy and intratympanic gentamicin injection. In addition to his vertigo spells, he suffered from insomnia, tinnitus, and anxiety. Tranquilizers such as benzodiazepines and antidepressants such as serotonin selective re-uptake inhibitors (SSRIs) failed to stop the vertigo and only slightly improved his insomnia. In December 2006, the patient began psychological counseling with a psychotherapist. After brief psychological counseling along with cognitive behavior therapy (CBT), he began AT. He diligently and regularly continued his AT training in his home according to a written timetable. His insomnia, tinnitus, and vertigo spells disappeared within a few weeks after only four psychotherapy sessions. In order to master the six standard formulas of AT, he underwent two more sessions. Thereafter, he underwent follow-up for 9 months with no additional treatment. He is now free from drugs, including tranquilizers, and has continued AT. No additional treatment was performed. When we examined him six and nine months later for follow-up, he was free of vertigo and insomnia.

Conclusions: AT together with CBT can be a viable and palatable treatment option for Meniereas disease patients who are not responsive to other therapies.

**Physiological and psychological stress reactivity in chronic tinnitus.**

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Several models of tinnitus maintenance emphasize the importance of cognitive, emotional and psychophysiological processes. These factors contribute to distress in patients with decompensated tinnitus symptoms. We investigated whether tinnitus patients show increased physiological levels of arousal, more intense stress reactivity patterns and exaggerated psychological strain compared to healthy controls. Seventy tinnitus patients and 55 healthy controls underwent various stress tests. Muscular reactivity and peripheral arousal as well as strain ratings were assessed. Tinnitus patients reported significantly more strain during stress tests compared to healthy controls. Few physiological reactivity patterns differed significantly between the two groups. The physiological data thus only partly supported a hyperreactivity hypothesis. Strain reports and physiological data were only marginally correlated. Tinnitus patients show maladaptive appraisal processes during stress exposure, yet physiological reactivity is only slightly affected. Treatment programs for patients with decompensated tinnitus symptoms should account for appraisal processes and coping mechanisms in stressful situations.

**Influence of silence and attention on tinnitus perception.**


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Objective: The purpose of this study was to study the effect of attention and sustained silence on the emergence of auditory phantom perception in normal-hearing adults.

Study design: Cross-sectional survey.

Subjects and methods: While sitting in a sound booth, 66 volunteers (age range, 18-65; mean age, 37.3) performed 3 experiments of 5 minutes each, consecutively and randomly presented. Two deviated attention from auditory system (Hanoi and visual attention experiments), and 1 drove attention to the auditory system (auditory attention). After each experiment, participants were asked about their auditory and visual perception. No sound or light change was given at any moment.
Results: Of the participants, 19.7% experienced tinnitus during Hanoi, 45.5% during visual attention, and 68.2% during auditory attention experiment, with no significant differences for studied variables.

Conclusion: Tinnitus-like perceptions may occur in a nonclinical population in a silent environment. Concomitant auditory attention plays an important role on the emergence of tinnitus.

IX Somatic Tinnitus

Somatosensory Pulsatile Tinnitus Syndrome: Somatic Testing Identifies a Pulsatile Tinnitus Subtype That Implicates the Somatosensory System

Abstract ARO-Meeting

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We report five cases of non-lateralized pulsatile tinnitus for whom no etiology was found from physical examination or ancillary testing but the pulsations could be suppressed by somatic testing. The three men and two women ranged in age between 49 and 75. All described their pulsatile tinnitus as high pitched and localized to both ears or in the head. Audiometry was symmetric in all subjects. Auscultation was normal in all. Jugular compression did not modulate any subject’s tinnitus. Carotid compression did suppress tinnitus in two subjects, but a similar effect occurred with sternocleidomastoid compression without carotid compression. Imaging studies were all unrevealing including one cerebral angiogram. All could suppress the pulsations with various strong neck or jaw muscle contractions, or strong pressure on the sternocleidomastoid muscle/carotid artery complex. In some the tinnitus was completely suppressed; in others only the pulsatile component of the tinnitus was suppressed; high pitched non-pulsatile tinnitus remained. with some maneuvers only one side was suppressed. The non-lateralized quality of the pulsatile tinnitus suggests either a central somatosensory or modulation of neural activity of either the central auditory system bilaterally or a level of the auditory system that can affect bilateral auditory perception. In consideration of (a) negative findings with auscultation and imaging and (b) suppression of the pulsations with activation of the somatosensory system, we suggest the following: some or all of these cases perceive nonlateralized high-pitched pulsatile tinnitus from (1) cardiac modulation of the somatosensory system, which, in turn, (2) modulates the central auditory system, thereby accounting for the pulsatile quality of their high-pitched tinnitus. Our data suggest the sternocleidomastoid muscle/carotid artery complex as a likely source of the somatosensory input.

The Role of Physical Therapy in Tinnitus: A Case Report

Abstract ARO-Meeting

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Tinnitus is a common disorder with limited treatment options. in the past ten years, research has identified that neck and jaw contractions can influence tinnitus. While treating patients for headaches, dizziness and temporomandibular dysfunction, we have been able to decrease the intensity and/or frequency of tinnitus despite this not being the focus of the interventions. to date there have been no published reports that identify specific physical therapy interventions for improving tinnitus. This abstract is based on a case description of a 42 year old man who is an avid weight lifter. He works as a line operator at a car manufacturing company. His job requires him to maintain prolonged positions where his head and neck are in flexion and protrusion. His tinnitus was described as a bilateral buzzing and was intermittent. It began six years ago and was worsening. Along with this he complained of headaches, blurry vision and neck tightness. On his initial evaluation his tinnitus was rated on VAS 4/10. His tinnitus handicap inventory score was 62/100. Evaluation revealed decreased cervical motion as measured by CROM. Resisted muscle contractions of the cervical spine in flexion, extension and rotation increased his tinnitus. Jaw contractions had no effect on his tinnitus. Tenderness of cervical and jaw musculature was noted as well as significant upper cervical spine dysfunction. Physical therapy focused on normalizing cervical spine mechanics via repeated movement assessment, joint mobilization and soft tissue massage. The patient demonstrated significant improvement in his tinnitus.
This was likely due to the noted improvement in cervical spine biomechanics and tone. This improvement was objectively measured by changes in the following disability measures upon discharge: THI, NDI, HDI, DHI. Given that tinnitus is a complex disorder, along with the lack of consistently effective treatments, it is imperative to identify potential contributions from the cervical spine and temporomandibular region. This may assist in the further understanding of this condition and the subsequent development of effective treatment strategies.

**Cutaneous-evoked tinnitus: first reported case without preceding posterior fossa surgery.**

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This is the first report of cutaneous-evoked tinnitus in the absence of posterior fossa surgery. A 56-year-old physician described brief bursts of clicking tinnitus in the right ear in response to rubbing a tiny area over the spine of the right scapula. He had cervical spondylosis and mild, stable, high-frequency, right-sided sensorineural hearing loss. Similarities to somatosensory Mitempfindung suggest that the condition may not be uncommon.

**Dorsal cochlear nucleus responses to somatosensory stimulation are enhanced after noise-induced hearing loss.**

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Multisensory neurons in the dorsal cochlear nucleus (DCN) achieve their bimodal response properties [Shore (2005) Eur. J. Neurosci., 21, 3334-3348] by integrating auditory input via VIIIth nerve fibers with somatosensory input via the axons of cochlear nucleus granule cells [Shore et al. (2000) J. Comp. Neurol., 419, 271-285; Zhou & Shore (2004) J. Neurosci. Res., 78, 901-907]. A unique feature of multisensory neurons is their propensity for receiving cross-modal compensation following sensory deprivation. Thus, we investigated the possibility that reduction of VIIIth nerve input to the cochlear nucleus results in trigeminal system compensation for the loss of auditory inputs. Responses of DCN neurons to trigeminal and bimodal (trigeminal plus acoustic) stimulation were compared in normal and noise-damaged guinea pigs. The guinea pigs with noise-induced hearing loss had significantly lower thresholds, shorter latencies and durations, and increased amplitudes of response to trigeminal stimulation than normal animals. Noise-damaged animals also showed a greater proportion of inhibitory and a smaller proportion of excitatory responses compared with normal. The number of cells exhibiting bimodal integration, as well as the degree of integration, was enhanced after noise damage. In accordance with the greater proportion of inhibitory responses, bimodal integration was entirely suppressive in the noise-damaged animals with no indication of the bimodal enhancement observed in a sub-set of normal DCN neurons. These results suggest that projections from the trigeminal system to the cochlear nucleus are increased and/or redistributed after hearing loss. Furthermore, the finding that only neurons activated by trigeminal stimulation showed increased spontaneous rates after cochlear damage suggests that somatosensory neurons may play a role in the pathogenesis of tinnitus.
Can oculomotricity be altered in patients with tinnitus only? A preliminary study.
Int Tinnitus J. 2007;13(2):152-156.

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The study of oculomotricity is performed by evaluating three systems: saccadic ocular movements (SOMs), optokinetic nystagmus (OKN), and smooth pursuit eye movements (SPEMs). Our aim was to study oculomotricity in patients with a complaint of only tinnitus and to compare it with the value of our control group. We studied the SOMs, OKN, and SPEMs in 25 patients complaining only about tinnitus and in 35 normal adults and compared the results. The data analysis showed a significant difference in the value of the SOMs and SPEMs between the two groups. Sensorineural tinnitus can originate in the organ of Corti, in the cochlear nerve, or in the auditory pathways of the central nervous system. The auditory cortex connects with visual areas and with the superior colliculus. The latter structure is involved in the origin of SOMs and OKN. In our study, we found an increased delay in saccadic tests. In the SPEMs, we observed an increase in the degree of distortion, and a reduction in the gain. This outcome is in accordance with the literature. However, we detected a few alterations in the OKN, and this finding is in partial agreement with the studies analyzed. Alterations in oculomotricity can indicate involvement of the central nervous system in patients with a complaint of only tinnitus.

