Dear friends and colleagues,

The Tinnitus Research field continues to grow, embracing otorhinolaryngologists, otologists, audiologists, neurologists, psychologists, psychiatrists, neurosurgeons and basic neuroscientists, to name a few of the specialists who enthusiastically met last March in Florianopolis, Brazil at the X International Tinnitus Seminars. It was clear during that meeting that more bright minds coming from different fields, with different experimental and clinical approaches are needed in order to accelerate the pace in our search for a tinnitus cure. In particular, neuroscience continues to be a pacesetter in the tinnitus field and more work coming from both the basics and clinical neuroscience will most likely pleasantly surprise us in the near future. In this regard, Madoux et al., presented recent findings showing changes in the brain’s resting state activity in tinnitus patients and Adamchic et al., showed their work on symptoms-related signatures of tinnitus related oscillatory brain activity.

As presented in the 15th Newsletter, tinnitus research has reached the top notch scientific journals, including Journal of Neuroscience, Neuron and Nature. In addition, a new study has now appeared in the Proceedings of the National Academy of Sciences, USA which has made use of the measurement of the magnitude and spatial spread of evoked circuit activity in the dorsal cochlear nucleus with flavoprotein autofluorescence imaging in mice with behavioral evidence of tinnitus. Moreover, an invited Perspective in the same journal on Phantom Perception dissects the neural brain networks underlying phantom pain and tinnitus. These manuscripts are referred to in the recently added “research highlights” section of the TRI Newsletter.

Following this hype in tinnitus research, Jos Eggermont and Larry Roberts are organizing a Special Topic „Ringing ears: the neuroscience of tinnitus“ for the innovative open access journal, Frontiers in Systems Neuroscience. This will contain a collection of articles aiming at bringing more awareness to our field.

The recent developments indicate that tinnitus is continuing to attract the best neuroscience minds. Following this trend this year’s TRI Meeting has been entitled “The neuroscience of Tinnitus”. We again invite all of you to join us in Buffalo in August to share your most recent and exciting research results and to discuss future directions and implications for the clinical management of tinnitus. More detailed information regarding the meeting can be found on www.tinnitusresearch.org

We wish to see you all in Buffalo in order to catch up with the most recent findings on tinnitus research and treatment, to foster further scientific collaborations, to meet old friends and to make new ones as the tinnitus family continues to expand.

Belén Elgoyhen  Dirk De Ridder  Berthold Langguth  Susanne Staudinger
RESEARCH HIGHLIGHTS

This study investigated the relationship between temporomandibular dysfunction and tinnitus in a large population based longitudinal study. This study demonstrated that pain in the TMJ increased the risk to develop tinnitus in the subsequent 5 years by the factor 2.4, further underscoring an important role of abnormal somatosensoric input in the etiology of tinnitus.

This perspective provides a testable model about the neurobiological substrates of tinnitus and phantom perception. Electrophysiologic and neuroimaging findings of these disorders are discussed in the context of neuroscientific knowledge about perception.

This study sheds light on molecular mechanisms involved in tinnitus genesis by demonstrating a reduction of GABAergic inhibition in the dorsal cochlear nucleus in mice with behavioural evidenc of tinnitus.

By demonstrating a strong association between audiologic findings and the tinnitus percept, this study highlights the relevance of disturbed cochlear function for tinnitus generation. Special emphasis is given on the DPOAE input-output function, which reflects gain-adaptation and is an important variable in addition to the audiogram for predicting the tinnitus percept.

Adamchic I, Hauptmann C, von Stackelberg T, Tass PA Changes of tinnitus-related spontaneous brain activity before and after treatmentinduced significant reduction of tinnitus symptoms.
Tinnitus is an auditory phantom sensation of sound in the absence of external auditory stimulus. Based on previous studies comparing tinnitus sufferers with healthy controls, tinnitus is assumed to be associated with an increase in oscillatory activity in delta and gamma frequency ranges and a decrease in alpha band power in specific auditory as well as non-auditroy brain areas. We here present an EEG study on the neurophysiological changes in one group of tinnitus patients measured under two conditions: with tinnitus and with a significant long-term reduction of their tinnitus. This enables us to relate changes in oscillatory power in different brain areas with tinnitus symptoms (TQ as well as VAS for loudness and burden). Objectives: The aim of this work was to reveal a hallmark of tinnitus-related spontaneous cerebral activity. Methods: Resting state EEG was recorded from 52 patients with chronic tonal subjective tinnitus. Tinnitus treatment was performed using acoustic Coordinated Reset (CR) stimulation. Each patient underwent two EEG recording sessions: 1st on the first treatment day prior to treatment begin; 2nd at the 12 weeks follow up. Surface EEG was transformed to brain source activity using a source montage approach from BESA. A source model was generated with sources placed in regions of interest predefined according to previous studies: primary auditory cortex (ACI), secondary auditory cortex (ACII), orbito-frontal cortex (OF), dorsolateral-prefrontal cortex (DP), parietal cortex (P), anterior and posterior cingulate area (AC and PC). The initial population of 52 patients has been divided in to 2 groups for EEG analysis: improved reliably and not improved reliably. Grouping was based on a reliable change in tinnitus symptoms (TQ) after 12 weeks of therapy that was determined on the individual basis for each patient using a reliable change index proposed by Jacobson. Power spectra of source waveforms in each region of interest were calculated for delta, theta, alpha, beta and gamma bands. To investigate the relationship between
power spectral changes and changes in clinical scores we applied multivariate data analysis using partial least squares regression (PLS) for all patients. For PLS analysis we have used spectral power in 1 Hz wide bands spanning from 1 to 90 Hz. Results: We have revealed that in the population of improved patients with one sided tinnitus there was a significant Time×Frequency band×Side interaction effect only in the ACI. This interaction resulted from a reduction in the delta band and increase in Alpha band power on the contralateral to the tinnitus side in the ACI in improved patients, no other significant changes were observed on both sides. After averaging sources from patients with bilateral tinnitus over hemispheres for each patient separately, we have found an increase in the alpha band and a decrease in gamma and delta in ACI and DP in the improved group. No significant changes were observed in the not reliably improved group. The PLS analysis revealed the oscillatory activity that most strongly covariables with tinnitus symptoms: Delta and Beta activity in the ACI as well as beta activity in the P cortex were most strongly positively related with the TQ scores. VAS loudness and burden were most strongly positively associated with delta and beta oscillatory activity in the ACI, ACII as well as with beta and delta oscillations in CP and P areas. Discussion: This study reveals symptoms-related signatures of tinnitus related oscillatory brain activity. Long-lasting changes in tinnitus symptoms according to the TQ was marked by a decrease in the delta oscillatory power in ACI and DP in the improved group compared with no change in non-improved group. Gamma oscillatory power decreased in ACI and DP. Alpha band power was increased in ACI and DP. Interestingly, symptoms covariliated more strongly with delta and beta band oscillatory powers in ACI, P and limbic areas. In addition, our study illustrates that it may be beneficial to analyze continuous spectra of oscillatory brain activity rather than restricting oneself to only a few pre-defined frequency bands.

Maudoux A, Lefebvre Ph, Cabay J-E, Vanhaudenhuyse A, Demertzi A, Laureys S, Soddu A

Resting-state activity in the tinnitus brain.

Coma Science Group, Cyclotron Research Center and Neurology Dept, University of Liège, ENT Department, CHU Sart Tilman Hospital, University of Liège, Radiology Department, CHU Sart Tilman Hospital, University of Liège, Belgium

Recently, increased focus has been directed to the study of the brain's baseline brain activity (the resting state). Through examination of spontaneous fluctuations in the functional MRI BOLD signal, past studies have shown that it was possible to identify consistent resting-state networks that have a functional relevance. Objectives: The aim of our study was to assess if there was a difference between the resting state auditory network in tinnitus patients compared to healthy controls. We also wanted to investigate the possibility that other regions of the brain could be involved in the tinnitus physiopathology. Materials and methods: We studied 12 tinnitus patients and 11 healthy volunteers, age matched. Resting-state BOLD data were acquired on a 3T-MRI scanner (Siemens). fMRI data were preprocessed and analyzed using the “Brain Voyager” software package. Data analysis was based on Independent Component Analysis (ICA) which decomposed the BOLD signal in thirty components. For each subject, the auditory component was selected by visual inspection and the corresponding time course was subsequently used as predictor in a Random Effect General Linear Model (GLM) analysis. Results and conclusion: Our preliminary results show that primary and secondary auditory regions present a higher level of connectivity in tinnitus patients respect to healthy controls and that the insula, the parahypiccompal region, the cingulate gyrus and the precentral gyrus seem also to be involved in the tinnitus physiopathology. Further study intends to investigate a bigger population in order to confirm or precise our preliminary results.
NEWS

The **website of the Tinnitus Subtyping Project** is now online. Recent news regarding the database and documents for download are available at

http://database.tinnitusresearch.org

The **5th International TRI Tinnitus Meeting - The Neuroscience of Tinnitus** will take place in August, 19-21, 2011, in Buffalo, NY, U.S.A. (see announcement the following page). You should reserve your hotel accommodation soon, because the rooms at the congress venue are running low.
Fifth International TRI Tinnitus Conference

The Neuroscience of Tinnitus

Holiday Inn Grand Island Resort and Conference Center
Grand Island, New York, U.S.A.
August 19 - 21, 2011

To obtain a registration form you can e-mail or call Carol Altman
phone: 716-829-5291, e-mail: caltmann@buffalo.edu

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Functional Imaging of Tinnitus

for more information please see
www.tinnitusresearch.org
or contact
Carol Altmann, University of New York at Buffalo, phone: 716-829-5291
e-mail caltmann@buffalo.edu or
TRI-office, Germany, phone +49 941 941 2096, mail: info@tinnitusresearch.org
Upcoming Meetings

82. Jahresversammlung der Deutschen Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie e.V.
When: June 1 – 5, 2011
Where: Freiburg, Germany
Contact: Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie, Hittorfstr. 7, 53129 Bonn
Phone: +49 (0)2 28/23 17 70
Fax: +49 (0)2 28/23 93 85
E-Mail: info@hno.org
Detailed Information: http://www.hno.org/veranstaltungen/ankuendigungen.html

Tinnitus Education for Audiologists
When: June 10 – 11, 2011
Where: Detroit, MI, USA
E-Mail: tinn_practitioners@snet.net
Detailed Information: http://www.tinnituspractitioners.org

10th EFAS Congress
When: June 22 – 25, 2011
Where: Warsaw, Poland
E-Mail: efas2011@ifps.org
Detailed Information: http://www.efas2011.org/

Human Brain Mapping Annual Meeting
When: June 26 – 30, 2011
Where: Quebec City, Canada
Detailed Information: www.humanbrainmapping.org

XXII IERASG Biennial Symposium
When: June 26 – 30, 2011
Where: Moscow, Russia
Detailed Information: http://www.ierasg2011.ru/

1st Congress of the Confederation of the European ORL-HNS
When: July 2 – 4, 2011
Where: Barcelona, Spain
Detailed Information: http://www.ceorlhsbarcelona2011.org/
Molecular Biology of Hearing and Deafness
When: July 6 – 9, 2011
Where: Cambridge, UK
E-Mail: p.garland@hinxton.wellcome.ac.uk
Detailed Information: https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=222

Conference on Implantable Auditory Prostheses 2011
When: July 24 – 29, 2011
Where: Pacific Grove, California
E-Mail: CIAP2011@gmail.com
Detailed Information: http://www.ciap2011home.org/

Biology of the inner ear - experimental and analytical approaches
When: August 7 – 27, 2011
Where: Woods Hole, MA, USA
Detailed Information: http://courses.mbl.edu/bie

5th International TRI Tinnitus Conference. The Neuroscience of Tinnitus.
When: August, 19 – 21, 2011
Where: Buffalo, NY, USA
E-Mail: meetings@tinnitusresearch.org
Detailed Information: http://www.tinnitusresearch.org/

Nineteenth annual conference on the management of the tinnitus patient
When: September 8 – 10, 2011
Where: Iowa, USA
Contact: conferences@uiowa.edu

American Academy of Otolaryngology, Head and Neck Surgery Annual Meeting
When: September 11 – 14, 2011
Where: San Francisco, CA, USA
Detailed Information: http://www.entnet.org
28. Politzer Society Meeting
When: September 29 – October 1, 2011
Where: Zappeion Exhibition Hall, Athens, Greece
Contact: GOLDAIR Congress, 15 Panepistimiou Avenue, 10564 Athens, Greece
Phone: +30 210 3274570
Fax: +30 210 3311021
E-Mail: info@politzer-athens2011.gr
and/or congress@goldair.gr

8th Meeting of the British Society of Neuro-Otology
When: October 14, 2011
Where: National Hospital for Neurology and Neurosurgery, Queen Square, London
Contact: Miss J. Mills, Neuro-Otology Group, Imperial College London, Charing Cross Hospital
Fulham Palace Road London W6 8RF
Phone: +44 (0)208 846 7285
Fax: +44 (0)208 846 7577
E-Mail: neuro-otology@imperial.ac.uk
Detailed Information: http://www.bsno.org.uk/8th%20meeting.html

56th International Congress of Hearing Aid Acousticians
When: October 19 – 21, 2011
Where: CongressCenter Nürnberg, CCN East, Germany
Detailed Information: http://www.euha.org

Asia Pacific Symposium on Cochlear Implant and Related Science
When: October 26 – 28, 2011
Where: Korea
Detailed Information: http://knuh.knu.ac.kr

162nd Meeting of the Acoustical Society of America
When: October 31 – November 4, 2011
Where: San Diego, California, United States
E-Mail: asa@aip.org
Detailed Information: http://asa.aip.org/meetings.html
I Epidemiology

Am J Audiol. 2011 Apr 7. [Epub ahead of print]
Helfer TM, Jordan NN, Lee RB, Pietrusiak P, Cave K, Schairer K.

PURPOSE: To evaluate noise-induced hearing injury (NIHI) and blast-related comorbidities among U.S. Army soldiers to understand the morbidity burden and future health service requirements for wounded warfighters returning from the Central Command (CENTCOM) Area of Responsibility, predominantly from Iraq and Afghanistan deployments. Methods Inpatient and outpatient records with diagnosed NIHI or blast-related comorbidities (e.g. significant threshold shifts (STS), noise-induced hearing loss, tinnitus, sensorineural hearing loss, eardrum perforations, mild traumatic brain injury, and post traumatic stress disorder) were extracted for active duty soldiers returning from combat deployments. Records were limited to those within 6 months of the soldier’s return date from April 2003 through June 2009. To account for changes in STS coding practice, STS rates observed after 1 October 2006 were used to extrapolate prior probable postdeployment STS.

RESULTS: Statistically significant increases were observed for tinnitus, dizziness, eardrum perforations, and speech language disorders. The combination of observed and extrapolated STS yielded a conservative estimate of 27,427 cases.

CONCLUSIONS: Estimates can be used to forecast resource requirements for hearing services among veterans. This paper could serve as a guide for resourcing and innovating prevention measures and treatment in this population. Data provided may also serve as a baseline for evaluating prevention measures.

Stress and prevalence of hearing problems in the Swedish working population.
Hasson D, Theorell T, Wallén MB, Leineweber C, Canlon B.