Surgical Treatment

Vascular loops causing otological symptoms: a systematic review and meta-analysis.

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Objective of review: To determine evidence for a relationship between vascular loops in contact with the vestibulocochlear nerve (CN VIII) and otological symptoms.
Type of review: Systematic review and meta-analysis of observational studies.
Search strategy: Comprehensive search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Clinical Evidence and Cochrane Central Register of Trials. Reference lists cross-referenced and authors contacted for missing data. No language restrictions.
Evaluation methods: Included studies: (1) compared symptoms in subjects with a vascular loop contacting CN VIII to subjects without (inter-subject control); (2) compared the prevalence of vascular loop in contact with CN VIII in symptomatic ears to contra-lateral asymptomatic ears (intra-subject control). Study quality systematically appraised.
Results: Five case-control studies included. A statistically significant association was demonstrated for the prevalence of vascular loops in contact with CN VIII, with unilateral sensorineural hearing loss: pooled odds ratio (OR) 2.0 [95% confidence interval (CI): 1.5-2.6]. No association was demonstrated for non-pulsatile tinnitus. A highly significant association with vascular loops was shown in subjects having pulsatile tinnitus, with pooled OR: 78.8 (95% CI: 10.9-821.8).
Conclusions: Vascular loops in contact with CN VIII are a normal variant. Subjects with unilateral hearing loss were twice as likely to have these vascular loops in the symptomatic ear, than in the asymptomatic ear. Subjects with pulsatile tinnitus were 80 times more likely to have a contacting vascular loop than patients with non-pulsatile tinnitus, suggesting in some cases a causal relationship exists for pulsatile tinnitus, where surgical intervention may be occasionally indicated.
The arteriovenous dural malformation (MAVD) is a rare entity between the vascular cranial anomalies with a not well known etiology and variability in treatments. We present eleven cases of MAVDs, between them five presented tinnitus as symptom of apparition. The importance of this pathology makes necessary to discard it before a patient consulting because of pulsatile tinnitus with normal otoscopy.

An otoneurosurgical approach to non-pulsatile and pulsatile tinnitus.
B-ENT. 2007;3 Suppl 7:79-86.
De Ridder D, Menovsky T, Van de Heyning P.
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Objective: Most treatments proposed for tinnitus are non-surgical, to such an extent that it is sometimes forgotten that a certain number of patients with tinnitus may benefit from a surgical solution. The aim of this paper is to review the possible otoneurosurgical approaches in tinnitus treatment, treating the tinnitus causally or symptomatically.

Methods: A Pubmed search on the words “surgery”, “tinnitus” and “pulsatile” was performed and compared to the authors’ personal experience with surgical approaches for alleviating tinnitus. The most relevant different pathologies presenting as pulsatile and non-pulsatile tinnitus are given and possible otoneurosurgical approaches for these identities summarised.

Results and Discussion: Non-pulsatile tinnitus can be the clinical expression of vestibular schwannomas and other cerebellopontine angle lesions, arachnoid cysts, Ménière’s disease, otosclerosis, brain tumours along the auditory pathways, Chiari malformations and microvascular compressions of the vestibulocochlear nerve. Symptomatic improvement of non-pulsatile tinnitus can also be obtained by electrical stimulation of the cochlea, auditory nerve or cortex. Pulsatile tinnitus can present as a venous hum resulting from benign intracranial hypertension, Chiari malformation and a high jugular bulb. Arterial-pulse-synchronous tinnitus can be caused by benign intracranial hypertension, arteria carotid stenosis, glomus tumours, vascular lesions of the petrous bone and skull base, ateriovenous malformations, aneurysms, and vascular loops inside the internal auditory canal.

Conclusion: Before people are told “to learn to live with their tinnitus” a thorough exploration of possible cause and potential surgical treatments should be provided for patients presenting with incapacitating tinnitus.

Difference in functional outcome of ipsilateral tinnitus after intraoperative occurrence of the trigemino-cardiac reflex in surgery for vestibular schwannomas.
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Objective: Surgical manipulation of the fifth cranial nerve in its intra- or extracranial course may lead to bradycardia or even asystole as well as arterial hypotension, a phenomenon described as the trigemino-cardiac reflex (TCR), first described by the authors previously [11]. The authors report here the impact of this reflex on post-operative ipsilateral tinnitus in patients undergoing vestibular schwannoma surgery.

Methods: Thirty six patients scheduled for vestibular schwannoma surgery were studied retrospectively for parameters influencing the post-operative ipsilateral tinnitus function. According to the occurrence of intra-operative TCR the patients were divided into a TCR-subgroup and a non-TCR subgroup. There was no difference in tumour size between these subgroups.
Results: The TCR occurred in 17% of the patients during vestibular schwannoma surgery and influenced the occurrence of post-operative ipsilateral tinnitus: the overall incidence of post-operative ipsilateral tinnitus was 22%. Sixty (60) percent of the patients in the TCR subgroup and 17% of those in the non-TCR subgroup experienced ipsilateral tinnitus postoperatively. There was no correlation between tinnitus and pre- or post-operative hearing function.

Conclusion: Hypotension after intra-operative TCR is not only a negative prognostic factor for hearing preservation but also for ipsilateral tinnitus in patients undergoing vestibular schwannoma surgery. In combination with worse hearing function after intra-operative TCR, the present finding underlines the importance of the TCR during skull base surgery in relation to improved functional outcome.

Treatment of dural arteriovenous fistula using ethylene vinyl alcohol (onyx) arterial embolization as the primary modality: short-term results.


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Object: A dural arteriovenous fistula (DAVF) typically involves meningeal feeding arteries and can cause clinical symptoms ranging from tinnitus to rupture of draining cortical or parenchymal veins. Surgical treatment may be technically demanding. Ethylene vinyl alcohol (Onyx, ev3 Neurovascular) has several properties that make it potentially useful as a primary treatment agent for DAVF. Onyx is expected to be a permanent embolic agent. It should have a decreased risk of catheter retention when compared with other permanent embolic materials.

Methods: The authors report a series of six patients with symptomatic DAVF who were treated initially with transarterial Onyx embolization and other endovascular techniques.

Results: Five patients had complete occlusion of their DAVF noted on the follow-up angiogram obtained between 2 and 4 months. One patient had residual filling via a small arterial branch that was stable on follow-up angiography. None of the patients had worsening of neurological function. One case was complicated by a retained catheter fragment.

Conclusions: Transarterial Onyx embolization and other endovascular methods can angiographically obliterate DAVF. In some cases, embolization allowed occlusion of multiple arterial feeding arteries from a single arterial injection. Technically, the embolization was optimized when a microcatheter position immediately adjacent to the point(s) of fistulization was achieved.

Clinical predictors of facial nerve outcome after translabyrinthine resection of acoustic neuromas.


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Purpose: The translabyrinthine approach to acoustic neuroma resection offers excellent exposure for facial nerve dissection with 95% preservation of anatomic continuity. Acceptable outcome in facial asymptomatic patients is reported at 64-90%, but transient postoperative deterioration often occurs. The objective of this study was to identify preoperative clinical presentation and intraoperative surgical findings that predispose patients to facial nerve dysfunction after acoustic neuroma surgery.

Methods: The charts of 128 consecutive translabyrinthine patients were examined retrospectively to identify new clinical and intraoperative predictors of facial nerve outcome. Postoperative evaluation of patients to normal function or mild asymmetry upon close inspection (House-Brackmann grades of I or II) was defined as an acceptable outcome, with obvious asymmetry to no movement (grades III to VI) defined as unacceptable. Intraoperative nerve stimulation was performed in all cases, and clinical grading was performed by a single neurosurgeon in all cases.
Results: Among patients with no preoperative facial nerve deficit, 87% had an acceptable result. Small size ($P < 0.01$) and low intraoperative nerve stimulation of $< 0.10$ mA ($P< 0.01$) were reaffirmed as predictive of functional nerve preservation. Additionally, preoperative tinnitus ($P = 0.03$), short duration of hearing loss ($P< 0.01$), and lack of subjective tumour adherence to the facial nerve ($P = 0.02$) were independently correlated with positive outcome.

Conclusions: Our experience with the translabyrinthine approach reveals the previously unestablished associations of facial nerve outcome to include presence of tinnitus and duration of hypoacusis. Independent predictors of tumour size and nerve stimulation thresholds were reaffirmed, and the subjective description of tumour adherence to the facial nerve making dissection more difficult appears to be important.

Are stage IV vestibular schwannomas preoperatively different from other stages?


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Objective: The aim of this study was to focus on the clinical and paraclinical symptoms of patients suffering from Stage IV vestibular schwannomas (VSs).

Patients: In this prospective study, we included 734 patients who have VS and candidates for operation. Main outcome measures: Patients were classified as having Stage I, II, III, or IV tumors according to Tos criteria as evaluated by magnetic resonance imaging.

Preoperativ clinical evaluation: We recorded the occurrence of complaints (%) and duration (yr) of hearing loss, tinnitus, and balance disorder. Preoperative paraclinical evaluation included pure-tone (PTA) and speech audiology, auditory brainstem response (ABR) patterns, and vestibular deficit at videonystamography (VNG). Continuous variables were compared between Stage IV and other stages using analysis of variance. Qualitative variables expressed as a percentage of presence were compared between Stage IV and other stages using percentage comparison.

Results: Quantitative Parameters. Patients with Stage IV VS were significantly younger as compared with patients with other stages. Stage IV hearing loss was greater compared with other stages at 250 and 500 Hz but smaller at 2,000 and 8,000 Hz. We found no difference in the loss of PTA between Stage IV and the other stages. Speech discriminancy score was smaller in Stage IV. The durations of hearing loss, tinnitus, and balance disorders were similar whatever the tumor stage. Auditory brainstem response patterns showed no difference in Wave III latency between Stage IV VS and other stages, whereas Wave V latency and V-I interval were higher in Stage IV. Both ABR threshold and VNG caloric deficit were higher in Stage IV VS compared with other stages. Qualitative Parameters. The percentage of patients with Stage IV was lower than that with Stages II and III. The percentage of men and women was similar in all stages. The occurrence of hearing loss was similar in all stages, whereas that of tinnitus was lower in Stage IV compared with Stages I and II. In contrast, the occurrence of balance disorder was higher in Stage IV compared with all other stages.

Conclusion: In clinical and paraclinical manifestation, Stage IV VS is different from the other stages. The PTA differences may be attributed to the younger age. Occurrence of clinical symptoms, ABR, and VNG pattern can be explained by the fact that Stage IV develops rapidly in the vestibular, rather than the cochlear nerve and by the fact that larger tumors can be cerebellar compression. This has been confirmed by the higher occurrence of balance disorders in Stage IV and the lower occurrence of tinnitus with similar hearing loss in all stages.
Glomus tumors in patients of advanced age: a conservative approach.
Laryngoscope. 2008 Feb;118(2):270-274.

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Objectives: Identify and discuss controversies in the management of paragangliomas in elderly patients. Assess and evaluate a conservative treatment strategy involving limited surgical resection and vigilant monitoring of the outcome measures of tumor control, peritreatment morbidity, symptom resolution, and hearing preservation.

Study design: Retrospective case review.

Methods: All of the patients in this study were over age 60 with temporal bone glomus tumors. Primary outcome assessment included length of hospitalization, perioperative morbidity, symptom resolution, hearing preservation, and long-term tumor control.

Results: Twelve female patients with mean age of 74.5 years (range 61-85 years) with follow-up from 24 months to 33 years (mean/median: 5/7.8 years) were identified. Nine (75%) of the patients presented with pulsatile tinnitus. Seven patients (58%) underwent surgical excision of the middle ear component of the paraganglioma. Tumors extending to the jugular foramen were purposely not resected. Five patients (45%) had relative or absolute contraindications to surgical resection and were treated with observation or primary radiation therapy. Post-treatment audiometric evaluation confirmed stable or improved hearing. Pulsatile tinnitus resolved in all patients. No patient experienced cranial nerve deficits, extended hospitalization, or blood transfusions. All patients were followed closely with radiological imaging. The majority of patients demonstrated no disease or stable disease, while two patients demonstrated tumor growth 6 years after diagnosis.

Conclusion: A prolonged natural history and the morbidity associated with surgical intervention have led to controversies in the treatment of glomus tumors in an elderly population. Our experience supports recent limited reports advocating conservative surgical excision and vigilant long-term monitoring in this population.

XI Holistics

XII Review

Cognitive neuroscience in tinnitus research: a current review.

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Advances in methods of examining the human brain have led to a dramatic increase in specific knowledge about the origins of tinnitus. Neural modeling, behavioral measurements of hearing performance and psychological state, neuro-morphology, metabolic measurements of neural activity, electromagnetic recordings of synaptic potentials, and optical measurements of action potentials are all modalities that have provided insights or the promise of new information about the pathophysiology of tinnitus. This review examines these techniques and their contributions to knowledge about tinnitus.
An otoneurosurgical approach to non-pulsatile and pulsatile tinnitus.
B-ENT. 2007;3 Suppl 7:79-86.

De Ridder D, Menovsky T, Van de Heyning P.
TRI Tinnitus Clinic Antwerp, Department of Neurosurgery, Belgium. dirk.de.ridder@uza.be

Objective: Most treatments proposed for tinnitus are non-surgical, to such an extent that it is sometimes forgotten that a certain number of patients with tinnitus may benefit from a surgical solution. The aim of this paper is to review the possible otoneurosurgical approaches in tinnitus treatment, treating the tinnitus causally or symptomatically.

Methods: A Pubmed search on the words “surgery”, “tinnitus” and “pulsatile” was performed and compared to the authors’ personal experience with surgical approaches for alleviating tinnitus. The most relevant different pathologies presenting as pulsatile and non-pulsatile tinnitus are given and possible otoneurosurgical approaches for these identities summarised.

Results and Discussion: Non-pulsatile tinnitus can be the clinical expression of vestibular schwannomas and other cerebellopontine angle lesions, arachnoid cysts, Ménière’s disease, otosclerosis, brain tumours along the auditory pathways, Chiari malformations and microvascular compressions of the vestibulocochlear nerve. Symptomatic improvement of non-pulsatile tinnitus can also be obtained by electrical stimulation of the cochlea, auditory nerve or cortex. Pulsatile tinnitus can present as a venous hum resulting from benign intracranial hypertension, Chiari malformation and a high jugular bulb. Arterial-pulse-synchronous tinnitus can be caused by benign intracranial hypertension, arteria carotid stenosis, glomus tumours, vascular lesions of the petrous bone and skull base, arteriovenous malformations, aneurysms, and vascular loops inside the internal auditory canal.

Conclusion: Before people are told “to learn to live with their tinnitus” a thorough exploration of possible cause and potential surgical treatments should be provided for patients presenting with incapacitating tinnitus.

Hyperbaric oxygen therapy for tinnitus.
B-ENT. 2007;3 Suppl 7:71-74.

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Objective: To assess the effect of hyperbaric oxygenation on tinnitus.


Results: No significant effect could be demonstrated in four prospective studies. Retrospective studies indicate greater improvement in tinnitus in acute cases (49-85%) compared with tinnitus episodes exceeding three months (34-38%). One study, however, showed significantly more improvement in patients with positive expectations before therapy (60.3%) compared with those with negative expectations (19%).

Conclusions: There are no significant data about the effect of hyperbaric oxygenation for tinnitus, but there are indications of a better effect in acute cases. However, a major psychological component and a low risk of enhancement of the tinnitus should be considered.

Tinnitus in children and adolescents.
B-ENT. 2007;3 Suppl 7:61-63.

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ENT practitioners are rarely confronted with tinnitus complaints from children. The present paper describes a literature review conducted in an attempt to identify possible reasons for this. Rather than applying the vast amount of information about tinnitus among adults, it seeks to highlight those domains where differences between children and adults are of importance.
An overview of animal models of tinnitus.

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Tinnitus, or the phantom perception of sound, is one of the great unsolved problems of otology. It is present in all patients with hearing loss and, in approximately 5-10% of individuals, it has a significant impact on quality of life. Progress in the treatment of tinnitus has been limited by a lack of animal models that can be used to study the neurophysiology of tinnitus and to examine prospective treatment. In the last ten years, several physiological and behavioural animal models of tinnitus have been developed that have significantly increased our understanding. The next ten years will see the application of these models to drug development and electrical stimulus approaches to curing tinnitus.

Tinnitus: a multidisciplinary clinical approach.
B-ENT. 2007;3 Suppl 7:3-10.

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This article provides a clinical step-by-step approach for assessing a patient with tinnitus as primary complaint. The medical diagnosis of the disease provoking the tinnitus has to be made first in a comprehensive evaluation, including imaging. The psycho-acoustic characteristics and the influence on health-related quality of life is a compulsory complementary assessment to establish a complete picture of the patient.

XIII Others

[Compensation for Somatoform (Psychogenic) Tinnitus in Private Accident Insurance].
[Article in German]
Laryngorhinootologie. 2008 Feb 20 [Epub ahead of print]

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Background: According to special arrangements in private accident insurance, it is now possible that tinnitus as exclusive sequel (psychogenic tinnitus) can be compensated. This new situation leads to the unanswered question of how such a psychogenic (somatoform) tinnitus should be compensated in regard to the valid compensation tables.
Methodology and results: The differentiation between an otogenic and somatoform tinnitus allows a judgement as defined by the general terms and conditions of the private accident insurance. An individual compensation of 5 % or of a complex, decompensated tinnitogenic psycho-syndrome 10 % of the sum insured is proposed.
Conclusions: All impairment of the psychic function as exhaustion, nervous excitability, sleeplessness, depression and concentration disturbances are included in this invalidity of 10 %. In case of a tinnitogenic psycho-syndrome, the medical assessment should be done by a neurologist/psychiatrist.
Acceptance of hearing protection aids in members of an instrumental and voice music band.
[Article in Portuguese]

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There are barriers to effective hearing protection among musicians.

Aim: To investigate the acceptance of hearing protection aids in members of an instrumental and voice music band.

Material and method: A prospective study of 34 members of the Municipal Indaial Band. Sound pressure levels were measured during a rehearsal, indicating mean levels ranging from 96.4 dB(A) to 106.9 dB(A). Subjects answered questionnaires and underwent audiometry. They attended a lecture in which folders and hearing protection aids were provided; subjects were asked to try using the protectors for 3 months.

Results: At the end of the study period, 56.2% reported not liking hearing protection, while 43.7% accepted such protection. The most common complaints were discomfort with sounds (58.8%) and tinnitus (47%). 77.1% said that music might cause hearing impairment. A statistically significant difference was observed in the right ear at 4 and 6 kHz and at the left ear in 3, 4 and 6 kHz when median thresholds were compared with those from unexposed controls.

Conclusion: Although most subjects seemed aware of the risk, few took preventive measures against hearing loss. This suggests the need for periodic educational campaigns and specific legislation tailored to music professionals.

Low-cholesterol diet and antilipid therapy in managing tinnitus and hearing loss in patients with noise-induced hearing loss and hyperlipidemia.
Int Tinnitus J. 2007;13(2):143-149.