Karolinska Institutet, Dept of Physiology and Pharmacology, Stockholm, Sweden. dan.hasson@ki.se

BACKGROUND: Current human and experimental studies are indicating an association between stress and hearing problems; however potential risk factors have not been established. Hearing problems are projected to become among the top ten disabilities according to the WHO in the near future. Therefore a better understanding of the relationships between stress and hearing is warranted. Here we describe the prevalence of two common hearing problems, i.e. hearing complaints and tinnitus, in relation to different work-and health-related stressors.

METHODS: A total of 18,734 individuals were invited to participate in the study, out of which 9,756 (52%) enrolled.

RESULTS: The results demonstrate a clear and mostly linear relationship between higher prevalence of hearing problems (tinnitus or hearing loss or both) and different stressors, e.g. occupational, poorer self-rated health, long-term illness, poorer sleep quality, and higher burnout scores.

CONCLUSIONS: The present study unambiguously demonstrates associations between hearing problems and various stressors that have not been previously described for the auditory system. These findings will open new avenues for future investigations.
Auditory complications in childhood cancer survivors: A report from the childhood cancer survivor study.

Dept of Pediatrics, Univ. of Alabama at Birmingham, Birmingham, Alabama. kwhelan@peds.uab.edu.

BACKGROUND: Studies have found associations between cancer therapies and auditory complications, but data are limited on long-term outcomes and risks associated with multiple exposures.

PROCEDURE: The Childhood Cancer Survivor Study is a retrospective cohort investigating health outcomes of long-term survivors (5+ years) diagnosed and treated between 1970 and 1986 compared to a randomly selected sibling cohort. Questionnaires were completed by 14,358 survivors of childhood cancer and 4,023 sibling controls. Analysis determined the first occurrence of four auditory conditions in two time periods: diagnosis to 5 years post-diagnosis, and ≥5 years post-diagnosis. Multivariable analyses determined the relative risks (RR) and 95% confidence interval (CI) of auditory conditions by treatment exposure.

RESULTS: Five or more years from cancer diagnosis, survivors were at increased risk of problems hearing sounds (RR=2.3; 95% CI: 1.8-2.8), tinnitus (RR=1.7; 95% CI: 1.4-2.1), hearing loss requiring and aid (RR=4.4; 95% CI 2.8-6.9), and hearing loss in 1 or both ears not corrected by a hearing aid (RR=5.2; 95% CI: 2.8-9.5), when compared to siblings. Temporal lobe and posterior fossa radiation was associated with these outcomes in a dose-dependent fashion. Exposure to platinum compounds was associated with an increased risk of problems hearing sounds (RR= 2.1; 95% CI: 1.3-3.2), tinnitus (RR= 2.8; 95 % CI: 1.9-4.2), and hearing loss requiring an aid (RR=4.1; 95 % CI: 2.5-6.7).

CONCLUSIONS: Childhood cancer survivors are at risk of developing auditory complications. Radiation and platinum compounds are determinants of this risk. Follow-up is needed to evaluate the impact of auditory conditions on quality of life. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

Tinnitus and its risk factors in the Beaver Dam Offspring Study.

Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, USA.

Abstract Objective: To assess the prevalence of tinnitus along with factors potentially associated with having tinnitus. Design: Data were from the Beaver Dam Offspring Study, an epidemiological cohort study of aging. Study Sample: After a personal interview and audiometric examination, participants (n = 3267, ages 21-84 years) were classified as having tinnitus if in the past year they reported having tinnitus of at least moderate severity or that caused difficulty in falling asleep. Results: The prevalence of tinnitus was 10.6%. In a multivariable logistic regression model adjusting for age and sex, the following factors were associated with having tinnitus: hearing impairment (Odds Ratio (OR) = 3.20), currently having a loud job (OR = 1.90), history of head injury (OR = 1.84), depressive symptoms (OR = 1.82), history of ear infection (men, OR = 1.75), history of target shooting (OR = 1.56), arthritis (OR = 1.46), and use of NSAID medications (OR = 1.33). For women, ever drinking alcohol in the past year was associated with a decreased risk of having tinnitus (OR = 0.56). Conclusions: These results suggest that tinnitus is a common symptom in this cohort and may be associated with some modifiable risk factors.
Hearing impairment after platinum-based chemotherapy in childhood.
Faculty of Medicine, University of Iceland, Reykjavík, Iceland; Department of Clinical Sciences, Lund University, Lund, Sweden. eje2@hi.is

BACKGROUND: Chemotherapy is used in the treatment of children and adolescents with malignant diseases. Some of the chemotherapeutic agents are highly toxic and may cause a number of side effects. The primary objective of this study was to evaluate the long-term effects on hearing in cancer survivors who had received platinum-based chemotherapy in childhood or adolescence. PROCEDURE: Medical records of 297 patients, who had received treatment for cancer at the Children’s Hospital, Landspitali University Hospital in Iceland between 1981 and 2006, were retrospectively reviewed. Fifteen subjects fulfilled the eligibility criteria for the study and underwent an extended audiometric evaluation. RESULTS: The results showed that three of the subjects had a high frequency hearing loss. In one subject, we observed a hearing recovery just after the completion of chemotherapy, but the hearing deteriorated again some years later. Nine of the 15 subjects (60%) had tinnitus after the cancer treatment. An evaluation of subjective hearing disability and handicap (The Hearing Measurements Scale) revealed that some subjects had great difficulties with hearing in certain situations. The Hearing Measurement Scale showed that the pure-tone audiogram findings were only partly associated with the apparent hearing difficulties. CONCLUSION: Regular follow-up hearing examinations, which include both pure-tone audiogram investigations and subjective hearing disability assessments, should be performed during and after chemotherapy to identify subjects who require particular attention. This will ensure that hearing impaired individuals are provided with the most suitable listening devices, to promote good speech and social development. Copyright © 2010 Wiley-Liss, Inc.

Otologic diagnoses in the elderly: Current utilization and predicted workload increase
The Laryngoscope 2011 (Apr)
Lin HW, Bhattacharyya N

Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA, Department of Otolaryngology and Laryngology, Harvard Medical School, Boston, MA, Division of Otolaryngology–Head and Neck Surgery, Brigham and Women’s Hospital, Boston.

Objective: To establish the current outpatient workload for otologic conditions in the elderly and to estimate its potential increase based on an anticipated aging population. Study design: Cross-sectional analysis of a national database. Methods: All outpatient clinic visits for patients aged ≥65 years receiving one of 5 common otologic diagnoses from 2005-2007 in the United States were determined from the National Ambulatory Medical Care Survey The distribution of the visits for these diagnoses across 15 specialties was assessed. The number of visits was projected to the 2020 population based on changes in population demographics predicted by the United States Census Bureau. Results: An estimated 4.48 ± 0.49 million clinic visits with an otologic issue as a coded diagnosis were conducted in 2005-2007 in patients aged ≥65 years. These consisted of 230,000 visits for benign positional paroxysmal vertigo, 263,000 visits for vestibular neuritis, 292,000 visits for Meniere’s disease, 1.09 million visits for tinnitus, and 2.85 million visits for sensorineural hearing loss. Otolaryngology, internal medicine, family practice, and neurology managed the most visits, seeing 57.0%, 21.0%, 14.3% and 2.2% of the cases, respectively. With expected changes in population demographics by 2020, annual clinic visits for an otologic diagnosis will increase from 1.49 ± 0.78 million to 2.14 million visits in the elderly, annualized, including 1.218 million visits to otolaryngology. Conclusion: These data quantify the current outpatient otology workload and predict a substantial increase for many specialties, including otolaryngology. Efforts to prepare for this increase including manpower planning and education appear imperative.
The objective of this study was to investigate the effect of chemical and environmental exposures during deployment on tinnitus among Australian Defence Force personnel previously deployed to Bougainville and East Timor. Participants were asked to self-report recent occurrence and severity of “ringing in the ears,” and identify any chemical and environmental exposures during their deployment. Self-reported exposure to loud noises, heavy metals, intense smoke, engine exhaust, solvents and degreasing agents, and chemical spills increased the risk of self-assessed moderate or severe tinnitus. Daily exposure to 4 or more ototoxic factors was associated with 2- to 4-fold increase in the risk. In addition to loud noises, chemical exposures may also play a role in the development of tinnitus among Australian Defence Force personnel serving overseas.

II Pathophysiology

Phantom percepts: Tinnitus and pain as persisting aversive memory networks.  
Proc Natl Acad Sci U S A. 2011 Apr 18. [Epub ahead of print]

De Ridder D, Elgoyhen AB, Romo R, Langguth B.

Tinnitus Research Initiative, Brain Research Center Antwerp for Innovative and Interdisciplinary Neuromodulation, and Department of Neurosurgery, University Hospital Antwerp, 2650 Edegem, Belgium.

Phantom perception refers to the conscious awareness of a percept in the absence of an external stimulus. On the basis of basic neuroscience on perception and clinical research in phantom pain and phantom sound, we propose a working model for their origin. Sensory deafferentation results in high-frequency, gamma band, synchronized neuronal activity in the sensory cortex. This activity becomes a conscious percept only if it is connected to larger coactivated “(self-)awareness” and “salience” brain networks. Through the involvement of learning mechanisms, the phantom percept becomes associated to distress, which in turn is reflected by a simultaneously coactivated nonspecific distress network consisting of the anterior cingulate cortex, anterior insula, and amygdala. Memory mechanisms play a role in the persistence of the awareness of the phantom percept, as well as in the reinforcement of the associated distress. Thus, different dynamic overlapping brain networks should be considered as targets for the treatment of this disorder.

Mice with behavioral evidence of tinnitus exhibit dorsal cochlear nucleus hyperactivity because of decreased GABAergic inhibition.  
Proc Natl Acad Sci U S A. 2011 Apr 18. [Epub ahead of print]

Middleton JW, Kiritani T, Pedersen C, Turner JG, Shepherd GM, Tzounopoulos T.

Departments of Otolaryngology and Neurobiology and Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA 15261.

Tinnitus has been associated with increased spontaneous and evoked activity, increased neural synchrony, and reorganization of tonotopic maps of auditory nuclei. However, the neurotransmitter systems mediating these changes are poorly understood. Here, we developed an in vitro assay that allows us to evaluate the roles of excitation and inhibition in determining the neural correlates of tinnitus. To measure the magnitude and spatial spread of evoked circuit activity, we used flavoprotein autofluorescence (FA) imaging, a metabolic indicator of neuronal activity. We measured FA responses after electrical stimulation of glutamatergic axons in slices containing the dorsal cochlear nucleus,
an auditory brainstem nucleus hypothesized to be crucial in the triggering and modulation of tinnitus. FA imaging in dorsal cochlear nucleus brain slices from mice with behavioral evidence of tinnitus (tinnitus mice) revealed enhanced evoked FA response at the site of stimulation and enhanced spatial propagation of FA response to surrounding sites. Blockers of GABAergic inhibition enhanced FA response to a greater extent in control mice than in tinnitus mice. Blockers of excitation decreased FA response to a similar extent in tinnitus and control mice. These findings indicate that auditory circuits in mice with behavioral evidence of tinnitus respond to stimuli in a more robust and spatially distributed manner because of a decrease in GABAergic inhibition.

Relationship between auditory thresholds, central spontaneous activity and hair cell loss after acoustic trauma.

Mulders WH, Ding D, Salvi R, Robertson D.
The Auditory Laboratory, School of Biomedical, Biomolecular and Chemical Sciences, The University of Western Australia, Crawley WA 6009, Australia. hmulders@cyllene.uwa.edu.au.

Acoustic trauma caused by exposure to a very loud sound increases spontaneous activity in central auditory structures such as the inferior colliculus. This hyperactivity has been suggested as a neural substrate for tinnitus, a phantom hearing sensation. In previous studies we have described a tentative link between the frequency region of hearing impairment and the corresponding tonotopic regions in the inferior colliculus showing hyperactivity. In this study we further investigated the relationship between cochlear compound action potential threshold loss, cochlear outer and inner hair cell loss and central hyperactivity in inferior colliculus of guinea pigs. Two weeks after a 10 kHz pure tone acoustic trauma, a tight relationship was demonstrated between the frequency region of compound action potential threshold loss and frequency regions in the inferior colliculus showing hyperactivity. Extending the duration of the acoustic trauma from 1 to 2 h did not result in significant increases in final cochlear threshold loss, but did result in a further increase of spontaneous firing rates in the inferior colliculus. Interestingly, hair cell loss was not present in the frequency regions where elevated cochlear thresholds and central hyperactivity were measured, suggesting that subtle changes in hair cell or primary afferent neural function are sufficient for central hyperactivity to be triggered and maintained. J. Comp. Neurol., 2011. © 2011 Wiley-Liss, Inc.

Expression of tumor necrosis factor-alpha and interleukin-1beta genes in the cochlea and inferior colliculus in salicylate-induced tinnitus.
J Neuroinflammation. 2011 Apr 9;8(1):30. [Epub ahead of print]

Hwang JH, Chen JC, Yang SY, Wang MF, Chan YC.

BACKGROUND: Changes in the gene expressions for tumor necrosis factor-alpha (TNF-alpha) and/or interleukin-1beta (IL-1beta) during tinnitus have not been previously reported. We evaluated tinnitus and mRNA expression levels of TNF-alpha, IL-1beta, and N-methyl D-aspartate receptor subunit 2B (NR2B) genes in cochlea and inferior colliculus (IC) of mice after intraperitoneal injections of salicylate. METHODS: Forty-eight 3-month-old male SAMP8 mice were randomly and equally divided into two groups: salicylate-treated and saline-treated. All mice were trained to perform an active avoidance task for 5 days. Once conditioned, an active avoidance task was performed 2 hours after daily intraperitoneal injections of salicylate, either alone or containing 300 mg/kg sodium salicylate. Total numbers of times (tinnitus score) the mice climbed during the inter-trial silent period for 10 trials were recorded daily for 4 days (days 7 to 10), and then mice were euthanized for determination of mRNA expression levels of TNF-alpha, IL-1beta, and NR2B genes in cochlea and IC at day 10. RESULTS: Tinnitus scores increased in response to daily salicylate treatments. The mRNA expression levels of TNF-alpha increased significantly for the salicylate-treated group compared to the control group in both cochlea (1.89 +/- 0.22 vs. 0.87 +/- 0.07, P<0.0001) and IC (2.12 +/- 0.23 vs. 1.73 +/- 0.22, p=0.0040). mRNA expression levels for the IL-1beta gene also increased significantly in the salicylate group compared to t
he control group in both cochlea (3.50 +/- 1.05 vs. 2.80 +/- 0.28, p<0.0001) and IC (2.94 +/- 0.51 versus 1.24 +/- 0.52, p=0.0013). Linear regression analysis revealed a significant positive association between tinnitus scores and expression levels of TNF-alpha, IL-1beta, and NR2B genes in cochlea and IC. In addition, expression levels of the TNF-alpha gene was positively correlated with that of the NR2B gene in both cochlea and IC; whereas, the expression levels of the IL-1beta gene were positively correlated with those of the NR2B gene in IC, but not in cochlea. CONCLUSION: We conclude that salicylate treatment resulting in tinnitus augments expression of the TNF-alpha and IL-1beta genes in cochlea and IC of mice, and we suggest that these proinflammatory cytokines might lead to tinnitus directly or via modulating the NMDA receptor.