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The aim of our study was to outline the prevalence of hyperlipidemia in patients who had high-frequency hearing loss and tinnitus due to noise exposure. We investigated the role of a low-cholesterol diet and antihyperlipidemic therapy to alleviate the severity of tinnitus and possibly promote hearing gain after therapy in patients with acoustic trauma. Forty-two hyperlipidemic patients with subjective tinnitus and hearing loss due to noise exposure were enrolled for the study. We placed patients on a low-cholesterol diet or antihyperlipidemic therapy and followed them for up to 24 months; then we designated two groups as either “unresponsive” (n = 22; no response to either of the therapies and still experiencing hyperlipidemia) or “responsive” (n = 20; lower cholesterol or triglyceride levels). We then compared tinnitus scores and hearing levels in the two groups. The difference between tinnitus scores in the unresponsive and responsive groups and the change in tinnitus scores before and after therapy in the responsive group were significant. When we compared self-rated tinnitus severity results in two groups after therapy, we found the difference was significant (p < .05). The difference between average air-conduction thresholds at high frequencies after the treatment in the two groups was also significant. The incidence of hyperlipidemia is high among patients with noise-induced hearing loss, and significant improvement by way of lowered tinnitus intensity and higher frequencies in average hearing thresholds can be achieved after lowering the serum lipid level.
HIV-associated cerebral lymphocyte infiltration mimicking vestibular schwannoma.
Eur Arch Otorhinolaryngol. 2008 Mar 4 [Epub ahead of print]

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The association of unilateral, rapidly progressive hearing loss, tinnitus and vestibular dysfunction in combination with a contrast-enhancing mass within the internal auditory canal on MRI is suggestive of a vestibular schwannoma (VS). We report the rare finding of a HIV-associated cerebral lymphocyte infiltration, most probably malignant lymphoma, which was presumed initially to be a VS. A 36-year-old male presented with progressive unilateral hearing loss accompanied by acute, ipsilateral tinnitus. Interpreted first as sudden sensorineural hearing loss, his symptoms were treated with rheologic therapy. Ipsilateral facial palsy appeared. MRI with gadolininium disclosed a contrast-enhancing mass within the internal auditory meatus of the left side. Within five weeks an extended leptomeningeal lymphocyte infiltration evolved and the diagnosis of an underlying HIV infection was made. Unilateral, rapidly progressive hearing loss and a fast growing cerebello-pontine mass is atypical for VS and highly suspicious of malignant disease. To our knowledge we report the first case of an HIV-associated cerebral lymphocyte infiltration, mimicking a VS. In such cases the diagnostic work-up should include a HIV test.

Tinnitus caused by vertebrobasilar dolichoectasia.

Titlic M, Tonkic A, Jukic I, Buca A, Kolic K, Batinic T.
Department of Neurology, University Hospital Split, Split, Croatia. marina.titlic@inet.hr

A 73-year old man presented with the tinnitus in the left ear for 11 months. Computer tomography (CT) showed an enlarged dolichoectasia of the left vertebral artery. Magnetic resonance imaging (MRI) of the brain shows dolichoectasia of the left vertebral artery and the initial part of the basilar artery. Multi-slices computer tomographic (MSCT) angiography showed an enlarged vertebrobasilar dolichoectasia of the left vertebral artery, which compressed the vestibulocochlear nerve. This study supports a vascular compression of cranial vestibulocochlear nerve and the brainstem as a cause of tinnitus, and demonstrates a MSCT angiography value as an excellent, non-invasive technique to demonstrate the compression (Fig. 1, Ref. 20). Full Text (Free, PDF) www.bmj.sk.

[Acoustic neurinoma shown as a facial palsy]
[Article in Spanish]

Sánchez-Legaza E, Meléndez Guerrero B, Sánchez Legaza B, Idelfonso Miranda J.
Hospital del Sas de la Línea - Cádiz. manpro1910@hotmail.com

Acoustic neurinoma is the most frequent benign tumour at the cerebellopontile angle. It causes compressive type lesions in adjacent cerebral structures. Its usual symptoms are sensorineural hearing loss and tinnitus with or without unilateral vertigo, which is why we have to know the wide variety of clinical signs it can present from its beginning, including facial palsy. We present the case of a vestibular schwannoma in a pregnant lady diagnosed by a peripheral facial palsy.
Objective tinnitus associated with essential palatal myoclonus: report in a child.

Elziere M, Roman S, Nicollas R, Triglia JM.
Service d’ORL Pédiatrique, CHU Timone, Marseille, France.

Palatal myoclonus is an uncommon, rhythmic, “shock-like” involuntary movement of the muscles of the soft palate, throat, and other structures derived from the branchial arcs. Objective tinnitus is frequently neglected in review articles about childhood tinnitus. Our aim was to present the case of a 7-year-old girl with bilateral objective tinnitus due to palatal myoclonus without hearing impairment (normal hearing thresholds between 250 Hz and 8 kHz) but with otherwise normal hearing thresholds (250 Hz-8 kHz) and no evidence of intracerebral or systemic disorders. No treatment was useful.

Arteriovenous malformation of the external ear: A case report.
Auris Nasus Larynx. 2008 Jan 18 [Epub ahead of print]

Woo HJ, Song SY, Kim YD, Bai CH.
Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Yeungnam University, 317-1, Daemyung 5-Dong, Nam-Gu, Daegu, 705-717, South Korea.

Arteriovenous malformation (AVM) is a direct communication between an artery and vein without capillary connections and it is mainly found in the intracranial region. However, in an extracranial region, an AVM of the external ear is relatively uncommon. Recently, we experienced a case of an AVM in the external ear. A 20-year-old male patient presented with pulsatile tinnitus over the past 7 months and a reddish and pulsatile mass of the left external ear. We successfully treated the patient for the AVM in the external ear by complete excision after preoperative selective embolization.

Endosurgical repair of an iatrogenic facial arteriovenous fistula due to percutaneous trigeminal balloon rhizotomy.

Lesley WS.
The Texas A&M University System, Health Science Center, College of Medicine, Scott & White Memorial Hospital, Scott, Sherwood and Brindley Foundation, Temple, Texas, USA. wlesley@swmail.sw.org

A 56-year-old woman with right-sided trigeminal neuralgia (TN), who underwent technically uneventful percutaneous balloon rhizotomy, developed significant bilateral pulsatile tinnitus on the first post-operative day. Although the patient reported significantly improved neuralgia, auscultation revealed a right facial bruit. Magnetic resonance angiography (MRA) of the face and brain demonstrated prominent right facial and jugular venous vascularity. Catheter angiography confirmed the suspected facial arteriovenous fistula (AVF). A transarterial approach was used to explore the AVF which arose from a laceration of the right internal maxillary artery and which fistulized directly with the pterygoid venous plexus. Endosurgical repair utilizing three non-fibered platinum coils was done under conscious sedation at the same setting as the diagnostic angiogram. Angiographically, the fistula was obliterated, and the patient’s bruit and tinnitus immediately resolved. Follow-up MRA at 3.5 months was normal, and, the patient had no clinical symptoms of recurrent AVF. In conclusion facial AVF can complicate percutaneous trigeminal rhizotomy. Iatrogenic facial AVF can be repaired via an endovascular approach.

A convenient sonographic technique for diagnosis of pulsatile tinnitus induced by a high jugular bulb.

Nakagawa M, Miyachi N, Fujiiwara K.
Department of Neurosurgery, Kosei General Hospital, Mihara, Hiroshima, Japan. ydhm18357@yahoo.co.jp

Objective: The purpose of this report is to describe our experience with sonography in a case of pulsatile tinnitus (PT) due to a high jugular bulb (HJB).
Methods: A 71-year-old woman came to our hospital with a 1-year history of right PT. A right HJB was shown on cerebral angiography, and enlargement of the right jugular blub compared with the left side was found. First, the ultrasound probe was placed on the anterior right upper neck at the anterior edge of the sternocleidomastoid muscle to identify the ipsilateral internal jugular vein (IJV) and measure the flow velocity. After the measurement, the ultrasound probe gradually compressed the skin until the flow in the IJV decreased.

Results: The patient reported that her PT decreased after the flow in the IJV decreased. We decided that the PT in this case was induced by the HJB.

Conclusions: This technique is less invasive and convenient for the diagnosis of PT caused by an HJB.

Modern management of pheochromocytoma.
Erratum in:

Kasturi S, Kutikov A, Guzzo TJ, Smith AL, Wein AJ.
Division of Urology, Department of Surgery, University of Pennsylvania Medical Center, 9 Penn Tower, 3400 Spruce Street, Philadelphia, PA 19104, USA.

Background: A 55-year-old male with poorly controlled hypertension and a history of coronary artery disease presented with a large adrenal mass. The patient also reported a long-standing history of profuse sweating, tinnitus, vomiting and headaches.

Investigations: Physical examination, 24-hour urine metanephrine level, CT, MRI and bone scan.

Diagnosis: Pheochromocytoma of the left adrenal gland.

Management: Preoperative alpha-blockade therapy with phenoxybenzamine followed by open left adrenalectomy

Dural arteriovenous fistula of the transverse-sigmoid sinus causing trigeminal neuralgia.

Lucas Cde P, Zabramski JM.
Department of Neurology and Neurosurgery, Instituto de Neurologia de Goiânia, Goiás, Brazil. cesar.lucas@uol.com.br

The authors analysed an unusual case of dural arteriovenous fistula (DAVF) of the transverse-sigmoid sinus causing trigeminal neuralgia is presented. Although progression to almost continuous facial pain has been reported, symptoms may be indistinguishable from typical trigeminal neuralgia. The patient had a 6-year history of right-sided trigeminal neuralgia initially well controlled by medical management. He was referred for surgical management after 10 months of progressively worsening of symptoms. At the time of consultation, the patient complained of pulsatile tinnitus in the right ear. Computed tomography imaging and angiography demonstrated a DAVF involving the right transverse-sigmoid sinus junction with retrograde venous drainage. Surgical resection of the DAVF provided both angiographic cure and complete relief of all symptoms. The authors discuss the pathophysiology of trigeminal neuralgia in patients with a DAVF.
### Clinical Trials

**Source:** clinicaltrials.gov (March 25, 2008)

#### Clinical Trial of Acamprosate for Tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
<th>Currently recruiting participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Oregon Health and Science University</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Oregon Health and Science University</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00596531</td>
</tr>
</tbody>
</table>

**Purpose**

The objective of this project is to determine whether acamprosate is more effective at providing relief for tinnitus than a placebo.

Acamprosate has been suggested to be effective in reducing tinnitus annoyance in a preliminary study. Study evidence indicates that tinnitus is related to increased excitatory spontaneous brain activities. Acamprosate may help restore the excitatory/inhibitory balance in the brain and thus reduce tinnitus.

The current study includes three phases. The first phase is an open-label screening study used to identify tinnitus subjects responding to acamprosate. These responding subjects will enter the second phase, which is a double blind, placebo-controlled study aimed at confirming the subjects’ responses to acamprosate. In the third phase, clinical parameters of both responders and non-responders will be compared using a multi-linear regression model to determine characteristics that define the sub-group of tinnitus patients that are likely to benefit from acamprosate treatment.

<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>Tinnitus</th>
</tr>
</thead>
</table>
| Interventions | Drug: Acamprosate  
Drug: Placebo |
| Phase | Phase I |
| Study type and design | Interventional; Treatment, Randomized, Double Blind (Subject, Investigator), Placebo Control, Crossover Assignment, Safety/Efficacy Study |
| Arms | A: Experimental  
Subjects taking acamprosate  
B: Placebo Comparator  
Subjects taking placebos |
| Official title: | Clinical Trial of Acamprosate for Tinnitus |
| Assigned Interventions | Drug: Acamprosate  
Oral administration, 666 mg, tid, for 6 months  
Drug: Placebo  
Oral administration of 2 pills, tid, for 6 months |
<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Tinnitus Handicap Index Tinnitus loudness score on visual analogue scale Tinnitus annoyance score on visual analogue scale [Time Frame: 15 months] [Designated as safety issue: No]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected total Enrollment</td>
<td>186</td>
</tr>
<tr>
<td>Study start</td>
<td>January 2008</td>
</tr>
<tr>
<td>Expected study completion date</td>
<td>December 2010</td>
</tr>
<tr>
<td>Expected primary completion date</td>
<td>December 2010 (final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 – 85 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Accepts health volunteers</td>
<td>No</td>
</tr>
</tbody>
</table>
| Eligibility Inclusion Criteria | - Concurrent treatments: Amplification, sound generators or cochlear implants are permitted, provided they have been in use for at least one year. A four-week washout from any other tinnitus treatment or management program is required prior to entering this study.  
- Hearing function: All levels of hearing function can be included recognizing that profound, bilateral losses will not be able to perform psychophysical tinnitus and hearing tests but will be able to rate subjective loudness, annoyance and impact on life.  
- Tinnitus etiology: All forms of tinnitus etiology will be accepted into Phase I providing they meet the following tinnitus criterion. Duration: 1 year or longer. Stability: Constant. Severity: > 50th percentile of OHSU Tinnitus Patients based upon Tinnitus Severity Index (TSI) scores. Rated loudness: > 7 cm from the left on a visual analog scale (VAS) 10 cm in length. Rated annoyance: > 7 cm from the left on a visual analog scale (VAS) 10 cm in length. Tinnitus location: Unrestricted. |
| Eligibility Exclusion Criteria | - Medical conditions: Active neurologic or otologic disease processes that may impact tinnitus perception. Auto-immune diseases. Pregnancy or planned pregnancy during the study.  
- Renal function: Subjects with documented renal disorders will be excluded if renal function has creatinine clearance is <50 mL/minute.  
- Digestive tract problems: Subjects with digestive tract disorders will be excluded.  
- Psychological status: Beck Depression Inventory score of greater than 15.  
- Tinnitus duration: Less than 1 year. Stability: pulsatile, intermittent, varying to a high degree in loudness or changing in location of perception. Severity: < 50th percentile of OHSU Tinnitus Patients based upon Tinnitus Severity Index (TSI) scores. Rated loudness: < 7 cm from the left on a visual analog scale (VAS) 10 cm in length. Rated annoyance: < 7 cm from the left on a visual analog scale (VAS) 10 cm in length. |
| Contact | William H Martin, Ph.D.  
Phone (503) 494-7954  
martinw@ohsu.edu |
Effect of Gabapentin on Idiopathic Subjective Tinnitus

Current status | Ongoing, but not recruiting
---|---
Sponsors and collaborators | Islamic Azad University of Mashhad
Information provided by | Islamic Azad University of Mashhad
ClinicalTrials.gov Identifier | NCT00555776
Purpose | The purpose of this study is to determine whether Gabapentin, which is useful for treating neuropathic pains, is effective on idiopathic subjective tinnitus.
Condition(s) | Subjective Tinnitus
Interventions | Drug: Gabapentin
| Other: placebo
Phase | Phase II
Study type and design | Intervventional; Treatment, Randomized, Double Blind (Subject, Investigator), Placebo Control, Parallel Assignment, Efficacy Study
Arms | 1: Active Comparator
Randomly, half of the subjects are given Gabapentin.
2: Placebo Comparator
Randomly, half of the subjects receive placebo.
Official title: | Phase 2 Effect of Gabapentin on Idiopathic Subjective Tinnitus
Assigned Interventions | Drug: Gabapentin
Gabapentin, 600 mg bid for the first two weeks, increased to a maximum dose of 1800 mg per day during the next 6 weeks if necessary.
Other: placebo
Placebo is given with the same definition as Gabapentin.
Further study details  
Tinnitus is the perception of sound in the absence of acoustic stimulation. It can be subjective or objective. Despite numerous researches, no effective treatment for people who suffer from tinnitus has yet been established.

As there are many evidences suggesting that loss of inhibition in the central nervous system may be responsible for many aspects of auditory dysfunction, including tinnitus; and as Gabapentin (Neurontin), a gamma-aminobutyric acid (GABA) analogue, is an effective medication in conditions where inhibition in the CNS is impaired; we guess that Gabapentin might be useful for treating idiopathic subjective tinnitus.

Primary Outcomes  
Reduction in the sensation of Tinnitus by the patient or complete resolution of tinnitus; by the patient’s scoring it from one to ten, before and after prescribing Gabapentin. [Time Frame: two months]

Secondary Outcomes  
Relieve of complications of tinnitus, such as sleep difficulties. [Time Frame: two months]

Expected total Enrollment  
70

Study start  
January 2007

Expected study completion date  
April 2008

Participants (age)  
18 – 75 years

Gender  
Both

Accepts health volunteers  
No

Eligibility Inclusion Criteria  
Patients with subjective idiopathic tinnitus

Eligibility Exclusion Criteria  
- tinnitus with known underlying cause
- pregnant women and patients younger than 18 or older than 75 years
- patients with impaired renal function

Locations  
Iran, Islamic Republic of, Khorasan razavi
ENT department of Mashhad Azad medical university
Mashhad, Khorasan razavi, Iran, Islamic Republic of, 91786 56553

Study chairs or principal investigators  
Mahboobeh Adami Dehkordi, MD
ENT department of Mashhad azad university of mashhad

Study ID Numbers  
Gaba-tinnitus-145

Last Updated  
November 26, 2007

Record first received  
November 8, 2007

ClinicalTrials.gov Identifier  
NCT00555776

Health Authority  
Iran: Ministry of Health
### Randomized Trial Of Tinnitus Retraining Therapy

<table>
<thead>
<tr>
<th>Current status</th>
<th>Currently recruiting participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>National Institute on Deafness and Other Communication Disorders (NIDCD)</td>
</tr>
<tr>
<td>Information provided by</td>
<td>National Institute on Deafness and Other Communication Disorders (NIDCD)</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00578058</td>
</tr>
<tr>
<td>Purpose</td>
<td>Millions of Americans suffer from tinnitus. However, there is no widely accepted treatment that has been shown to be effective in controlled investigations. The purpose of this study is to evaluate the effectiveness of Tinnitus Retraining Therapy (TRT). This study will investigate the contributions of counseling, the use of hearing aids and sound generators, and the importance of setting masking noise to a particular level. All groups will receive the same Counseling. In pilot studies we have developed a picture-based counseling protocol. The results of this study will determine if TRT is more effective than masking or counseling alone.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>Other: Counseling and Sound Therapy</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase II</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Interventional; Treatment, Randomized, Single Blind (Subject), Parallel Assignment</td>
</tr>
</tbody>
</table>
| Arms | 1) Counseling plus everyday noise type 1  
2) Counseling plus static noise type 2  
3) Counseling plus static noise type 3  
4) Hearing aid and counseling plus everyday noise type 1  
5) Hearing aid and counseling plus static noise type 2  
6) Hearing aid and counseling plus static noise type 3 |
| Official title: | Randomized Trial Of Tinnitus Retraining Therapy |
| Assigned Interventions | 1) – 6) Other: Counseling and Sound Therapy  
Tinnitus counseling and sound therapy |
| Primary Outcomes | Iowa Tinnitus Handicap Questionnaire [Time Frame: 18 months]  
[Designated as safety issue: No] |
<p>| Secondary Outcomes | Tinnitus measures [Time Frame: 18 months] [Designated as safety issue: No] |
| Expected total Enrollment | 180 |
| Study start | January 2004 |
| Expected study completion date | November 2008 |
| Expected primary completion date | November 2008 (Final data collection date for primary outcome measure) |</p>
<table>
<thead>
<tr>
<th>Participants (age)</th>
<th>18 years and older</th>
</tr>
</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 | - Have experienced tinnitus for at least 4 months.  
- Have the ability to participate in research. |
| Eligibility Exclusion Criteria | - Have a treatable otological disorder.  
- Are involved in litigation.  
- Have or are suspected of having a serious psychiatric problem. |
| Contact           | Anne Gehringer, M.A., anne-gehringer@uiowa.edu  
Stephanie Gogel, M.A., 319-384-6612 |
| Locations         | United States, Iowa, University of Iowa, Iowa City, Iowa, United States, 52242; recruiting  
United States, Michigan, University of Michigan, Ann Arbor, MI, United States 48109; recruiting; contact: Paul Kileny, Ph.D.  
United States, New York, University at Buffalo, State University of New York, Buffalo, New York, United States, 14214; recruiting; Contact: Christina Stocking, Au.D.  
United States, Tennessee, East Tennessee State University, Johnson City, Tennessee, United States, 37614; recruiting; Contact: Marc Fagelson, Ph.D. |
| Study chairs or principal investigators | Richard S Tyler, Ph.D. |
| Study ID Numbers  | R01DC005972        |
| Last Updated      | December 19, 2007  |
| Record first received | December 18, 2007  |
| ClinicalTrials.gov Identifier | NCT00578058 |
| Health Authority  | United States: Federal Government |
Collaborative Tinnitus Research at Washington University (CTRWU)