**Salicylate Initiates Apoptosis in the Spiral Ganglion Neuron of Guinea Pig Cochlea by Activating Caspase-3.**

Neurochem Res. 2011 Mar 31. [Epub ahead of print]

**Feng H, Yin SH, Tang AZ, Tan SH.**

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Salicylate-induced ototoxicity leading to sensorineural hearing loss (SNHL) and tinnitus is well documented. However, the exact mechanisms are poorly defined. Caspase-3 is a member of the class of effector caspases and has been activated in nearly every model of apoptosis. To examine its role in salicylate-induced injury, we subjected guinea pigs to treatment with a specific inhibitor zDEVD-FMK via the round window niche (RWN) followed by a systemic injection of salicylate at a dose of 200 mg•kg(-1)•d(-1) i.p. for 10 consecutive days. For those animals administered with salicylate, immunohistochemical studies revealed that caspase-3 was activated in the spiral ganglion neurons (SGNs) and method of terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling (TUNEL) to identify neuronal apoptosis showed that fragmented nuclei were distributed in Rosenthal’s canal. Topical administration of the zDEVD-FMK at a concentration of 500 mM blocked caspase-3 activation and had an effect in reducing the number of TUNEL-positive auditory neurons. In contrast, the inhibitor at a concentration of 125 or 250 mM caused no variation in the expression of activated caspase-3, or in the ratio of TUNEL-positive neurons. These results indicate that caspase-3 is a crucial mediator of apoptosis induced by salicylate in the primary auditory neuron in vivo, and suggest that the specific inhibitor at a relatively high concentration may be therapeutically beneficial in salicylate-induced apoptosis.

**Electrophysiological and psychological studies in tinnitus.**

Auris Nasus Larynx. 2011 Mar 1. [Epub ahead of print]

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OBJECTIVES: Tinnitus can be accompanied by depression, anxiety, insomnia, problems with auditory perception and poor general and mental health. This work was designed to evaluate the cognitive and psychological status in tinnitus patients using different subjective and objective measures. METHODS: This work included 40 patients complaining of tinnitus without any vestibular complaints. Those patients were compared with 40 healthy age and sex matched controls. All subjects were evaluated through: basic audiologic evaluation, electrophysiological test (P300), oculomotor tests (smooth-pursuit, optokinetic, gaze and saccadic eye movements) and psychological evaluation (Hamilton depression and anxiety scales, Mini Mental Status Examination and Trail making tests). RESULTS: Patients with tinnitus showed abnormalities at both electrophysiological and psychological levels when compared with normal subjects. CONCLUSION: This study provides evidences that different pathological mechanisms are involved in tinnitus generation which are more extensive than we thought. Copyright © 2011 Elsevier Ireland Ltd. All rights reserved.
Acoustic trauma that can cause tinnitus impairs impulsive control but not performance accuracy in the 5-choice serial reaction time task in rats.

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Although tinnitus is an auditory disorder, it is often associated with attentional and emotional problems. Functional neuroimaging studies in humans have revealed that the hippocampus, amygdala and anterior cingulate, areas of the brain involved in emotion, attention and spatial processing, are also involved in auditory memory and tinnitus perception. However, few studies of tinnitus-evoked emotional and cognitive changes have been reported using animal models of tinnitus. In the present study, we investigated whether acoustic trauma that could cause tinnitus would affect attention and impulsivity in rats. Eight male Wistar rats were exposed to unilateral acoustic trauma (110 dB, 16 kHz for 1 h under anaesthesia) and eight rats underwent the same anaesthesia without acoustic trauma. Tinnitus was tested in noise-exposed rats using a frequency-specific shift in a discrimination function with a conditioned lick suppression paradigm. At 4 months after the noise exposure, the rats were tested in a 5-choice serial reaction time task. The behavioural procedure involved training the rats to discriminate a brief visual stimulus presented randomly in one of the five spatial locations and responding by poking its nose through the illuminated hole and collecting a food pellet from the magazine. While all of the animals performed equally well in making correct responses, the animals exposed to acoustic trauma made significantly more premature responses. The results suggest that rats exposed to acoustic trauma and some of which have chronic tinnitus are impaired in impulsive control, but not performance accuracy.

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[Association between auditory pathway efferent functions and genotoxicity in young adults].
[Article in Portuguese]

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Efferent auditory pathways modulate outer hair cells of the cochlea, protect against noise, and improve the detection of sound sources in noisy environments. Genotoxicity is DNA damage. AIM: To study the association between auditory pathway efferent functions with genotoxic markers. The study also considered smoking and gender as two main variables. METHODS: A prospective-clinical, quantitative, cross-sectional, contemporary study. The function of efferent auditory pathways and genotoxicity tests in 60 healthy young subjects were assessed. RESULTS: The mean age of subjects was 24.86 years +/- 3.68 years; there were 30 males and 30 females, 15 of each gender smokers and 15 non-smokers. Male smokers had a higher incidence of DPOEA suppression effect at 2000 and 6000 Hz in the left ear; female smokers had a higher prevalence of complaints of difficulty to hear in noisy environments; smokers and women had a higher mean DNA damage; subjects with complaints of hearing loss and tinnitus had higher genotoxicity. CONCLUSIONS: In young normal-hearing adults that complain about efferent auditory pathways functions, such as tinnitus and hearing impairment, there are possible associations with genotoxicity; interactions between gender and smoking are considered.
Multiple origins of cholinergic innervation of the cochlear nucleus.

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Acetylcholine (Ach) affects a variety of cell types in the cochlear nucleus (CN) and is likely to play a role in numerous functions. Previous work in rats suggested that the acetylcholine arises from cells in the superior olivary complex, including cells that have axonal branches that innervate both the CN and the cochlea (i.e. olivocochlear cells) as well as cells that innervate only the CN. We combined retrograde tracing with immunohistochemistry for choline acetyltransferase to identify the source of ACh in the CN of guinea pigs. The results confirm a projection from cholinergic cells in the superior olivary complex to the CN. In addition, we identified a substantial number of cholinergic cells in the pedunculopontine tegmental nucleus (PPT) and the laterodorsal tegmental nucleus (LDT) that project to the CN. On average, the PPT and LDT together contained about 26% of the cholinergic cells that project to CN, whereas the superior olivary complex contained about 74%. A small number of additional cholinergic cells were located in other areas, including the parabrachial nuclei. The results highlight a substantial cholinergic projection from the pontomesencephalic tegmentum (PPT and LDT) in addition to a larger projection from the superior olivary complex. These different sources of cholinergic projections to the CN are likely to serve different functions. Projections from the superior olivary complex are likely to serve a feedback role, and may be closely tied to olivocochlear functions. Projections from the pontomesencephalic tegmentum may play a role in such things as arousal and sensory gating. Projections from each of these areas, and perhaps even the smaller sources of cholinergic inputs, may be important in conditions such as tinnitus as well as in normal acoustic processing. Copyright © 2011 IBRO. Published by Elsevier Ltd. All rights reserved.

Salicylate-induced peripheral auditory changes and tonotopic reorganization of auditory cortex.

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The neuronal mechanism underlying the phantom auditory perception of tinnitus remains elusive at present. For over 25 years, temporary tinnitus following acute salicylate intoxication in rats has been used as a model to understand how a phantom sound can be generated. Behavioral studies have indicated that the pitch of salicylate-induced tinnitus in the rat is approximately 16 kHz. In order to better understand the origin of the tinnitus pitch measurements were made at the levels of auditory input and output; both cochlear and cortical physiological recordings were performed in ketamine/xylazine anesthetized rats. Both compound action potentials and distortion product otoacoustic emission measurements revealed a salicylate-induced band-pass-like cochlear deficit in which the reduction of cochlear input was least at 16 kHz and significantly greater at high and low frequencies. In a separate group of rats, frequency receptive fields of primary auditory cortex neurons were tracked using multichannel microelectrodes before and after systemic salicylate treatment. Tracking frequency receptive fields following salicylate revealed a population of neurons that shifted their frequency of maximum sensitivity (i.e. characteristic frequency) towards the tinnitus frequency region of the tonotopic axis (∼16 kHz). The data presented here supports the hypothesis that salicylate-induced tinnitus results from an expanded cortical representation of the tinnitus pitch determined by an altered profile of input from the cochlea. Moreover, the pliability of cortical frequency receptive fields during salicylate-induced tinnitus is likely due to salicylate’s direct action on intracortical inhibitory networks. Such a disproportionate representation of middle frequencies in the auditory cortex following salicylate may result in a finer analysis of signals within this region which may pathologically enhance the functional importance of spurious neuronal activity concentrated at tinnitus frequencies. Copyright © 2011 IBRO. Published by Elsevier Ltd. All rights reserved.
mGluRs modulate neuronal firing in the auditory midbrain.

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The mechanisms underlying sound-evoked suppression of neuronal firing in the auditory system are poorly understood. To explore these mechanisms in the inferior colliculus (IC), agonists and antagonists targeting different groups of metabotropic glutamate receptors (mGluRs) were applied iontophoretically to IC neurons in awake mice. We found that a group I-specific mGluR agonist predominantly increased neuronal firing in 52% of neurons, whereas group I antagonist had the opposite effect in 51% of neurons. A group II specific agonist showed no effect on neuronal firing but an antagonist increased firing rate in 48% of neurons. Neither a group III-specific mGluR agonist nor an antagonist had an effect on neuronal firing in the IC. We also found that sound stimuli triggered suppression of spontaneous firing in 70% of IC neurons. This suppression was reversibly blocked by group I mGluR antagonists. There is a possible link between this suppression and two perceptual phenomena: forward masking and „residual inhibition,” the brief reduction/elimination of tinnitus following an appropriate masking sound. Published by Elsevier Ireland Ltd.

[Sensorineural hearing loss after dull head injury or concussion trauma].
[Article in German]

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A dull head injury can lead to isolated damage of the inner ear (cochlear labyrinthine concussion) or damage of the otolithic organ (vestibular labyrinthine concussion) due to a bone conduction pressure. A typical sign is a high frequency SNHL in form of a c5-dip. The c5-dip can be bilateral or unilateral or different on each side - dependant on the side of injury. In case of a unilateral skull base fracture a contralateral labyrinthine concussion is also possible. Moreover a lot of cases also show an accompanying tinnitus. This knowledge is based on animal and human experiments, as well as data from clinical and medical report examinations over decades. It is important to differentiate between a SNHL caused by accident or uni- or bilateral endogenic degenerative hearing loss. © Georg Thieme Verlag KG Stuttgart • New York.

Does caloric vestibular stimulation modulate tinnitus?

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Caloric vestibular stimulation (CVS) has been demonstrated to transiently modulate a variety of cognitive functions. These effects are associated with the brain activation induced by CVS, involving the temporal-parietal cortex, anterior cingulate cortex and insular cortex, which are thought to form a multimodal vestibular cortical network. The present study investigated the effect of CVS upon tinnitus. Twenty patients undergoing vestibular function tests for symptoms of imbalance and who reported tinnitus were asked to rate their tinnitus using visual analogue measures of pitch and intensity immediately before and after CVS (H(2)O at 44°C) in the ear ipsilateral to the tinnitus. One patient was excluded due to test findings indicative of a central vestibular abnormality. The mean VAS pitch (pre-post) changed from 5.65 to 5.28 (95% confidence interval (-0.87, 0.12), p-value 0.13) and the mean change in intensity changed from 5.21 to 4.43 (95% confidence interval (-1.60, 0.04), p-value 0.06).
Inhibitory neurotransmission in animal models of tinnitus: Maladaptive plasticity.
Hear Res. 2011 Apr 21. [Epub ahead of print]

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Tinnitus is a phantom auditory sensation experienced by up to 14% of the United States population with a smaller percentage experiencing decreased quality of life. A compelling hypothesis is that tinnitus results from a maladaptive plastic net down-regulation of inhibitory amino acid neurotransmission in the central auditory pathway. This loss of inhibition may be a compensatory response to loss of afferent input such as that caused by acoustic insult and/or age-related hearing loss, the most common causes of tinnitus in people. Compensatory plastic changes may result in pathologic neural activity that underpins tinnitus. The neural correlates include increased spontaneous spiking, increased bursting and decreased variance of inter-spike intervals. This review will examine evidence for chronic plastic neuropathic changes in the central auditory system of animals with psychophysically-defined tinnitus. Neurochemical studies will focus on plastic tinnitus-related changes of inhibitory glycinergic neurotransmission in the adult dorsal cochlear nucleus (DCN). Electrophysiological studies will focus on functional changes in the DCN and inferior colliculus (IC). Tinnitus was associated with increased spontaneous activity and altered response properties of fusiform cells, the major output neurons of DCN. Coincident with these physiologic alterations were changes in glycine receptor (GlyR) subunit composition, its anchoring/trafficking protein, gephyrin and the number and affinity of membrane GlyRs revealed by receptor binding. In the IC, the primary afferent target of DCN fusiform cells, multi-dimensional alterations in unit-spontaneous activity (rate, burst rate, bursting pattern) were found in animals with behavioral evidence of chronic tinnitus more than 9 months following the acoustic/cochlear insult. In contrast, immediately following an intense sound exposure, acute alterations in IC spontaneous activity resembled chronic tinnitus-related changes but were not identical. This suggests that long-term neuroplastic changes responsible for chronic tinnitus are likely to be responsible for its persistence. A clear understanding of tinnitus-related plasticity in the central auditory system and its associated neurochemistry may help define unique targets for therapeutic drug development. Copyright © 2011 Elsevier B.V. All rights reserved.
Ill Diagnostics

Acoustic neuroma diagnosis.

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Pure tone audiometry, PTA, has been regarded as an initial step when starting acoustic neuroma, AN, diagnostic service. If observing unilateral/asymmetrical sensorineural hearing loss, electronystagmography, ENG, and registration of auditory brainstem responses, ABRs, are instructed to perform. The measures of the methods are listed appearing particularly effective for AN detecting. Efficacy of ENG and ABR approaches in verification of ANs of even initial stages has been stated to reach the absolute identification score, 100%. In tinnitus and/or vertigo complaints, ENG and ABR examinations are recommended to utilize under normal PTA even. The positive evidence of ANs via ENG and ABR has to validate by contrasting magnetic resonance imaging, MRI, while MRI data are advised to utilize for assessment of concrete strategy of surgical intervention. Under negative ENG and ABR outcomes, on the other hand, MRI is considered as a hardly urgent procedure.

Influence of depressive symptoms, state anxiety, and pure-tone thresholds on the tinnitus handicap inventory in Japan.
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Abstract Objective: To assess factors that contribute to Tinnitus Handicap Inventory (THI) scores in Japan. Design: Case series with chart review. Study sample: Two hundred and eighty-five tinnitus patients at tertiary referral center, who completed the Japanese version of the THI, the Self-rating Depression Scale (SDS), and the State Trait Anxiety Inventory (STAI). Results: In multiple regression analysis, the SDS score contributed the most to the THI score. The state section of the STAI score and pure tone average (PTA) at four high frequencies also contributed significantly, but to lesser degrees. The other following factors were not statistically significant: age, gender, time from the onset of tinnitus to the first clinical visit, PTA at three mid frequencies, and trait section of the STAI score. This model may account for approximately 45% of THI score variability. Conclusions: The THI scores may be influenced by depressive symptoms, state anxiety, and pure tone thresholds in Japan.

Tinnitus Severity and the Relation to Depressive Symptoms: A Critical Study.


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Objective: In this study, the authors investigated whether tinnitus severity is a problem related to depression. If so, the following 2 conditions should be fulfilled: first, there should be evidence for the presence of moderate to severe depressive symptomatology in a substantial group of tinnitus patients; second, there should be evidence of a substantial relationship between depressive symptoms and tinnitus severity. Study Design: Cross-sectional. Setting. Ear, Nose, and Throat (ENT) Department of the Ghent University Hospital. Subjects and Methods. In total, 136 consecutive help-seeking tinnitus patients were seen by a psychologist, an audiologist, and an ENT specialist. All patients filled in the Beck Depression Inventory II (BDI-II) and the Tinnitus Handicap Inventory (THI) and underwent...
psychoacoustic measurement. Results: Mean scores indicate the presence of no or minimal depressive symptoms. There was a positive correlation (P < .01) between the BDI-II and the THI. No correlations were found between psychoacoustic measures and the self-report questionnaires. Linear regression analysis was performed to examine the predictive role of the 3 components of depression (cognitive, somatic, and affective) in tinnitus severity. Results show that only the somatic depression subscale of the BDI-II significantly predicted tinnitus severity, which can be explained because of content overlap between the BDI-II and the THI. Conclusion: Tinnitus does not appear to be a problem related to depression. The authors did not find a substantial group of tinnitus patients with moderate to severe depressive symptoms. The relation between depressive symptoms and tinnitus severity seems to be an artifact of content overlap between the BDI-II and the THI.


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Arterial hypertension belongs to the most important factors of origin and lasting of tinnitus. We have studied 18 subjects suffering from tinnitus without the history of diagnosed or treated arterial hypertension. ABPM method was used for diagnosing arterial hypertension. 12 patients (66%) fulfilled the criteria for arterial hypertension. Our results illustrate that arterial hypertension diagnosis is devoted an insufficient attention in patients with tinnitus. ABPM should therefore be used in all patients with tinnitus, immediately after its manifestation and also repeatedly during its course. With early diagnosis and treatment of hypertension, some complications, such as myocardial infarction, stroke, heart and/or kidney failure can be thus prevented (Tab. 1, Fig. 5, Ref. 10). Full Text in free PDF www.bmj.sk.


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BACKGROUND: The role of endovascular interventions in managing dural arteriovenous fistulas (DAVFs) is increasing. Furthermore, in patients with aggressive DAVFs, different surgical interventions are required for complete obliteration or disconnection. Our objective was to evaluate the management of patients with intracranial DAVFs treated in our institution to identify the parameters that may help guide the long-term management of these lesions. METHODS: The hospital records of 53 patients with intracranial DAVFs were reviewed. We then conducted a systematic telephone interview to obtain long-term follow-up information. RESULTS: The main presenting symptoms were tinnitus and headache. Nineteen (35%) patients presented with intracranial bleeding, 84% of patients scored between 0 and 2 using a modified Rankin Scale at the last follow-up visit. Twenty-four patients were treated surgically. Overall postoperative complications occurred in seven (29%) surgically treated patients, but only two patients permanently worsened. For patients with Borden type II and III fistulas, the annual incidence of hemorrhage was 30%. Two patients had late recurrences of surgically and endovascularly occluded DAVFs. Long-term follow-up showed that compared with spinal DAVFs, only 50% of intracranial DAVFs showed complete remission of symptoms, 41% partial remission, 6% no remission and 4% deterioration of symptoms that led to treatment of the DAVF. CONCLUSION: In general, intracranial DAVFs can be successfully surgically managed by simple venous disconnection in many cases. However, half of the patients do not show complete remission of symptoms. Age and the occurrence of perioperative complication were the most important determinants of outcome.
CT angiography as a screening tool for dural arteriovenous fistula in patients with pulsatile tinnitus: feasibility and test characteristics. 

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BACKGROUND AND PURPOSE: The diagnosis of intracranial DAVF with noninvasive cross-sectional imaging such as CTA is challenging. We sought to determine the sensitivity and specificity of CTA compared with cerebral angiography for DAVF in patients presenting with PT. MATERIALS AND METHODS: Following approval of the institutional review board, we reviewed all patients who underwent CTA for PT from 2004 to 2009 and collected clinical and imaging data. Seven patients with PT and proved DAVF and 7 age- and sex-matched control patients with PT but no DAVF composed the study group. CTA images were blindly interpreted by 2 experienced neuroradiologists for the presence of 5 variables: asymmetric arterial feeding vessels, „shaggy“ appearance of a dural venous sinus, transcalvarial venous channels, asymmetric venous collaterals, and abnormal size and number of cortical veins. Asymmetric attenuation of jugular veins was additionally assessed. RESULTS: The presence of arterial feeders showed good test characteristics for screening, with a sensitivity of 86% (95% CI, 42-99) and a specificity of 100% (95% CI, 52-100). A shaggy sinus or tentorium was highly specific: sensitivity of 42% (95% CI, 11-79) and specificity of 100% (95% CI, 56-100). The presence of transcalvarial venous channels demonstrated a poor sensitivity of 29% (95% CI, 5-70) but a high specificity 86% (95% CI, 42-99). CT attenuation of the jugular veins showed statistically significant asymmetry in the DAVF group versus the control group (P < .05). CONCLUSIONS: CTA can be used to screen for DAVF in patients with PT. The presence of asymmetrically visible and enlarged arterial feeding vessels has a high sensitivity and specificity for the diagnosis of DAVF.

Catastrophizing and Fear of Tinnitus Predict Quality of Life in Patients With Chronic Tinnitus.
Ear Hear. 2011 Mar 10. [Epub ahead of print]

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OBJECTIVES: It is well established that catastrophic misinterpretations and fear are involved in the suffering and disability of patients with chronic pain. This study investigated whether similar processes explain suffering and disability in patients with chronic tinnitus. We hypothesized that patients who catastrophically (mis)interpret their tinnitus would be more fearful of tinnitus, more vigilant toward their tinnitus, and report less quality of life. Moreover, tinnitus-related fear was expected to act as a mediator in reduced quality of life. DESIGN: Sixty-one tinnitus patients from an outpatient ENT department of the University Hospital of Antwerp (Belgium) completed a number of questionnaires about their tinnitus. Hierarchical regression analyses were performed to test hypothesized associations and to assess mediation by tinnitus-related fear. RESULTS: Analyses revealed significant associations between catastrophizing and fear and between catastrophizing and increased attention toward the tinnitus. Furthermore, both tinnitus-related catastrophizing and fear were negatively associated with quality of life; moreover, tinnitus-related fear fully mediated the association between catastrophizing about the tinnitus and quality of life. CONCLUSIONS: The findings confirm earlier suggestions that tinnitus-related concerns and fears are associated with impaired quality of life, which is in line with a cognitive behavioral account of chronic tinnitus. Future research avenues and clinical applications are discussed.
Re-examining the relationship between audiometric profile and tinnitus pitch.

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Abstract Objective: We explored the relationship between audiogram shape and tinnitus pitch to answer questions arising from neurophysiological models of tinnitus: ‘Is the dominant tinnitus pitch associated with the edge of hearing loss?’ and ‘Is such a relationship more robust in people with narrow tinnitus bandwidth or steep sloping hearing loss?’ Design: A broken-stick fitting objectively quantified slope, degree and edge of hearing loss up to 16 kHz. Tinnitus pitch was characterized up to 12 kHz. We used correlation and multiple regression analyses for examining relationships with many potentially predictive audiometric variables. Study Sample: 67 people with chronic bilateral tinnitus (43 men and 24 women, aged from 22 to 81 years). Results: In this ample of 67 subjects correlation failed to reveal any relationship between the tinnitus pitch and the edge frequency. The tinnitus pitch generally fell within the area of hearing loss. The pitch of the tinnitus in a subset of subjects with a narrow tinnitus bandwidth (n = 23) was associated with the audiometric edge. Conclusions: Our findings concerning subjects with narrow tinnitus bandwidth suggest that this can be used as an a priori inclusion criterion. A large group of such subjects should be tested to confirm these results.

Impaired cochlear function correlates with the presence of tinnitus and its estimated spectral profile.
Hear Res. 2011 Mar 2. [Epub ahead of print]

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The presence of tinnitus often coincides with hearing loss. It has been argued that reduced peripheral input leads to frequency-specific increase in neuronal gains resulting in tinnitus-related hyper-activity. Following this gain-adaptation hypothesis, impaired cochlear function should be predictive of the presence and spectral characteristics of tinnitus. To assess cochlear function, perceptual thresholds and distortion product otoacoustic emissions (DPOAEs) were measured with high frequency resolution for subjects with tinnitus and non-tinnitus control subjects (N = 29 and N = 18) with and without hearing loss. Subjects with tinnitus also provided a ‘tinnitus likeness spectrum’ by rating the similarity of their tinnitus to tones at various frequencies. On average, subjects with tinnitus had elevated thresholds, reduced DPOAE, and increased slope of the DPOAE input-output function in the range from 4 to 10 kHz. These measures were strongly correlated and were equally predictive of the presence of tinnitus. Subjects with a pronounced edge to their hearing loss profile were very likely to have tinnitus. In the group average, the tinnitus likeness spectrum was correlated with perceptual thresholds (r = 0.98, p < 0.01), confirming previous reports. For 19 of 29 of subjects, perceptual thresholds were correlated with the tinnitus likeness ratings across frequencies and this correlation was significantly improved when low input-level DPOAE were included as an additional variable (r = 0.83 ± 0.09, N = 19). Thus, cochlear function is strongly associated with the tinnitus percept and measures of cochlear function using DPOAEs provide additional diagnostic information over perceptual thresholds alone. Published by Elsevier B.V

Electrophysiological and psychological studies in tinnitus.
Auris Nasus Larynx. 2011 Mar 1. [Epub ahead of print]

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OBJECTIVES: Tinnitus can be accompanied by depression, anxiety, insomnia, problems with auditory perception and poor general and mental health. his work was designed to evaluate the cognitive and psychological status in tinnitus patients using different subjective and objective measures.
METHODS: This work included 40 patients complaining of tinnitus without any vestibular complaints. Those patients were compared with 40 healthy age and sex matched controls. All subjects were evaluated through: basic audiologic evaluation, electrophysiological test (P300), oculomotor tests (smooth-pursuit, optokinetic, gaze and saccadic eye movements) and psychological evaluation (Hamilton depression and anxiety scales, Mini Mental Status Examination and Trail making tests). RESULTS: Patients with tinnitus showed abnormalities at both electrophysiological and psychological levels when compared with normal subjects. CONCLUSION: This study provides evidences that different pathological mechanisms are involved in tinnitus generation which are more extensive than we thought. Copyright © 2011 Elsevier Ireland Ltd. All rights reserved.

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BACKGROUND: This study sought to assess the vestibulo-cochlear organ in patients meeting radiologic criteria of vascular compression syndrome (VCS) of the eighth cranial nerve. MATERIAL/METHODS: The authors performed a retrospective analysis of 34 patients (18 women, 16 men; mean age, 49 years) treated in between 2000 and 2007, with VCS of the eighth cranial nerve by MRI. Contrasted magnetic resonance imaging identified an anterior inferior cerebellar artery vascular loop adhering to the vestibule-cochlear nerve in all 34 cases. All patients were given pure tone audiometry, distortion product otoacoustic emissions, auditory brainstem response, and electroneurographic examinations. RESULTS: Most-common symptoms were unilateral hearing loss (82%), unilateral tinnitus (80%), and dizziness (74%). Most-frequent abnormalities in performed examinations were specific auditory brainstem response changes (interpreted according to Möller's criteria) in 86% of cases and sensorineural hearing loss in pure tone audiometry (82%). Abnormal changes in electroneystagmography were found in the absence (12%) or weakness (35%) of a caloric response. No patients were surgically treated. CONCLUSIONS: Significantly, there is no more weakness or absence of the caloric response of a vestibular organ in a patient with vascular compression of the vestibulo-cochlear nerve. Despite an absence of electrophysiologic testing of vestibular organ dysfunction, most examined patients (meeting the radiologic criteria of VCS of the eighth cranial nerve) had subjective symptoms like vertigo and dizziness. Disabling positional vertigo should be considered in the differential diagnosis of vertigo when accompanied by tinnitus or deafness.

Accuracy of 3.0 Tesla magnetic resonance imaging in the diagnosis of intracochlear schwannoma
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Intracochlear schwannomas (ICSs) are rare tumors. The diagnosis of ICS is based on high-resolution magnetic resonance imaging (MRI), which should be used for the accurate determination of the location of tumors. Recent advancements in imaging technologies and software enable the precise regional diagnosis of ICS. We experienced a case of intracochlear schwannoma with a diagnosis of progressive hearing loss and tinnitus. Audiometry revealed severe hearing loss in the right ear with remaining low-frequency hearing. MRI showed an abnormal lesion in the cochlea. Three-dimensional real inversion recovery (3D rIR) and constructive interference in steady state (CISS) MRI revealed the size and shape of the tumor via identification of the cochlear nerve and cochlear fluid space. CISS and 3D rIR sequences provide useful information regarding the boundaries of tumors and the tissues that surround them.
CT Angiography as a Screening Tool for Dural Arteriovenous Fistula in Patients with Pulsatile Tinnitus: Feasibility and Test Characteristics

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BACKGROUND AND PURPOSE: The diagnosis of intracranial DAVF with noninvasive cross-sectional imaging such as CTA is challenging. We sought to determine the sensitivity and specificity of CTA compared with cerebral angiography for DAVF in patients presenting with PT. MATERIALS AND METHODS: Following approval of the institutional review board, we reviewed all patients who underwent CTA for PT from 2004 to 2009 and collected clinical and imaging data. Seven patients with PT and proved DAVF and 7 age- and sex-matched control patients with PT but no DAVF composed the study group. CTA images were blindly interpreted by 2 experienced neuroradiologists for the presence of 5 variables: asymmetric arterial feeding vessels, „shaggy“ appearance of a dural venous sinus, transcalvarial venous channels, asymmetric venous collaterals, and abnormal size and number of cortical veins. Asymmetric attenuation of jugular veins was additionally assessed. RESULTS: The presence of arterial feeders showed good test characteristics for screening, with a sensitivity of 86% (95% CI, 42–99) and a specificity of 100% (95% CI, 52–100). A shaggy sinus or tentorium was highly specific: sensitivity of 42% (95% CI, 11–79) and specificity of 100% (95% CI, 56–100). The presence of transcalvarial venous channels demonstrated a poor sensitivity of 29% (95% CI, 5–70) but a high specificity 86% (95% CI, 42–99). CT attenuation of the jugular veins showed statistically significant asymmetry in the DAVF group versus the control group (P < .05). CONCLUSIONS: CTA can be used to screen for DAVF in patients with PT. The presence of asymmetrically visible and enlarged arterial feeding vessels has a high sensitivity and specificity for the diagnosis of DAVF.

IV Imaging

Variable changes in PET activity before and after rTMS treatment for tinnitus.