<table>
<thead>
<tr>
<th>Current status</th>
<th>not yet open for participant recruitment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>National Institute on Deafness and Other Communication Disorders (NIDCD)</td>
</tr>
<tr>
<td>Information provided by</td>
<td>National Institute on Deafness and Other Communication Disorders (NIDCD)</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00567892</td>
</tr>
</tbody>
</table>

**Purpose**

The goal of this trial is to see if repetitive transcranial magnetic stimulation (rTMS) to the hearing area of the brain can lessen the perception of tinnitus. rTMS uses a strong magnet and when placed against the scalp generates a small electrical field within the brain. Depending on the frequency of the stimulation, this electrical field can either decrease or increase the electrical excitability of the brain. In this study, low-frequency stimulation will be used, which decreases nerve activity. It is this electrical excitability of the brain that is thought to be responsible for tinnitus.

The hypothesis of this study is that rTMS can decrease the perception of tinnitus. Each participant will receive either active rTMS or sham rTMS (placebo) for 2 weeks. After the 2 weeks, the participant will rest for 2 weeks. After the 2 week rest, the participant will then receive either active rTMS or sham rTMS, depending on what they received at the first 2 weeks. The order of the treatments received will be randomly selected and the participant will not be told which treatment they are receiving. Each participant will undergo magnetic resonance imaging (MRI) and positive emission tomography (PET) scanning of the brain at the beginning of the study and after each treatment.

<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>subjective Tinnitus</th>
</tr>
</thead>
</table>
| Interventions         | Device: rTMS  
Device: Sham |
| Phase                 | Phase II, Phase III |
| Study type and design | Interventional; Treatment, Randomized, Single Blind (Subject), Placebo Control, Crossover Assignment, Safety/Efficacy Study |
| Arms                  | 1) rTMS: Experimental  
Stimulation Settings: Frequency -- 1Hz on 330 sec (5 min 30 sec.) per train for the first 5 trains with the last train 350 sec. (5 min. 50 sec.) in duration  
Off -- 90 sec (1 min. 30 sec.) Intensity -- 110% of motor threshold  
Duration -- 42½ minutes (total 2000 pulses in 6 trains)  
2. Sham: Sham Comparator  
Sham |
| Official title         | Collaborative Tinnitus Research at Washington University |
| Assigned Interventions | 1) Device: rTMS  
Stimulation Settings: Frequency -- 1Hz on 330 sec (5 min 30 sec.) per train for the first 5 trains with the last train 350 sec. (5 min. 50 sec.) in duration  
Off -- 90 sec (1 min. 30 sec.) Intensity -- 110% of motor threshold  
Duration -- 42½ minutes (total 2000 pulses in 6 trains)  
2) Device: Sham  
rTMS magnet turned so as to direct magnetic current away from scalp |
<table>
<thead>
<tr>
<th><strong>Primary Outcomes</strong></th>
<th>The primary outcome measure is defined as the change in the Tinnitus Handicap Inventory score between active rTMS and sham rTMS. [Time Frame: 8 weeks] [Designated as safety issue: No]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td>Participant’s response to the Patient Global Impression of Change question to be completed at the end of each treatment arm. Participants will also be asked if they would continue treatment and if they would recommend this treatment to a friend. [Time Frame: 12 weeks] [Designated as safety issue: No]</td>
</tr>
<tr>
<td><strong>Expected total Enrollment</strong></td>
<td>55</td>
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<tr>
<td><strong>Study start</strong></td>
<td>January 2008</td>
</tr>
<tr>
<td><strong>Expected study completion date</strong></td>
<td>December 2011</td>
</tr>
<tr>
<td><strong>Participants (age)</strong></td>
<td>18 – 60 years</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Both</td>
</tr>
<tr>
<td><strong>Accepts health volunteers</strong></td>
<td>Yes</td>
</tr>
</tbody>
</table>
| **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.  
- Tinnitus Handicap Inventory (THI) score of 38 or greater.  
- Subjects of child-bearing potential using an appropriate form of birth control acceptable to the research team and with a negative urine pregnancy test or undergone sterilization procedure.  
- Able to give informed consent.  
- Available for once daily therapy, during working hours, Mon.-Fri.  
- English-speaking |
| **Eligibility Exclusion Criteria** | - History of seizures, history of loss of consciousness requiring medical care, any other CNS pathology that increases a subject’s risk for treatment with rTMS.  
- 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.  
- Any contraindication for receiving FDG PET, as determined by established clinical criteria.  
- 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 psychiatric 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 psychiatric sub-investigator, may complicate the interpretation of study results. |
- Any psychiatric co-morbidity that, in the opinion of the psychiatric sub-investigator, may complicate the interpretation of study results.
- Pregnancy
- Currently breast-feeding
- Previous treatment with rTMS
- Patients with tinnitus related to Workman’s Compensation claim or litigation-related event.
- Patients with a history of diabetes.
- Fasting glucose > 150mg/Dl.
- Patients taking any medication(s), in the opinion of the investigator, that is(are) deemed to be etiologically related to the development of tinnitus.
- Unable to elicit a motor threshold with rTMS.
- A Mini-Mental Status Exam score less than 27.
- Untreated or newly diagnosed hypertension, (systolic blood pressures above 140 mm or diastolic pressure above 90 mm).
- 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 ETOH 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 for MRI or PET scanning.

<table>
<thead>
<tr>
<th>Contact</th>
<th>Joyce Nicklaus, RN, BSN; 314.362.7508, <a href="mailto:nicklausj@ent.wustl.edu">nicklausj@ent.wustl.edu</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Locations</td>
<td>United States, Missouri, Washington University Medical Center, St. Louis, Missouri, United States, 63110</td>
</tr>
<tr>
<td>Study chairs or principal investigators</td>
<td>Jay F Piccirillo, MD, Washington University School of Medicine</td>
</tr>
<tr>
<td>Study ID Numbers</td>
<td>07-0689, R01DC009095</td>
</tr>
<tr>
<td>Last Updated</td>
<td>December 3, 2007</td>
</tr>
<tr>
<td>Record first received</td>
<td>December 3, 2007</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00567892</td>
</tr>
<tr>
<td>Health Authority</td>
<td>United States: Federal Government</td>
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</tbody>
</table>
**Effects of Caffeine in Tinnitus**

<table>
<thead>
<tr>
<th>Current status</th>
<th>Ongoing, but not recruiting participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Faculdade de Medicina de Valenca</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Faculdade de Medicina de Valenca</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00628316</td>
</tr>
<tr>
<td>Purpose</td>
<td>Caffeine intake is reported by many authors to enhance the perception of tinnitus. The aim of this study is to determine the effects of 1 month caffeine intake reduction in the scores of validated questionnaire Tinnitus Handicap Inventory(THI) and in a visual-analog scale (VAS).</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>Dietary Supplement: caffeine</td>
</tr>
<tr>
<td></td>
<td>caffeine daily intake will be reduced from 150 ml per day</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Interventional; Treatment, Open Label, Single Group Assignment, Efficacy Study</td>
</tr>
<tr>
<td>Official title</td>
<td>Effects of Caffeine Consumption on Tinnitus Perception</td>
</tr>
<tr>
<td>Further study details</td>
<td>A group of 50 patients who takes more than 3 small cups (50 ml) of caffeine daily and have tinnitus will be asked to reduce caffeine intake for 1 month. Scores of THI and VAS will be taken before and after this period.</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Tinnitus Handicap Inventory [Time Frame: 30 days] [Designated as safety issue: No]</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Visual Analog Scale [Time Frame: 30 days] [Designated as safety issue: No]</td>
</tr>
<tr>
<td>Expected total Enrollment</td>
<td>50</td>
</tr>
<tr>
<td>Study start</td>
<td>January 2008</td>
</tr>
<tr>
<td>Expected study completion date</td>
<td>December 2008</td>
</tr>
<tr>
<td>Expected primary completion date</td>
<td>September 2008 (Final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 years and older</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Accepts health volunteers</td>
<td>No</td>
</tr>
<tr>
<td>Eligibility Inclusion Criteria</td>
<td>- tinnitus for more than 6 months &lt;br&gt;- THI &gt; 38 &lt;br&gt;- no central acting drugs in the last 6 months &lt;br&gt;- tympanogram type A-n &lt;br&gt;- daily intake of caffeine greater than 150 ml</td>
</tr>
</tbody>
</table>
Eligibility Exclusion Criteria - vascular and muscular tinnitus
- concomitant TMJ disorders
- abnormal otoscopy
- mixed and conductive hearing losses
- Ménière disease