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OBJECTIVES/HYPOTHESIS: The objective was to determine whether low-frequency repetitive transcranial magnetic stimulation (rTMS) improves tinnitus by decreasing neural activity in auditory processing regions of the temporal cortex and the utility of positron emission tomography (PET) for targeting treatment. STUDY DESIGN: Randomized, sham-controlled crossover. METHODS: Patients received a five-day course of active and sham 1-Hz rTMS (1800 pulses at 110% of motor threshold) to the temporal cortex, with a week separating active and sham treatment. Visual analogue ratings of tinnitus loudness (VARL) were assessed at baseline and the end of each treatment week; regional brain blood flow (rBBF) and glucose metabolism (via PET) were measured before and after treatment in regions of interest (ROI) beneath the stimulating coil and control sites. RESULTS: The VARL for both ears significantly decreased after active but not sham treatment. Responders comprised 43% of patients, experiencing at least a 33% drop in tinnitus loudness. The site most consistently associated with a positive response was the secondary auditory cortex (Brodmann Area 22) in either hemisphere. PET asymmetries were variable across patients and not always accessible to rTMS. Whereas PET activity decreased significantly beneath the stimulating coil following active treatment, similar changes occurred at control sites and after sham stimulation. Change in tinnitus perception did not correlate significantly with change in PET activity at the treatment site ROI.
CONCLUSIONS: Active TMS led to a significant reduction in tinnitus loudness, but PET scans failed to support the hypothesis that low-frequency rTMS improves tinnitus by reducing cortical activation at the stimulation site, questioning the utility of PET for targeting rTMS. Laryngoscope, 2011. Copyright © 2011 The American Laryngological, Rhinological, and Otological Society, Inc.

Structural neuroanatomy of tinnitus and hyperacusis in semantic dementia.
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Introduction Tinnitus and hyperacusis are common symptoms of excessive auditory perception in the general population; however, their anatomical substrates and disease associations continue to be defined. Patients with semantic dementia (SemD) frequently report tinnitus and hyperacusis but the significance and basis for these symptoms have not been elucidated. Methods: 43 patients with a diagnosis of SemD attending a specialist cognitive disorders clinic were retrospectively studied. 14 patients (32% of the cohort) reported at least moderately severe chronic auditory symptoms: seven had tinnitus and a further seven had hyperacusis, and all had brain MRI while symptomatic. MRI data from SemD patients with and without auditory symptoms were compared using voxel based morphometry in order to identify neuroanatomical associations of tinnitus and hyperacusis. Results: Compared with SemD patients with no history of auditory symptoms, patients with tinnitus or hyperacusis had relative preservation of grey matter in the posterior superior temporal lobe and reduced grey matter in the orbitofrontal cortex and medial geniculate nucleus. Conclusions: Tinnitus and hyperacusis may be a significant issue in SemD. Neuroanatomical evidence in SemD supports previous work implicating a distributed cortico-subcortical auditory and limbic network in the pathogenesis of these abnormal auditory percepts.

V Pharmacotherapy

Efficacy of gabapentin on subjective idiopathic tinnitus: A randomized, double-blind, placebo-controlled trial.

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Tinnitus can cause extreme morbidity. Despite many attempts to find a treatment for idiopathic cases, they remain difficult to manage. Because nerve injury is one of the suspected etiologies of tinnitus and because gabapentin has been found to be effective in treating nerve injuries, some authors have attempted to determine if gabapentin has a role in treating tinnitus. Although gabapentin was found to be ineffective for tinnitus in these previous studies, to the best of our knowledge no studies have been performed that took into consideration the presence of various accompanying factors and concomitant diseases that might influence its effect. We conducted a prospective, randomized, double-blind, placebo-controlled clinical trial of gabapentin for idiopathic tinnitus. We treated 40 patients with gabapentin and measured its effectiveness by comparing differences between pre- and post-treatment Tinnitus Severity Index (TSI) values and tinnitus loudness scores. We also compared these outcomes with those of a group of 40 matched placebo controls. At study’s end, we found no significant differences between the gabapentin and control groups in mean decreases in TSI value and loudness score (p = 0.85 and p = 0.12, respectively). However, we did find that patients with hypertension, diabetes, and/or dyslipidemia showed a better response to gabapentin than did those with tinnitus alone (p = 0.01). We conclude that although there was no statistically significant difference between gabapentin and placebo in treating isolated tinnitus or tinnitus overall, patients with concomitant hypertension, diabetes, and/or dyslipidemia may benefit from gabapentin.
Tinnitus control by dopamine agonist pramipexole in presbycusis patients: A randomized, placebo-controlled, double-blind study.

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OBJECTIVES/HYPOTHESIS: Since the concept of tinnitus dopaminergic pathway emerged, studies have been proposed to investigate if dopaminergic agents influence tinnitus. We hypothesized that pramipexole, an agonist on D2/D3 receptors, may antagonize tinnitus in the presbycusis patients (in the frequency range of 250 to 8,000 Hz) in a dose schedule accepted for the treatment of Parkinson’s disease in elderly people. STUDY DESIGN: We designed a randomized, prospective, placebo-controlled and double-blind trial. METHODS: Forty presbycusis patients aged 50 years or older with subjective tinnitus were randomized to two groups (20 patients in both). Patients in the drug group took pramipexole over a period of 4 weeks according to a treatment schedule as follows: week 1, 0.088 mg t.i.d.; week 2, 0.18 mg t.i.d.; week 3, 0.7 mg t.i.d.; week 4, 0.18 mg t.i.d. over 3 days and 0.088 mg t.i.d. the rest of the week. Patients in the second group received placebo. Determination of subjective grading of tinnitus perception, the tinnitus handicap inventory (THI) questionnaire and electrocochleography (ECOG) examinations served as the end points. Subjective audiometry was used to produce secondary data. A significant improvement in tinnitus annoyance is found in the group treated with pramipexole versus placebo with respect to inhibition of tinnitus and a decrease of tinnitus loudness greater than 30 dB. However, neither ECOG nor subjective pure-tone threshold audiometry revealed any change in hearing threshold in response to either pramipexole or placebo. CONCLUSIONS: Pramipexole is an effective agent against subjective tinnitus associated with presbycusis at a dose schedule used for the treatment of Parkinson’s disease. The drug did not change hearing threshold. Laryngoscope, 2011. Copyright © 2011 The American Laryngological, Rhinological, and Otological Society, Inc.

Administration of the Combination Clonazepam-Deanxit as Treatment for Tinnitus.
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HYPOTHESIS: Present study investigates the combination of Deanxit and clonazepam (Rivotril) intake for relief of tinnitus complaints, respecting a double-blind placebo-controlled approach for Deanxit in a crossover setup. BACKGROUND: Although several pharmacologic treatments-including antidepressants, prostaglandins, and aminobutyric acid (GABA)-active drugs-were already presented as promising in tinnitus treatment, no drug has yet been approved by the Food and Drug Administration and European Medicine Agency for the treatment of tinnitus. METHODS: Patients were randomly assigned to patient group A or patient group B in a double-blind way. Patient group A first received 3 weeks of Deanxit, followed by 1 week of washout and 3 weeks of placebo. Treatment was given in opposite order to subjects from Patient group B. All patients received a daily treatment consisting of clonazepam 1 mg once daily, starting on Day 1. RESULTS: Significant tinnitus reduction was seen after intake of the combination clonazepam-Deanxit, whereas no differences in tinnitus could be demonstrated after the administration of clonazepam-placebo. This was true for all patients according to the following parameters: time patients are annoyed by the tinnitus (p = 0.026) and the visual analogue scale for tinnitus annoyance (p = 0.024). CONCLUSION: Although tinnitus reduction was recorded as modest, this article provides valuable data demonstrating a placebo-controlled tinnitus reduction after clonazepam and Deanxit intake.
VI Auditive Stimulation

[Cochlear implantation: A changing indication.]
[Article in German]
HNO. 2011 Apr 21. [Epub ahead of print]

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In recent years the indication criteria for cochlear implantation (CI) have changed. To gain optimal benefits, early implantation in prelingually deaf children is necessary. Even additional disabilities are no longer contraindications for CI. Nowadays the criteria for implantation not only include deafness but also residual hearing. Combined electric-acoustic stimulation has been established as a treatment option in patients with hearing still functioning in the low frequencies. Due to the benefits of binaural hearing, bilateral CI has become standard over the last decade. Recent experience has shown the benefits of CI in unilateral deafness and in cases of severe tinnitus. The actual benefit of CI shows great inter-individual differences. We usually expect (re-)habilitation of language communication skills with implantation.

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Silverstein Institute, Sarasota, Florida; Cleveland Clinic, Cleveland, Ohio; Ear Institute of Chicago, Chicago, Illinois; ENT Associates of South Florida, Boca Raton, Florida; and House Ear Institute, Los Angeles, California, U.S.A.

OBJECTIVE: The purpose of this study is to evaluate the efficacy of a customized acoustical stimulus (Neuromonics) system in the treatment of chronic tinnitus. STUDY DESIGN: Multi-institutional prospective. SETTING: Nine U.S. Tertiary Otological referral centers; ambulatory. PATIENTS: Fifty-two adults with chronic tinnitus for a minimum of 6 months, with poor or no response to previous treatments, and not undergoing concomitant therapies were enrolled. INTERVENTIONS: Treatment was delivered in 2 stages: Stage 1 consisted of stimulation with the patient-customized musical tracks and white noise masking of the tinnitus for 2 months, 2 to 4 hours a day. Stage 2 consisted of listening to the same tracks, with no tinnitus masking for 4 months. Both phases included education, cognitive therapy, and periodic follow-up. MAIN OUTCOME MEASURES: Treatment response was measured through validated psychometric testing: the Tinnitus Reaction Questionnaire and the Tinnitus Handicap Inventory. Other measures included the Hospital Anxiety Depression Scale and loudness discomfort levels. RESULTS: Patients’ responses were recorded from 38 patients at 6 months, 28 patients at 12 months, and 12 patients at 24 months after initiation of treatment. A total of 14 patients withdrew or were lost to follow-up, and the rest had not reached the 12- or 24-month testing interval. The Tinnitus Reaction Questionnaire score was significantly reduced in 74% of patients at 12 months and 84% of patients at 24 months. Tinnitus Handicap Inventory scores were significantly reduced in 77% of patients at 12 months and 50% at 24 months. CONCLUSION: The customized acoustical stimulus system offers a safe and effective means of tinnitus management for patients with chronic tinnitus.
Tinnitus suppression by low-rate electric stimulation and its electrophysiological mechanisms.
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Tinnitus is a phantom sensation of sound in the absence of external stimulation. However, external stimulation, particularly electric stimulation via a cochlear implant, has been shown to suppress tinnitus. Different from traditional methods of delivering speech sounds or high-rate (>2000 Hz) stimulation, the present study found a unique unilaterally-deafened cochlear implant subject whose tinnitus was completely suppressed by a low-rate (<100 Hz) stimulus, delivered at a level softer than tinnitus to the apical part of the cochlea. Taking advantage of this novel finding, the present study compared both event-related and spontaneous cortical activities in the same subject between the tinnitus-present and tinnitus-suppressed states. Compared with the results obtained in the tinnitus-present state, the low-rate stimulus reduced cortical N100 potentials while increasing the spontaneous alpha power in the auditory cortex. These results are consistent with previous neurophysiological studies employing subjects with and without tinnitus and shed light on both tinnitus mechanism and treatment.

The Impact of Cochlear Implantation on Tinnitus, Stress and Quality of Life in Postlingually Deafened Patients
Audiol Neurotol 2012;17:2-11 (DOI: 10.1159/000323847)

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Tinnitus is a common complaint in the candidates for cochlear implantation (CI). Tinnitus-related distress has often been measured in these patients using categorical ratings, which lack information about tinnitus severity, stress and health-related quality of life or their correlation. Here, using 4 validated questionnaires, we evaluated psychometric parameters and the quality of life of 32 postlingually deafened patients before and after CI. The data regarding pre-CI were collected retrospectively. Of all patients included in this study, 28 (87.5%) suffered from tinnitus before implantation. Following a mean of 24 months after surgery, these patients reported a significant decrease (39.2%) of tinnitus impairment, as measured by the Tinnitus Questionnaire. In none of the 28 patients has tinnitus worsened. Moreover, the 4 tinnitus-free patients remained so after the CI surgery. In addition, the implant supply resulted in 36.7% reduction in perceived stress and in 15.4% reduction in evasive coping. In addition, the focus on positive coping has improved by 12.3%, whereas the health-related quality of life improved by 53.4% in all patients. Tinnitus impairment and stress were reduced more strongly in patients who had initially higher scores. Interestingly, a significant correlation between the psychometric scores was found mainly after CI. Our results indicate that patients with higher tinnitus-related distress have a lower quality of life, lesser coping abilities and perceive more stress, but before implantation it is masked by deafness. We conclude that tinnitus-related screening of patients before and after CI is an important step in the identification of individuals who would benefit from specific fitting and/or tinnitus therapy after implantation. Copyright © 2011 S. Karger AG, Basel.
**VII  Brain Stimulation**

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


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BACKGROUND: Repetitive transcranial magnetic stimulation (rTMS) of the temporal cortex has shown beneficial effects in patients with chronic tinnitus. Recent preclinical data in healthy controls suggest that the effects of low-frequency rTMS can be enhanced by dopaminergic drugs. OBJECTIVE: We investigated whether application of the dopamine reuptake inhibitor bupropion increases the clinical effects of low-frequency rTMS over the auditory cortex in tinnitus patients. SUBJECTS AND METHODS: Eighteen subjects with chronic tinnitus received 10 sessions of 1 Hz rTMS (2000 pulses/day, 110% motor threshold) applied to the left temporal cortex. In addition, these subjects received one dosage of 150 mg bupropion (Wellbutrin XL/Elontril) 4 hours before each TMS session. Treatment outcome was assessed with a tinnitus questionnaire over a 3-month period. Treatment effects were compared with a control group of 100 tinnitus patients matched for age, tinnitus duration, and tinnitus questionnaire baseline scores, who received the same rTMS treatment without prior bupropion application. RESULTS: For the whole sample, there was a significant effect of rTMS treatment over time. There were no significant differences between the bupropion and the control group. CONCLUSIONS: Our data suggest that 150 mg bupropion administration does not enhance the effect of rTMS in the treatment of tinnitus.

**Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation.**

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A significant proportion of the population suffers from tinnitus, a bothersome auditory phantom perception that can severely alter the quality of life. Numerous experimental studies suggests that a maladaptive plasticity of the auditory and limbic cortical areas may underlie tinnitus. Accordingly, repetitive transcranial magnetic stimulation (rTMS) has been repeatedly used with success to reduce tinnitus intensity. The potential of transcranial direct current stimulation (tDCS), another promising method of noninvasive brain stimulation, to relieve tinnitus has not been explored systematically. In a double-blind, placebo-controlled and balanced order design, 20 patients suffering from chronic untreatable tinnitus were submitted to 20 minutes of 1 mA anodal, cathodal and sham tDCS targeting the left temporoparietal area. The primary outcome measure was a change in tinnitus intensity or discomfort assessed with a Visual Analogic Scale (VAS) change-scale immediately after tDCS and 1 hour later. Compared to sham tDCS, anodal tDCS significantly reduced tinnitus intensity immediately after stimulation; whereas cathodal tDCS failed to do so. The variances of the tinnitus intensity and discomfort VAS change-scales increased dramatically after anodal and cathodal tDCS, whereas they remained virtually unchanged after sham tDCS. Moreover, several patients unexpectedly reported longer-lasting effects (at least several days) such as tinnitus improvement, worsening, or changes in tinnitus features, more frequently after real than sham tDCS. Anodal tDCS is a promising therapeutic tool for modulating tinnitus perception. Moreover, both anodal and cathodal tDCS seem able to alter tinnitus perception and could, thus, be used to trigger plastic changes.
Short duration repetitive transcranial magnetic stimulation for tinnitus treatment: A prospective Asian study.
Clin Neurol Neurosurg. 2011 Apr 19. [Epub ahead of print]

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BACKGROUND: Tinnitus is a subjective auditory perception of sounds or noise not triggered by external auditory stimuli. To date, treatment in severe cases is generally unsatisfactory. Characteristic functional brain imaging changes associated with tinnitus include hyperactivity encompassing both the primary auditory cortex (AC) and the secondary or associative cortex. Brief repetitive transcranial magnetic stimulation (rTMS) trains applied to the scalp overlying the hyperactive left AC is known to produce moderate tinnitus attenuation. OBJECTIVE: Although Western studies have documented the value of rTMS in tinnitus treatment, we evaluate the efficacy of a short duration rTMS protocol for the first time in the Asian setting. METHOD: Consecutive patients were recruited at our tinnitus clinic. Detailed history, examination, audiogram and baseline tinnitus scales were recorded. RTMS consisted of 1000 pulses/day at 1Hz and 110% of the motor threshold, for five consecutive days over the left temporoparietal cortex. Tinnitus ratings were determined weekly for 4 weeks after rTMS. RESULT: Fifteen patients completed the trial; none experienced significant side effects. Repeated measures ANOVA showed significant linear decrease in Tinnitus Handicap Inventory (THI) scores over the time period (F((1,14))=4.7, p=0.04). However, none of the other parameters (severity, annoyance, effect on lifestyle and overall impression: visual analogue scale) showed beneficial outcomes. CONCLUSIONS: Our findings point to a positive effect of short duration rTMS in tinnitus treatment using the THI. However, no significant benefits were demonstrated for other subjective patient ratings. Although well tolerated and convenient, short duration rTMS may prove inadequate for modulating maladaptive plastic changes at the cortical level, and our results suggest the need for delivery of more stimuli. Future studies will utilize at least 2000 pulses/day, in line with previous experience in Western settings.

Auditory neuroscience: how to stop tinnitus by buzzing the vagus.

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Recent observations linking the vagus nerve to plasticity in the central nervous system could pave the way to new treatments for one of the most common and intractable disorders of the auditory system.

Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression.

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Tinnitus is an ongoing phantom percept. It has been demonstrated that bifrontal transcranial direct current stimulation (tDCS) can reduce tinnitus. In this study, one group of patients reported a substantial improvement in their tinnitus perception, whereas another group described minor or no beneficial effect at all. The objective was to verify whether the activity and connectivity of the resting brain is different for people who will respond to bifrontal tDCS for tinnitus in comparison with non-responders. Higher gamma band activity was demonstrated in right primary and secondary auditory cortex and right parahippocampus for responders. It has been shown that gamma band activity in the auditory cortex is correlated with tinnitus loudness and that the anterior cingulate is involved in tinnitus distress.
People who were going to respond to bifrontal tDCS also demonstrated an increased functional connectivity in the gamma band between the right dorsolateral prefrontal cortex (DLPFC) and the right parahippocampus as well as the right DLPFC and subgenual anterior cingulate cortex (sgACC). An analysis revealed that responders to bifrontal tDCS also experienced a larger suppression effect on TMS placed over the right temporal cortex (i.e. auditory cortex) than non-responders. Responders to bifrontal tDCS seem to differ in resting brain activity compared to non-responders in the right auditory cortex and parahippocampal area. They also have a different functional connectivity between DLPFC and, respectively, the sgACC and parahippocampal area. These connectivities might explain the suppression effect for both tinnitus loudness and tinnitus-related distress.

Repetitive transcranial magnetic stimulation frequency dependent tinnitus improvement by double cone coil prefrontal stimulation.

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Background A double cone coil (DCC) with large angled windings has been developed to modulate deeper brain areas such as the dorsal and subcallosal anterior cingulate cortex. Methods Seventy-eight tinnitus patients received transcranial magnetic stimulation (TMS) using a DCC placed over the dorsal frontal cortex. Treatment effects were assessed with visual analogue scale for intensity and distress. Results The results showed that 1 and 3 Hz of DCC frontal TMS can improve both tinnitus intensity and tinnitus distress, 5 Hz is equal to sham and 20 Hz is significantly worse than sham. Of the 78 tinnitus patients, 52 had no control response. Of these 52 placebo negative participants, 21 showed no suppressive response to stimulation and 31 patients were TMS responders. For this latter group, mean transient tinnitus suppression was obtained in 34.38% for tinnitus intensity and in 26% for tinnitus related distress. Conclusion Frontal TMS using a DCC is capable of suppressing tinnitus transiently dependent on the repetitive TMS frequency used. These data further support the idea that non-auditory areas are involved in tinnitus intensity and tinnitus distress modulation.

Low-frequency repetitive transcranial magnetic stimulation to the temporoparietal junction for tinnitus.


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OBJECTIVE: To examine the effectiveness and safety of low-frequency repetitive transcranial magnetic stimulation (rTMS) to the temporoparietal junction in a cohort of patients with bothersome tinnitus. DESIGN: Crossover, double-blind, randomized clinical trial. SETTING: Outpatient academic medical center. PARTICIPANTS: Fourteen adults aged 42 to 59 years with subjective, unilateral or bilateral, nonpulsatile tinnitus of 6 months’ duration or longer and a score of 38 or greater on the Tinnitus Handicap Inventory (THI). INTERVENTIONS: Low-frequency (1-Hz) 110% motor threshold rTMS or sham treatment to the left temporoparietal junction for 2 weeks. MAIN OUTCOME MEASURE: The difference in the change of the THI score between active and sham rTMS. RESULTS: Active treatment was associated with a median (95% confidence interval) reduction in THI score of 5 (0-14) points, and sham treatment was associated with a median reduction in THI score of 6 (-2 to 12) points. The difference in THI scores between the change associated with active and sham rTMS ranged from a 34-point reduction in THI score after active treatment to a 22-point increase after sham treatment, with a median difference change of only 1 point (-6 to 4 points). CONCLUSIONS: Daily low-frequency rTMS to the left temporoparietal junction area for 2 weeks is no more effective than placebo for patients.
with chronic bothersome tinnitus. Possible explanations for the negative findings are short duration of treatment, failure of rTMS stimulation over the temporoparietal area to affect the auditory cortex buried within the Sylvian fissure, or more widespread cortical network changes associated with severe bothersome tinnitus not amenable to localized rTMS effects. Trial Registration clinicaltrials.gov Identifier: NCT00567892. Copyright © 2011 Elsevier Masson SAS. All rights reserved.


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OBJECTIVE: To investigate the safety and efficacy of intermittent theta-burst stimulation (iTBS) in the treatment of motor symptoms in Parkinson disease (PD). BACKGROUND: Progression of PD is characterized by the emergence of motor deficits, which eventually respond less to dopaminergic therapy and pose a therapeutic challenge. Repetitive transcranial magnetic stimulation (rTMS) has shown promising results in improving gait, a major cause of disability, and may provide a therapeutic alternative. iTBS is a novel type of rTMS that may be more efficacious than conventional rTMS.

METHODS: In this randomized, double-blind, sham-controlled study, we investigated safety and efficacy of iTBS of the motor and dorsolateral prefrontal cortices in 8 sessions over 2 weeks (evidence Class I). Assessment of safety and clinical efficacy over a 1-month period included timed tests of gait and bradykinesia, Unified Parkinson’s Disease Rating Scale (UPDRS), and additional clinical, neuropsychological, and neurophysiologic measures. RESULTS: We investigated 26 patients with mild to moderate PD: 13 received iTBS and 13 sham stimulation. We found beneficial effects of iTBS on mood, but no improvement of gait, bradykinesia, UPDRS, and other measures. EEG/EMG monitoring recorded no pathologic increase of cortical excitability or epileptic activity. Few reported discomfort or pain and one experienced tinnitus during real stimulation. CONCLUSION: iTBS of the motor and prefrontal cortices appears safe and improves mood, but failed to improve motor performance and functional status in PD. Classification of evidence: This study provides Class I evidence that iTBS was not effective for gait, upper extremity bradykinesia, or other motor symptoms in PD.


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OBJECTIVES/HYPOTHESIS: The objective was to determine whether low-frequency repetitive transcranial magnetic stimulation (rTMS) improves tinnitus by decreasing neural activity in auditory processing regions of the temporal cortex and the utility of positron emission tomography (PET) for targeting treatment. STUDY DESIGN: Randomized, sham-controlled crossover. METHODS: Patients received a five-day course of active and sham 1-Hz rTMS (1800 pulses at 110% of motor threshold) to the temporal cortex, with a week separating active and sham treatment. Visual analogue ratings of tinnitus loudness (VARL) were assessed at baseline and the end of each treatment week; regional brain blood flow (rBBF) and glucose metabolism (via PET) were measured before and after treatment in regions of interest (ROI) beneath the stimulating coil and control sites. RESULTS: The VARL for both ears significantly decreased after active but not sham treatment. Responders comprised 43% of patients, experiencing at least a 33% drop in tinnitus loudness. The site most consistently associated with a positive response was the secondary auditory cortex (Brodmann Area 22) in either hemisphere. PET asymmetries were variable across patients and not always accessible to rTMS. Whereas PET activity
decreased significantly beneath the stimulating coil following active treatment, similar changes occurred at control sites and after sham stimulation. Change in tinnitus perception did not correlate significantly with change in PET activity at the treatment site ROI. CONCLUSIONS: Active TMS led to a significant reduction in tinnitus loudness, but PET scans failed to support the hypothesis that low-frequency rTMS improves tinnitus by reducing cortical activation at the stimulation site, questioning the utility of PET for targeting rTMS. Laryngoscope, 2011. Copyright © 2011 The American Laryngological, Rhinological, and Otological Society, Inc.

VIII  Behavioral Therapy

Catastrophizing and Fear of Tinnitus Predict Quality of Life in Patients With Chronic Tinnitus.
Ear Hear. 2011 Mar 10. [Epub ahead of print]

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OBJECTIVES: It is well established that catastrophic misinterpretations and fear are involved in the suffering and disability of patients with chronic pain. This study investigated whether similar processes explain suffering and disability in patients with chronic tinnitus. We hypothesized that patients who catastrophically (mis)interpret their tinnitus would be more fearful of tinnitus, more vigilant toward their tinnitus, and report less quality of life. Moreover, tinnitus-related fear was expected to act as a mediator in reduced quality of life. DESIGN: Sixty-one tinnitus patients from an outpatient ENT department of the University Hospital of Antwerp (Belgium) completed a number of questionnaires about their tinnitus. Hierarchical regression analyses were performed to test hypothesized associations and to assess mediation by tinnitus-related fear. RESULTS: Analyses revealed significant associations between catastrophizing and fear and between catastrophizing and increased attention toward the tinnitus. Furthermore, both tinnitus-related catastrophizing and fear were negatively associated with quality of life; moreover, tinnitus-related fear fully mediated the association between catastrophizing about the tinnitus and quality of life. CONCLUSIONS: The findings confirm earlier suggestions that tinnitus-related concerns and fears are associated with impaired quality of life, which is in line with a cognitive behavioral account of chronic tinnitus. Future research avenues and clinical applications are discussed.

IX  Somatic Tinnitus

Signs and symptoms of temporomandibular disorders and the incidence of tinnitus.

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In a cross-sectional analysis of data from the Study of Health in Pomerania (SHIP 0), temporomandibular disorders (TMD) were the strongest predictors for tinnitus beside headache. The aim of this study was to investigate whether signs and symptoms of TMD can be identified as risk factors for developing tinnitus. The SHIP 1 is a population-based 5-year longitudinal study intended to systematically describe the prevalence of and risk factors for diseases common in the population of Pomerania in northern Germany. A total of 3300 subjects (76% response) were reevaluated after 5 years for tinnitus and signs and symptoms of TMD using the same questionnaires and examination tools as baseline.
To estimate the relative risk (RR) appropriately, a modified Poisson regression was used. After exclusion of prevalent cases with diagnosed tinnitus, 3134 subjects were analysed. Among the 191 exposed subjects with palpation pain in the temporomandibular joint (TMJ), 24 subjects (12.6%) received diagnosed tinnitus after 5 years, whereas among the 2643 unexposed subjects 142 subjects (5.8%) received tinnitus yielding a risk difference of 7.7% (95% confidence interval [CI]: 3.0%-12.5%) and a risk ratio of 2.60 (95% CI: 1.7-3.9). The risk ratio was 2.4 (95% CI: 1.6-3.7) after adjustment for gender, age, school education and frequent headache. Pain on palpation of the TMJ, however, did not worsen the prognosis for tinnitus in prevalent tinnitus cases (RR=0.8, P=0.288). Signs of TMD are a risk factor for the development of tinnitus.

Surgical Treatment

Functional outcomes in retrosigmoid approach microsurgery and gamma knife stereotactic radiosurgery in vestibular schwannoma.
Eur Arch Otorhinolaryngol. 2011 Apr 11. [Epub ahead of print]

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Although vestibular schwannomas (VSs) are relatively rare as compared to other intracranial tumors, growing attention is required to achieve better outcomes with less morbidities among patients. In this retrospective study, we compared functional outcomes of retrosigmoid approach microsurgery (RSAMS) and gamma knife stereotactic radiosurgery (GKSRS) in VSs patients with serviceable hearing. Forty-six patients in inclusion criteria, who underwent RSAMS (n = 15) or GKSRS (n = 31) between January 2004 and June 2009 were reviewed. We evaluated symptoms at initial presentation, pre- and posttreatment pure-tone audiometry, speech discrimination score, tumor size, pre- and posttreatment assessments of facial nerve function, and pre- and posttreatment tinnitus, dizziness and facial paresthesia in vestibular schwannoma patients, who were treated with RSAMS or GKSRS. Hearing disturbance was the most common presenting symptom in both the groups. The hearing preservation rates in the RSAMS and GKSRS patients were 7% (1/15) and 45% (14/31), respectively. Two RSAMS patients and one GKSRS patient developed new facial neuropathy, defined as a temporary or permanent decline in House-Brackmann facial nerve grade. Tumor recurrence was observed in one RSAMS patient, whereas tumor size increase was observed in one GKSRS patient (3%). Tinnitus score was decreased after the treatment in both the groups. The results imply that GKSRS for vestibular schwannoma can possibly preserve hearing preservation with proper indication and treatment planning.

Longitudinal Assessment of Quality of Life and Audiometric Test Outcomes in Vestibular Schwannoma Patients Treated With Gamma Knife Surgery.
Otol Neurotol. 2011 Mar 23. [Epub ahead of print]

Park SS, Grills IS, Bojrab D, Pieper D, Kartush J, Maitz A, Martin A, Perez E, Hahn Y, Ye H, Martinez A, Chen P.