Contact http://www.otosul.com.br/projetos.htm

Locations
Brazil, RJ, OTOSUL Otorrinolaringologia Sul-Fluminense, Volta Redonda, RJ, Brazil, 27255-650;
Faculdade de Medicina de Valença, Valença, RJ, Brazil, 27600-000

Study chairs or principal investigators Ricardo R Figueiredo, MD,MSc

Study ID Numbers FMV 001 2008

Last Updated March 21, 2008

Record first received February 25, 2008

ClinicalTrials.gov Identifier NCT00628316

Use of Modafinil in the Treatment of Tinnitus

Current status Currently recruiting participants

Sponsors and collaborators University of Arkansas

Information provided by University of Arkansas

ClinicalTrials.gov Identifier NCT00591019

Purpose A study on the effects of the FDA approved drug Modafinil upon attention problems associated with tinnitus. This is considered to be a safe drug with few side effects. Each subject will be asked to participate in 3 sessions each lasting approximately 1 hour in which cognitive testing and recordings will be taken. The study involves each subject taking a 2- week supply of Modafinil and a 2- week supply of placebo. We hypothesize inattention related to thalamocortical dysrhythmia found in tinnitus can be reduced by Modafinil thus improving tinnitus symptoms and vigilance.

Condition(s) Tinnitus

Interventions Drug: Modafinil
Drug: Placebo

Study type and design Interventional; Treatment, Randomized, Single Blind (Subject), Placebo Control, Crossover Assignment, Efficacy Study

Official title: Use of Modafinil in the Treatment of Tinnitus
| Arms                  | 1: Experimental  
The drug group will be instructed to take Modafinil (200mg/day taken in the morning) for 14 days.  
2: Placebo Comparator  
The placebo group will be instructed to take a 14 days’ supply of placebo. |
|----------------------|---------------------------------------------------------------|
| Assigned Interventions | Drug: Modafinil  
Modafinil (200mg/day taken in the morning) for 14 days.  
Drug: Placebo  
Placebo sugar pill taken in morning for 14 days. |
| Primary Outcomes     | Data from each subject on Modafinil will be compared to his/her data when placed on placebo in an effort to determine the differences in level of arousal with and without drug. [Time Frame: 5 weeks] [Designated as safety issue: No] |
| Secondary Outcomes   | Data from each subject on Modafinil will be compared to his/her data when placed on placebo in an effort to determine the differences in level of habituation, and reaction time performance with and without drug. [Time Frame: 5 weeks] [Designated as safety issue: No] |
| Expected total Enrollment | 10 |
| Study start          | August 2006 |
| Expected study completion date | August 2008 |
| Expected primary completion date | August 2008 (Final data collection date for primary outcome measure) |
| Participants (age)   | 20 years and older |
| Gender               | Both |
| Accepts health volunteers | Yes |
| Eligibility Inclusion Criteria | - The diagnosis of tinnitus should be established by subject through exam and history performed by study physician in ENT clinic.  
- Subjects will be age 20 or older.  
- Subjects should have tinnitus symptoms severe enough to seek medical attention.  
- Subjects will have been seen in the Hearing and Balance Center at UAMS.  
- Subjects will have had an audiogram.  
- Signed informed consent.  
- Women of childbearing potential must have a negative pregnancy test at screening and before being prescribed the study drug.  
- Peripheral neuropathy: must be < grade 1 according to NCI CTC version 3 guidelines (Appendix B).  
- Hematologic (minimal values) at screening Absolute neutrophil count > 1,500/mm3 Hemoglobin > 8.0 g/dl Platelet count > 100,000/mm3 |
<table>
<thead>
<tr>
<th>Eligibility Exclusion Criteria</th>
<th>Disease-Specific Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Subjects who have locally advanced breast cancer with skin ulceration will be excluded from this study due to the risk of worsening ulcers and healing difficulties</td>
</tr>
<tr>
<td></td>
<td>Stage IV breast cancer</td>
</tr>
<tr>
<td></td>
<td>- Inflammatory breast cancer</td>
</tr>
<tr>
<td>General Medical Concerns</td>
<td>- Subjects with ECOG performance status 2, 3, and 4 are not eligible for this study</td>
</tr>
<tr>
<td></td>
<td>- Allergy to any component of the treatment regimen</td>
</tr>
<tr>
<td></td>
<td>- Women who are breast feeding</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy or refusal to use effective contraception while participating in this study</td>
</tr>
<tr>
<td></td>
<td>- Inability to comply with study and/or follow-up procedures</td>
</tr>
<tr>
<td></td>
<td>- Subjects with secondary malignancy other than superficial skin cancer (squamous cell carcinoma and basal cell carcinoma of the skin) should be excluded</td>
</tr>
<tr>
<td>Bevacizumab-Specific Concern</td>
<td>- Current, recent (within 4 weeks of the first infusion of this study), or planned participation in an experimental drug study</td>
</tr>
<tr>
<td></td>
<td>- Blood pressure of &gt; 150/100 mmHg. Essential hypertension well controlled with antihypertensive is not an exclusion criterion</td>
</tr>
<tr>
<td></td>
<td>- Unstable angina</td>
</tr>
<tr>
<td></td>
<td>- New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix D)</td>
</tr>
<tr>
<td></td>
<td>- History of myocardial infarction within 6 months</td>
</tr>
<tr>
<td></td>
<td>- History of stroke within 6 months</td>
</tr>
<tr>
<td></td>
<td>- Clinically significant peripheral vascular disease</td>
</tr>
<tr>
<td></td>
<td>- Evidence of bleeding diathesis or coagulopathy</td>
</tr>
<tr>
<td></td>
<td>- Presence of central nervous system or brain metastases</td>
</tr>
<tr>
<td></td>
<td>- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 0, anticipation of need for major surgical procedure during the course of the study</td>
</tr>
<tr>
<td></td>
<td>- Minor surgical procedures such as fine needle aspirations or core biopsies within 7 days prior to Day 0</td>
</tr>
<tr>
<td></td>
<td>- Pregnant (positive pregnancy test) or lactating</td>
</tr>
<tr>
<td></td>
<td>- Urine protein: creatinine ratio &gt;1.0 at screening</td>
</tr>
<tr>
<td></td>
<td>- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to Day 0</td>
</tr>
<tr>
<td></td>
<td>- Serious, non-healing wound, ulcer, or bone fracture</td>
</tr>
</tbody>
</table>

**Contact**  
Jeff Myhill, MD, 501-526-7171; jamyhilli@uams.edu

**Locations**  
United States, Arkansas, University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States, 72205

**Study chairs or principal investigators**  
John L Dornhoffer, MD

**Study ID Numbers**  
# 65171
Does Aspirin Have a Protective Role Against Chemotherapeutically Induced Ototoxicity?

Current status: not yet open for participant recruitment.

Sponsors and collaborators: University Health Network, Toronto

Information provided by: University Health Network, Toronto

ClinicalTrials.gov Identifier: NCT00578760

Purpose: Aspirin (ASA) has been shown, in an animal model, to attenuate the ototoxic properties of cisplatin. The researchers plan to investigate this in patients undergoing cisplatin chemotherapy. The researchers hypothesise that low-dose aspirin can prevent cisplatin induced ototoxicity in the clinical setting.

Condition(s): Hearing Loss, Ototoxicity

Interventions: Drug: aspirin 325mg ASA OD during course of chemotherapy

Study type and design: Interventional; Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment

Number of arms in study: 2: Placebo Comparator
placebo OD during course of chemotherapy
1: Experimental
325mg ASA OD during course of chemotherapy

Official title: Does Aspirin Have a Protective Role Against Chemotherapeutically Induced Ototoxicity?

Assigned Interventions: Drug: placebo OD for course of cisplatin chemotherapy
Drug: aspirin 325mg ASA OD for the duration of the cisplatin

Primary Outcomes: hearing loss [Time Frame: before and after chemotherapy] [Designated as safety issue: No]

Expected total Enrollment: 110

Study start: February 2008
<table>
<thead>
<tr>
<th><strong>Expected study completion date</strong></th>
<th>February 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants (age)</strong></td>
<td>18 years and older</td>
</tr>
</tbody>
</table>
| **Eligibility Inclusion Criteria**| Patients undergoing cisplatin treatment for the following malignancies:  
- germ-cell  
- bladder  
head and neck (Only head and neck patients requiring only 2 cycles of post-operative chemo-radiotherapy, and therefore not requiring a gastrostomy tube, will be enrolled.)  
Over 18 years of age  
Normal otoscopic examination  
Informed consent |
| **Eligibility Exclusion Criteria**| - Not able to grasp the study implications or unable to consent.  
- History of peptic ulcer disease  
- Severe renal impairment (U&E, Cr clearance)  
- Haemophilia  
- Severe hepatic impairment  
- Cerebrovascular haemorrhage  
- Acute gout  
- Hypersensitivity to NSAIDs |
| **Contact**                       | Emma Barker, FRCS, PhD, 001-416-946-4501 ext 4353, emmabarker@doctors.org.uk |
| **Locations**                     | Canada, Ontario, Princess Margaret Hospital, Toronto, Ontario, Canada |
| **Study chairs or principal investigators** | Sub-investigator: Emma Barker |
| **Study ID Numbers**              | Aspirin-01 |
| **Last Updated**                  | December 19, 2007 |
| **Record first received**         | December 18, 2007 |
| **ClinicalTrials.gov Identifier**| NCT00578760 |
| **Health Authority**              | United States: Food and Drug Administration |
## Phase out as a treatment for chronic untreatable tinnitus: a double blind crossover trial