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OBJECTIVE: To prospectively assess the quality of life (QOL) and hearing acuity in vestibular schwannoma (VS) patients after gamma knife surgery (GKS). PATIENTS: Fifty-nine VS patients. INTERVENTION: GKS. MAIN OUTCOME MEASURES: Prospective follow-up algorithm included 36-item Short Form Health Survey (SF-36), Hearing Handicap Inventory (HHI), Dizziness Handicap Inventory (DHI), Tinnitus Handicap Inventory (THI), pure-tone average, and speech discrimination hearing scores (Gardner-Robertson and American Academy of Otolaryngology), performed before and after GKS at 1-, 3-, 6-, 12-, and 18-month posttreatment intervals.
RESULTS: From December 2006 to November 2008, 59 VS patients were treated with a median follow-up of 15 months. At baseline, mean scores for SF-36, HHI, DHI, and THI were 73, 37, 17, and 23, respectively. Median baseline Gardner-Robertson and American Academy of Otolaryngology hearing acuity scores were 2 and B, respectively. No significant decline in SF-36 health survey was noted after GKS. Mean SF-36 score at baseline was 73, compared with a range of 70 to 77 at predetermined posttreatment intervals. Similarly, no significant changes in DHI, HHI, and THI were noted. Approximately 47% of patients with baseline serviceable hearing maintained serviceable hearing at 12 months. Significant acute and chronic worsening in hearing acuity were noted at 1 and 18 months, respectively. No correlative decline in QOL was noted as assessed by SF-36 or HHI. CONCLUSION: No significant decline in global QOL occurred after GKS with relatively short follow-up and approximately 50% survey completion. When discussing therapy options with VS patients, anticipated treatment-related QOL outcomes should be considered.

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BACKGROUND: The role of endovascular interventions in managing dural arteriovenous fistulas (DAVFs) is increasing. Furthermore, in patients with aggressive DAVFs, different surgical interventions are required for complete obliteration or disconnection. Our objective was to evaluate the management of patients with intracranial DAVFs treated in our institution to identify the parameters that may help guide the long-term management of these lesions. METHODS: The hospital records of 53 patients with intracranial DAVFs were reviewed. We then conducted a systematic telephone interview to obtain long-term follow-up information. RESULTS: The main presenting symptoms were tinnitus and headache. Nineteen (35%) patients presented with intracranial bleeding, 84% of patients scored between 0 and 2 using a modified Rankin Scale at the last follow-up visit. Twenty-four patients were treated surgically. Overall postoperative complications occurred in seven (29%) surgically treated patients, but only two patients permanently worsened. For patients with Borden type II and III fistulas, the annual incidence of hemorrhage was 30%. Two patients had late recurrences of surgically and endovascularly occluded DAVFs. Long-term follow-up showed that compared with spinal DAVFs, only 50% of intracranial DAVFs showed complete remission of symptoms, 41% partial remission, 6% no remission and 4% deterioration of symptoms that led to treatment of the DAVF. CONCLUSION: In general, intracranial DAVFs can be successfully surgically managed by simple venous disconnection in many cases. However, half of the patients do not show complete remission of symptoms. Age and the occurrence of perioperative complication were the most important determinants of outcome.

Early complications and symptoms of cerebellopontine angle tumor surgery: a prospective analysis.
Eur Arch Otorhinolaryngol. 2011 Mar 4. [Epub ahead of print]
Lazard DS, Tosello M, Bozorg-Grayeli A, Vitte E, Bouccara D, Kalarides M, Sterkers O.
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Our objective is to prospectively report very early complications and outcomes of cerebellopontine angle (CPA) surgery. Between January and August 2007, 72 patients were operated on by different transpetrosal approaches in a tertiary referral center. During preoperative assessment, facial nerve function (House-Brackmann grading system), the presence of vertigo or tinnitus and caloric test results were recorded and correlated with complications and symptoms occurring daily from day (D) 1 to D 8. The overall number of complications did not differ from those of former retrospective studies; nevertheless, the prospective feature of this study prompts several comments.

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Even slight (grade II) preoperative facial impairments increased the risk of severe postoperative facial dysfunction. Keratitis was frequent (42%) even in patients with normal facial function. Thrombo-embolic complications only occurred after long air-travel (≥5 h). Preoperative caloric test status was predictive of postoperative vestibular disturbance occurrence. With respect to the activity recovery; younger patients (<40 years old) displayed faster central compensations than the older (>60 years old) patients. This study highlights several features that may be used for preoperative patient counseling and complication management. In particular, the practitioner has to pay attention to even minor preoperative clinical signs of facial dysfunction to properly inform the patient of facial outcome. Routine ophthalmologic evaluation should be practiced, even when facial function is normal or subnormal. Level of evidence: 1b.

Endovascular treatment of dural arteriovenous fistula involving marginal sinus with emphasis on the routes of transvenous embolization.
Neuroradiology. 2011 Mar 3. [Epub ahead of print]

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INTRODUCTION: Dural arteriovenous fistulas involving marginal sinus are relatively rare. Transvenous embolization is a curative treatment of choice for them. Regional anatomy surrounding the marginal sinus comprises complex craniocervical bony structures and abundant venous interconnections. Therefore, dural arteriovenous fistulas involving marginal sinus may have various routes for a transvenous approach. The purpose of this article was to analyze endovascular treatment of marginal sinus dural arteriovenous fistulas with emphasis on the routes of transvenous embolization. METHODS: Five patients with dural arteriovenous fistulas (DAVFs) involving the marginal sinus who were treated with transvenous embolization were retrospectively analyzed in terms of endovascular treatment: angiographic architecture, routes of venous approach, and treatment results case by case. RESULTS: There were no significant complications except for headache, ocular pain, and facial flushing after transvenous embolization. Immediate angiographic outcomes were complete in four patients and partial in one patient. Clinical outcomes during follow-up were complete recovery in four patients and intermittent tinnitus in one patient. Three different transvenous approaches were used for transvenous coil embolization: ipsilateral internal jugular vein in three patients, contralateral internal jugular vein in one patient, and vertebral venous plexus in one patient. CONCLUSION: Transvenous coil embolization in treating marginal sinus DAVF is a safe and effective method. In case of failure of an internal jugular venous approach, alternative routes of embolization should be considered. Understanding the regional venous anatomy of the craniocervical junction is important for targeting fistulous sites and selecting routes for transvenous embolization.

CT-Guided Epidural Blood Patching of Directly Observed or Potential Leak Sites for the Targeted Treatment of Spontaneous Intracranial Hypotension.

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BACKGROUND AND PURPOSE: Optimal diagnosis and management of spontaneous intracranial hypotension remains uncertain. CT-guided blood patching has been described but has not been evaluated in larger case series. We sought to evaluate the efficacy of CT-guided blood patching of observed or potential CSF leaks in spontaneous intracranial hypotension. MATERIALS AND METHODS: Patients referred for evaluation of spontaneous intracranial hypotension were retrospectively reviewed. Inclusion criteria were findings of intracranial hypotension on pretreatment brain MR imaging, evaluation and treatment with CT-guided myelography and blood patching, and availability of posttreatment brain MR images. Eight patients met inclusion criteria. Imaging findings, treatment details, and clinical outcomes were assessed.
RESULTS: Pretreatment imaging findings included dural enhancement, tonsillar ectopia, subdural collections, and syrinx. All findings resolved or significantly improved on posttreatment imaging. Presenting clinical symptoms included positional headache, neck/interscapular/shoulder pain, and tinnitus. Headaches and neck/interscapular/shoulder pain improved in all patients; tinnitus improved in 1 of 2 patients. CSF leak sites were directly visualized in 37% of patients and were targets for patching when seen. When no direct visualization of leaks was seen, irregular spinal nerve root diverticula were targeted as potential leak sites. The average number of blood patching sessions was 3 (range, 1-6) and the average number of individual sites patched per session was 5 (range, 1-10). CONCLUSIONS: Our results suggest that CT-guided blood patching targeting observed or potential leak sites can be effective in the treatment of intracranial hypotension. Prospective controlled studies are needed to confirm efficacy and compare outcomes with other treatment options.

[Linear accelerator radiosurgery for the treatment of vestibular schwannoma].


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INTRODUCTION AND AIM: Radiosurgery is among the treatment options for patients with vestibular schwannoma. We present the experience in our institution in the treatment of this disease with this technique. PATIENTS AND METHODS: A retrospective study was made including 20 patients (11 women and 9 men; median age: 55.15 years-old) with vestibular schwannoma who received linear accelerator radiosurgery treatment since April 2005 until December 2008. Follow-up period was between 12 and 42 months, considering clinical examination of cranial nerves VII (House-Brackmann scale) and VIII (Gardner-Robertson scale) as well as radiological findings (considering tumor volume). For statistical analysis, the Fisher's exact test and logistic regression test were used. RESULTS: Certain worsening of hearing function was present in 25% of the patients. Five patients had large tumors at the moment of the treatment (equal or larger than 3.5 cm3), from which four deteriorated from headache, unsteady gait, dizziness/vertigo, facial numbness and tinnitus, with statistical significance (p < 0.05). From the first year of treatment on, there was a tumor volume decrease tendency, with no tumor growth in the medium/long term follow-up, achieving a local control rate of 100%. CONCLUSIONS: Radiosurgery has become an alternative in the treatment of patients with vestibular schwannoma of appropriate size, with high safety level, using low radiation doses, low rate of complications and good tumor control rate in the medium term follow-up.

Tinnitus in patients with chronic otitis media before and after middle ear surgery.
Eur Arch Otorhinolaryngol. 2011 Feb 18. [Epub ahead of print]

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The objective of this study was to investigate the clinical features of tinnitus in patients with chronic otitis media (COM) and to evaluate changes in tinnitus following middle ear surgery in relation to audiologic outcome. Medical records were reviewed for 117 patients with COM who underwent middle ear surgery between March 2009 and March 2010. Of them, 44 patients who pre-operatively reported tinnitus on a tinnitus questionnaire and 28 patients who completed a tinnitus questionnaire 8 weeks after surgery were evaluated to determine the clinical characteristics of tinnitus in patients with COM and any change in tinnitus following middle ear surgery, respectively. New tinnitus symptoms that developed after surgery were also evaluated in previously asymptomatic patients. The pre-operative incidence of tinnitus in patients with COM was 43% (50/117), with 87% of these patients displaying sensorineural tinnitus.
After middle ear surgery, tinnitus handicap inventory scores were reduced in 82% of patients (23/28). Mean values of loudness, annoyance, effect on life, and awareness of tinnitus were also significantly reduced. One patient displayed newly developed tinnitus after surgery. Analysis of the relationship between improvement in tinnitus and audiologic outcome demonstrated that the group of patients whose tinnitus handicap inventory was reduced by more than 10 showed significantly greater improvements in mean air-conduction thresholds than did patients in the other group. In conclusion, following middle ear surgery, most patients experienced a reduction in tinnitus and restored hearing, with surgery perceived as an important contributory factor.

**Vertebral artery pexy for microvascular decompression of the facial nerve in the treatment of hemifacial spasm.**

*J Neurosurg.* 2011 Jan 28. [Epub ahead of print]

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Object Hemifacial spasm (HFS) is caused by arterial or venous compression of cranial nerve VII at its root exit zone. Traditionally, microvascular decompression of the facial nerve has been an effective treatment for posterior inferior and anterior inferior cerebellar artery as well as venous compression. The traditional technique involves Teflon felt or another construct to cushion the offending vessel from the facial nerve, or cautery and division of the offending vein. However, using this technique for severe vertebral artery (VA) compression can be ineffective and fraught with complications. The authors report the use of a new technique of VA pexy to the petrous or clival dura mater in patients with HFS attributed to a severely ectatic and tortuous VA, and detail the results in a series of patients. Methods Six patients with HFS due to VA compression underwent a retrosigmoid craniotomy, combined with a far-lateral approach in some patients. On identification of the site of VA compression, the vessel was mobilized adequately for the decompression. Great care was taken to avoid kinking the perforating vessels arising from the VA. Two 8-0 nylon sutures were passed through to the wall of the VA and then through the clival or petrous dura, and then tied to alleviate compression on cranial nerve VII. Results Patients were followed for at least 1 year postoperatively (mean 2.7 years, range 1-4 years). All 6 patients had complete resolution of their HFS. Facial function was tested postoperatively, and was stable when compared with the preoperative baseline. Two of the 3 patients with preoperative tinnitus had resolution of this symptom after the procedure. Postoperative imaging demonstrated VA decompression of the facial nerve and no evidence of stroke in all patients. One patient suffered from hearing loss, another developed a postoperative transient unilateral vocal cord paralysis, and a third patient developed a pseudomeningocele that resolved with the placement of a lumbar drain. Conclusions Hemifacial spasm and other neurovascular syndromes are effectively treated by repositioning the compressing artery. Careful study of the preoperative MR images may identify a select group of patients with HFS due to an ectatic VA. Rather than traditional decompression with only pledget placement, these patients may benefit from a VA pexy to provide an effective, safe, and durable resolution of their symptoms while minimizing surgical complications.

**XI Holistic**

no publications this time
Phantom percepts: Tinnitus and pain as persisting aversive memory networks.
Proc Natl Acad Sci U S A. 2011 Apr 18. [Epub ahead of print]

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Phantom perception refers to the conscious awareness of a percept in the absence of an external stimulus. On the basis of basic neuroscience on perception and clinical research in phantom pain and phantom sound, we propose a working model for their origin. Sensory deafferentation results in high-frequency, gamma band, synchronized neuronal activity in the sensory cortex. This activity becomes a conscious percept only if it is connected to larger coactivated „(self-)awareness“ and „salience“ brain networks. Through the involvement of learning mechanisms, the phantom percept becomes associated to distress, which in turn is reflected by a simultaneously coactivated nonspecific distress network consisting of the anterior cingulate cortex, anterior insula, and amygdala. Memory mechanisms play a role in the persistence of the awareness of the phantom percept, as well as in the reinforcement of the associated distress. Thus, different dynamic overlapping brain networks should be considered as targets for the treatment of this disorder.

Ménière's Disease: A Challenging and Relentless Disorder.

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Ménière's disease (MD) is characterized by episodic vertigo, fluctuating hearing loss and tinnitus, and by the presence of endolymphatic hydrops on postmortem examination. This disease continues to be a diagnostic and therapeutic challenge. Patients with MD range from minimally symptomatic, highly functional individuals to severely affected, disabled patients. Current management strategies are designed to control the acute and recurrent vestibulopathy but offer minimal remedy for the progressive cochlear dysfunction. Recent research highlights the role of neurotoxicity in the pathogenesis of the cochleovestibular deterioration. This article discusses a patient with MD, and provides an algorithm for the management of this disease.