<table>
<thead>
<tr>
<th>Current status</th>
<th>ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>University Medical Centre Groningen (UMCG) (The Netherlands)</td>
</tr>
<tr>
<td>Information provided by</td>
<td>University Medical Centre Groningen (UMCG) (The Netherlands)</td>
</tr>
<tr>
<td>ISRCTN Identifier</td>
<td>ISRCTN17631678</td>
</tr>
<tr>
<td>Purpose</td>
<td>This study examines the effect of the Phase Out treatment on chronic, incurable tinnitus in adult subjects in comparison with placebo sound. The expectation of this study is that Phase Out treatment is effective for a longer duration and results in increased residual inhibition than placebo sound.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>A subject will receive Phase Out treatment for thirty minutes three times a week for one week and placebo sound treatment on the same regime during another. One month interval is in between these two sets of treatment. If a treatment is started, the subject fills in a report mark on the „tinnitus loudness” and „tinnitus annoyance” in the tinnitus diary every evening till three weeks after the treatment session. One week after each week of therapy a subject receives the evaluating questionnaires and will send them back after filling in.</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Randomised, placebo controlled, crossover, double blinded trial</td>
</tr>
<tr>
<td>Official title:</td>
<td>Phase out as a treatment for chronic untreatable tinnitus: a double blind crossover trial</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>The major aim of this study is disappearance (report mark) of the tinnitus lasting many hours (time). Outcomes will be measured at weeks five and nine</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Besides the major aims, different questionnaires will be used to determine for which kind of tinnitus patients, this treatment is most effective: 1. Tinnitus Handicap Inventory (THI) 2. Tinnitus Reaction Questionnaire (TRQ) 3. Vital Exhaustion (VE) questionnaire 4. Hospital Anxiety and Depression Scale (HADS) 5. Short Form questionnaire (SF-36) 6. Eysenck Personality Questionnaire 7. Type D Personality Scale 8. Social Support Questionnaire (SSQ) 9. Tinnitus Coping Style Questionnaire (TCSQ) Outcomes will be measured at weeks five and nine.</td>
</tr>
<tr>
<td>Expected total Enrollment</td>
<td>60</td>
</tr>
<tr>
<td>Study start</td>
<td>May 2007</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Expected study completion date</td>
<td>May 2009</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 years and older</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
</tr>
</tbody>
</table>
| Eligibility Inclusion Criteria | 1. Subjects greater than 18 years  
|                   | 2. Unilateral or bilateral tinnitus  
|                   | 3. Predominant tone tinnitus by history  
|                   | 4. Tinnitus for minimum of three months |
| Eligibility Exclusion Criteria | 1. Acoustic neurinoma  
|                   | 2. Aortic/outflow tract stenosis  
|                   | 3. Pulsatile tinnitus  
|                   | 4. Pregnancy  
|                   | 5. Inability to correct use of test equipment: unable to cooperate during audiologic examination  
|                   | 6. Known tinnitus etiology, which would demand other treatment  
|                   | 7. Hearing loss greater than 60 decibel compared with standardised normal hearing on standard frequencies of a tone audiogram (250, 500, 1000, 2000, 4000 and 8000 hertz) |
| Contact          | Dr K M Heijneman, Universitair Medisch Centrum Groningen, Afd. Keel-,Neus-, Oorheelkunde, P.O. Box 30001, Groningen, Netherlands, 9700 RB; phone +31 (0)50 361 8053; k.m.heijneman@kno.umcg.nl |
| Study ID Numbers | N/A               |
| Last Updated     | 25/03/2008        |
| ISRCTN Identifier| ISRCTN17631678    |
| Health Authority | Medical Ethical Committee of Groningen as of 12/04/2007. |
Repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of chronic tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
<th>ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Deutsche Forschungsgemeinschaft</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Deutsche Forschungsgemeinschaft</td>
</tr>
<tr>
<td>ISRCTN Identifier</td>
<td>ISRCTN89848288</td>
</tr>
<tr>
<td>Purpose</td>
<td>Chronic tinnitus is a severe and disabling disease with so far no efficient treatment. Accumulating data point to the involvement of dysfunctional neuronal activity in the central nervous system as one possible underlying cause of chronic tinnitus. rTMS has been shown to be able to non-invasively modulate cortical activity and holds therapeutic potential in other treatment-resistant diseases such as major depression. Pilot studies revealed promising therapeutic potential of rTMS in the treatment of chronic tinnitus. The primary objective of this trial is to evaluate the efficacy of real rTMS versus sham rTMS in the treatment of chronic tinnitus by means of change of tinnitus severity according to the tinnitus questionnaire of Goebel and Hiller (baseline versus day 12).</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Chronic tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>rTMS will be administered according to current safety guidelines. Figure-of-eight-coils will be used for real stimulation. Sham stimulation will be carried out by tilting the coil 45° away from the skull with one wing touching the skull. The stimulation parameters have been chosen according to successful pilot studies. Patients will be randomized to 2 parallel treatment groups: Group A will receive real stimulation: 2 x 5 sessions, 1 Hz rTMS, stimulation intensity 110% related to the individual motor threshold, 2000 stimuli per session, coil position 10-20 guided over left primary auditory cortex. Group B will receive sham stimulation by angulation of the magnetic coil 45° away from the skull with one wing touching the skull. Coil positioning and stimulation parameters as for group A. Treatment will be conducted over a period of 2 weeks, at a frequency of 5 sessions/week</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Randomized, double-blind, placebo-controlled, multi-center trial.</td>
</tr>
<tr>
<td>Official title:</td>
<td>Repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of chronic tinnitus</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Change of tinnitus severity according to the tinnitus questionnaire of Goebel and Hiller (baseline versus day 12).</td>
</tr>
</tbody>
</table>
**Secondary Outcomes**

The secondary outcome parameter is a change of tinnitus severity according to the tinnitus questionnaire of Goebel and Hiller, Tinnitus Handicap Inventory (THI), Tinnitus Severity scale and Clinical Global Impression Scale during the follow-up period (screening versus baseline versus days 5, 67 and 181).

Further outcome measures:
1. Changes in quality of life of patients as measured by the 12-item Short Form health survey (SF-12) (baseline versus days 5, 12, 18, 67 and 181)
2. Changes in depressive symptoms, measured by the Beck Depression Inventory (BDI) (baseline versus days 5, 12, 18, 67 and 181).
3. Changes of psychometric parameters of tinnitus, assessed by audiological evaluation (screening versus day 18)
4. Changes in structural neuroplastic adaptation processes, detected by voxel-based morphometry (baseline versus day 12)
5. Changes in cortical excitability, assessed by paired-pulse TMS (baseline versus day 12)

<table>
<thead>
<tr>
<th>Expected total Enrollment</th>
<th>138</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study start</td>
<td>January 2007</td>
</tr>
<tr>
<td>Expected study completion date</td>
<td>January 2010</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 – 70 years</td>
</tr>
<tr>
<td>Eligibility Inclusion Criteria</td>
<td></td>
</tr>
</tbody>
</table>
1. Male or female in- and outpatients, age 18-70 years.
2. Diagnosis of chronic tinnitus.
3. Patient has a score of greater than or equal to 38 on the Tinnitus Handicap Inventory.
4. Tinnitus duration of more than 6 months.
5. Age-adjusted normal sensorineuronal hearing determined by an audiogram within the last 4 weeks, i.e. no more than 5 dB below the 10% percentile (DIN EN ISO 7029) of the appropriate age and gender group in all measured standard frequencies. Furthermore, no conductive hearing loss of more than 15 dB in neither of the measured standard frequencies.
6. Patient naïve to rTMS-treatment

| Eligibility Exclusion Criteria |
1. Objective tinnitus
2. Other forms of tinnitus treatment at the same time
3. Clinically relevant psychiatric comorbidity as judged by an experienced psychiatrist
4. Concomitant treatment with psychotropic drugs
5. History of or evidence of significant brain malformation or neoplasm, head injury, cerebral vascular events, neurodegenerative disorder affecting the brain or prior brain surgery
6. Severe unstable somatic comorbidity
7. Cardiac pace makers, other electronic implants, intracranial metallic particles
8. History of seizures or epileptiform activity
9. Pregnancy and lactation
10. Women in child bearing age without contraception
11. Patients who cannot communicate reliably with the investigator or who are not likely to cope with the requirements of the trial
12. Patient unwilling or unable to give written informed consent
13. Participation in a clinical trial within the last 30 days before start of this clinical trial or similar participation in another clinical trial

<table>
<thead>
<tr>
<th>Contact</th>
<th>Prof Dr. Goeran Hajak, +49 (0)941 941 2011, fax +49 (0)941 941 2015; <a href="mailto:goeran.hajak@medbo.de">goeran.hajak@medbo.de</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Locations</td>
<td>University of Regensburg, Dept. of Psychiatry, Psychosomatics and Psychotherapy, Universitaetsstr. 84, 93053 Regensburg, Germany;</td>
</tr>
<tr>
<td>Study chairs or principal investigators</td>
<td>Prof. Dr. Goeran Hajak</td>
</tr>
<tr>
<td>Study ID Numbers</td>
<td>HA 3547/4-1</td>
</tr>
<tr>
<td>Last Updated</td>
<td>January 18, 2008</td>
</tr>
<tr>
<td>Record first received</td>
<td>September 12, 2007</td>
</tr>
<tr>
<td>ISRCTN Identifier</td>
<td>ISRCTN89848288</td>
</tr>
<tr>
<td>Health Authority</td>
<td>Ethics committee of the University of Regensburg</td>
</tr>
</tbody>
</table>