Systematic review and meta-analyses of RCTs examining tinnitus management
The Laryngoscope 2011

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Objectives/Hypothesis: To evaluate the existing level of evidence for tinnitus management strategies identified in the UK Department of Health's Good Practice Guideline. Study Design: Systematic review of peer reviewed literature and meta-analyses. Methods: Searches were conducted in PubMed, Cambridge Scientific Abstracts, Web of Science and EMBASE (earliest to August 2010), supplemented by hand searches in October 2010. Only randomized controlled trials that used validated questionnaire measures of symptoms (i.e. measures of tinnitus distress, anxiety, depression) were included.
Results: Twenty-eight randomized controlled trials met our inclusion criteria, most of which provide moderate levels of evidence for the effects they reported. Levels of evidence were generally limited by the lack of blinding, lack of power calculations, and incomplete data reporting in these studies. Only studies examining cognitive behavioural therapy were numerous and similar enough to perform meta-analysis, from which the efficacy of cognitive behavioural therapy (moderate effect size) appears to be reasonably established. Antidepressants were the only drug class to show any evidence of potential benefit. Conclusions: The efficacy of most interventions for tinnitus benefit remains to be demonstrated conclusively. In particular, high-level assessment of the benefit derived from those interventions most commonly used in practice, namely hearing aids, maskers, and TRT, needs to be performed.

XIII Others

Tinnitus Handicap Inventory for Evaluating Treatment Effects: Which Changes Are Clinically Relevant?
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Objective. To determine the minimum change of the Tinnitus Handicap Inventory (THI) score that could be considered clinically relevant, the authors compared the absolute change of the THI with the Clinical Global Impression-Improvement (CGI-I) score. Study Design. International studies register with standardized data collection. Setting. Tinnitus Research Initiative (TRI). Subjects and Methods. Two hundred ten patients of the TRI database were eligible for this study. In the first analysis, the THI score change and CGI-I ratings were compared with equipercentile linking. In a second analysis, the authors categorized the CGI-I into the 4 groups much better or better, minimally better, no change, and worse and calculated the corresponding differences of the THI score and the effect sizes. An effect size separating the minimally better and the no-change groups was chosen, and the referring THI mean score difference was calculated. Results. According to the linking method, a CGI-I value of 3 (minimally better) corresponded to a THI score reduction of 6 to 16, whereas the CGI-I value of 4 (no change) corresponded to the range between improvement by 5 points and worsening by 4 points. For separating the no-change and minimally better groups, an effect size d = 0.5 was determined, resulting in a minimal clinically relevant difference of ΔTHI = 7. Conclusion. Two different methods yielded comparable results in identifying a reduction in the THI score of 6 and 7 points, respectively, as the minimal clinically relevant change. This study provides a first orientation for sample size calculations and for planning the design of future studies.

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BACKGROUND: Despite the high prevalence and morbidity, tinnitus still remains an obscure symptom. We assessed the efficacy of low-level laser for treatment of tinnitus. METHODS: It was a self controlled clinical trial study on 61 outpatients with subjective tinnitus. The patients were irradiated with a 650-nm, 5-mW soft laser for twenty days and twenty minutes per day. The sensation of tinnitus was measured on a Visual Analog Scale (VAS) before and two weeks after treatment and they were compared by means of Wilcoxon signed rank test. RESULTS: Thirty-eight (62.3%) patients were men and twenty-three (37.7%) were women. Fourteen patients (31.8%) worked in noisy environment. The VAS mean difference before and after the treatment was statistically significant (p < 0.0001). The best treatment effect was in the youngest group and there were significant differences between this group and the middle age and
older groups (p = 0.018 and 0.001, respectively). The mean VAS score reduction was not statistically significant between male and female patients (p = 0.23). Also, the treatment outcome according to the noise level in patient's workplaces was not significantly different in women (p = 0.693), but it was significant in men (p = 0.029).

CONCLUSIONS: Transmeatal low-level laser irradiation is effective for the treatment of tinnitus and some variables like age and job can affect the treatment outcome.

Readability of Patient-Reported Outcome Questionnaires For Use With Persons With Tinnitus. Ear Hear. 2011 Mar 18. [Epub ahead of print]

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OBJECTIVES: The readability of 15 tinnitus-focused, patient-reported outcome (PRO) questionnaires was analyzed. DESIGN: Reading grade levels were analyzed using the Flesch Reading Ease, FOG, and FORCAST formulas as computed by a readability calculations software package. RESULTS: The results of this study demonstrate that the majority of questionnaires exceeded the fifth- to sixth-grade reading levels recommended by health literacy experts regardless of the formula applied. CONCLUSIONS: In the demand for standardization of tinnitus assessment tools, developers and clinicians should consider readability as another testable construct, as poor readability may affect both validity and reliability.

A two-choice sound localization procedure for detecting lateralized tinnitus in animals. Behav Res Methods. 2011 Mar 17. [Epub ahead of print]

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Rats were trained in a two-choice procedure to respond in the direction of left and right sounds. Silent trials, on which no sound was presented and for which the animals received no feedback, were interspersed among the sound trials to determine each animal's natural side preference. Following training, the rats were exposed to a loud tone in the ear opposite their side preference. A shift in responding on the silent trials to the side of the exposed ear indicated that the animals were hearing a sound in that ear (i.e., tinnitus). Simulating lateralized tinnitus by presenting a low-level, continuous sound on one side also caused the rats to shift their responding on the silent trials to that side. Sham exposures indicated that halothane/nitrous oxide anesthesia could reinstate tinnitus in animals that had previously tested positive for it. Exposing rats to loud tones of various frequencies indicated that frequencies near the limits of the rat's hearing range were less likely to cause tinnitus than tones in the midrange.


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OBJECTIVE: The response rates and effects of being placed on a wait-list control condition are well documented in psychiatric populations. Despite the usefulness of such estimates and the frequent use of no-treatment controls in clinical trials for tinnitus, the effect of waiting in a tinnitus trial has not been investigated systematically. The aim of the present study was to quantify the overall effect of wait-list control groups on tinnitus distress. METHODS: Studies were retrieved via a systematic review of randomised controlled trials of cognitive behaviour therapy for tinnitus distress. Outcomes of psychometrically robust tinnitus-specific measures (Tinnitus Handicap Inventory, Tinnitus Questionnaire,
Tinnitus Reaction Questionnaire) from wait-list control groups were quantified using meta-analytic techniques. Percentage of change and standard mean difference effect sizes were calculated using the pre and post wait period. RESULTS: Eleven studies involving 314 wait-list subjects with tinnitus were located. The analysis for a waiting period of 6 to 12 weeks revealed a mean decrease in scores on tinnitus-specific measures of 3% to 8%. Across studies, a statically significant small mean within-group effect size was obtained (Hedges' g=.17). The effects were moderated by methodological quality of the trial, sample characteristics (i.e., age, tinnitus duration), time of the wait-list and how diagnosis was established. CONCLUSION: Subjects in a tinnitus trial improve in tinnitus distress over a short waiting phase. The effects of waiting are highly variable and depend on the characteristics of the sample and of the trial. Copyright © 2011 Elsevier Inc. All rights reserved.

A Hebrew adaptation of the tinnitus handicap inventory.
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Objective: To establish a Hebrew version of the English THI. Design: The English THI (THI-E) was translated into Hebrew by two bilingual investigators, independently. A third investigator then constructed the final Hebrew THI version (THI-H) from the two translations. This version was administered to fifty consecutive patients at the tinnitus clinic. Participants also assessed tinnitus severity and loudness, and completed the Hebrew versions of the Beck’s depression inventory and the state anxiety inventory. Study sample: The participants were fifty consecutive patients (older than 18 years of age, with a tinnitus lasting over three months) who were referred to a tinnitus clinic (none of them declared compensation seeking). Results: A very good internal consistency was found (α = 0.93), with significant correlation between the subscales of the THI-H and the Beck depression inventory score and the state anxiety inventory score. Conclusions: A valid and reliable THI-H questionnaire was constructed.

Tinnitus Interferes With Daily Life Activities: A Psychometric Examination of the Tinnitus Disability Index.
Ear Hear. 2011 Feb 17. [Epub ahead of print]

Cima RF, Vlaeyen JW, Maes IH, Joore MA, Anteunis LJ.
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Objectives: Tinnitus Disability Index (TDI) is presented as a novel and brief self-report measure for the assessment of the interference of tinnitus with performance in specific daily life activities. We hypothesized that the TDI is a reliable and valid measure and that tinnitus disability is strongly associated with tinnitus severity, subjective tinnitus intensity ratings, and ratings of general health. Design: Six hundred fifteen tinnitus patients from across the Netherlands completed online a number of questionnaires about their tinnitus, their general health, and demographics. Two samples were extracted by a random split: Sample I (N = 311) for exploratory factor analysis and Sample II (N = 304) for confirmatory analysis, using structural equation modeling. One hundred forty-three of the first included respondents repeated assessment after a 2-wk time interval for test/retest analysis. Regression analyses were employed to investigate construct validity. Results: Present analyses reveal that tinnitus disability, as measured with the TDI, might be best understood as a single-component construct, that is, one single underlying factor. The TDI is reliable over time, and tinnitus-related disability, as measured with the TDI, is strongly associated with subjective ratings of tinnitus intensity, negatively associated with quality of life ratings, and distress due to tinnitus. Conclusions: The TDI is a brief and easily administered index measuring a unique construct, namely the experienced interference of the tinnitus with daily life activities, which is invaluable in the assessment and treatment of tinnitus patients.
Better protection from blasts without sacrificing situational awareness.

Killion MC, Monroe T, Drambarean V.
Eymotic Research, Inc., Elk Grove Village, Illinois, USA. M_Killion@etymotic.com

A large number of soldiers returning from war report hearing loss and/or tinnitus. Many deployed soldiers decline to wear their hearing protection devices (HPDs) because they feel that earplugs interfere with their ability to detect and localize the enemy and their friends. The detection problem is easily handled in electronic devices with low-noise microphones. The localization problem is not as easy. In this paper, the factors that reduce situational awareness—hearing loss and restricted bandwidth in HPD devices—are discussed in light of available data, followed by a review of the cues to localization. Two electronic blast plug earplugs with 16-kHz bandwidth are described. Both provide subjectively transparent sound with regard to sound quality and localization, i.e., they sound almost as if nothing is in the ears, while protecting the ears from blasts. Finally, two formal experiments are described which investigated localization performance compared to popular existing military HPDs and the open ear. The tested earplugs performed well regarding maintaining situational awareness. Detection-distance and acceptance studies are underway.

Otologic diagnoses in the elderly: Current utilization and predicted workload increase
The Laryngoscope 2011 (Apr)

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Dept of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA, Dept of Otology and Laryngology, Harvard Medical School, Boston, MA, Division of Otolaryngology–Head and Neck Surgery, Brigham and Women’s Hospital, Boston.

Objective: To establish the current outpatient workload for otologic conditions in the elderly and to estimate its potential increase based on an anticipated aging population. Study design: Cross-sectional analysis of a national database. Methods: All outpatient clinic visits for patients aged ≥65 years receiving one of 5 common otologic diagnoses from 2005-2007 in the United States were determined from the National Ambulatory Medical Care Survey. The distribution of the visits for these diagnoses across 15 specialties was assessed. The number of visits was projected to the 2020 population based on changes in population demographics predicted by the United States Census Bureau. Results: An estimated 4.48 ± 0.49 million clinic visits with an otologic issue as a coded diagnosis were conducted in 2005-2007 in patients aged ≥65 years. These consisted of 230,000 visits for benign positional paroxysmal vertigo, 263,000 visits for vestibular neuritis, 292,000 visits for Meniere’s disease, 1.09 million visits for tinnitus, and 2.85 million visits for sensorineural hearing loss. Otolaryngology, internal medicine, family practice, and neurology managed the most visits, seeing 57.0%, 21.0%, 14.3% and 2.2% of the cases, respectively. With expected changes in population demographics by 2020, annual clinic visits for an otologic diagnosis will increase from 1.49 ± 0.78 million to 2.14 million visits in the elderly, annualized, including 1.218 million visits to otolaryngology. Conclusion: These data quantify the current outpatient otology workload and predict a substantial increase for many specialties, including otolaryngology. Efforts to prepare for this increase including manpower planning and education appear imperative.
Pulsatile tinnitus in perimenopausal period.  

Hou ZQ, Han DY.
Department of Otolaryngology Head and Neck Surgery, Chinese PLA General Hospital, Beijing.

Sigmoid sinus diverticulum-induced pulsatile tinnitus is a rare medical problem. Here we report a case where pulsatile tinnitus occurred in the perimenopause with evidence of sigmoid sinus diverticulum. The tinnitus disappeared with the restoration of hearing after surgery. While diagnosis is critical for the treatment, this disorder can be diagnosed relatively easily, and a satisfactory therapeutic outcome can be achieved using a simple surgical approach. The sigmoid sinus diverticulum may be a clinical manifestation of osteoporosis occurring in the perimenopausal period.

Objective tinnitus from palatal myoclonus. Use of botulinum toxin: a case report.  
[Article in English, Spanish]  
Acta Otorrinolaringol Esp. 2011 Apr 20. [Epub ahead of print]

Conill Tobias N, Paula Vernetta CD, García Callejo FJ, Marco Algarra J.
Servicio Otorrinolaringología, Hospital Clínico Universitario, Valencia, España.

Objective tinnitus can have many different etiologies, palatal myoclonus being one of the less frequent. This type of tinnitus is generated by involuntary rhythmic contraction of the soft palate, which generates an audible click for the patient and for the explorer. Botulinum toxin achieves temporary muscle paralysis through presynaptic inhibition of the acetylcholine level at the neuromuscular union. We present a patient with long-term objective tinnitus, along with this patient’s response to botulinum toxin injection.

Peripheral facial palsy after embolization of a dural arteriovenous fistula with Onyx®  
[Article in German]  
HNO. 2011 Apr 21. [Epub ahead of print]

Kupfer TJ, Aumann K, Laszig R, Meckel S.
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Dural arteriovenous fistulas (DAVF) are intracranial vascular malformations which can cause severe complications, such as intracranial bleeding and neurological deficits. We report the case of a patient presenting with pulsatile tinnitus caused by a DAVF. The DAVF was endovascularly treated including transarterial embolization with the liquid embolic agent Onyx®. The fistula and tinnitus were cured successfully, however, the rare complication of facial nerve palsy due to reflux of Onyx® into the vasa nervorum occurred. This could be confirmed directly during surgery and by histological analysis.

Cochlear implant device failure after cardioversion.  
[Article in German]  
HNO. 2011 Apr 21. [Epub ahead of print]

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Cochlear implantation has become the standard procedure for the treatment of severe to profound hearing loss, even in patients with underlying diseases. We report the case of a CI patient who underwent cardiac defibrillation, following which he reported a reduction in sound quality, a worsening of tinnitus, as well as headaches. An integrity test showed multiple electrode anomalies which could
not be directly attributed to the cardioversion. We performed explantation and reimplantation of the CI. During the course of rehabilitation, the patient showed good results in speech comprehension. Since cardioversion, like any electrical monopolar treatment, may damage CI, it should be avoided in CI patients wherever possible. If it cannot be avoided, we strongly recommend removing the sound processor during treatment sessions. When device-related problems occur, the treatment of choice is reimplantation.

Vogt-Koyanagi-Harada disease occurring during pegylated interferon-α2b and ribavirin combination therapy for chronic hepatitis C.
Lim JH, Lee YN, Kim YS, Kim SG, Jeong SW, Jang JY, Kim HS, Lee SH, Park TK.

Department of Internal Medicine, Soon Chun Hyang University College of Medicine, Bucheon, Korea.

Vogt-Koyanagi-Harada (VKH) disease is a multisystem syndrome characterized by ocular (uveitis and retinal detachment), neurological (headache, tinnitus, and meningitis), and integumentary (vitiligo, alopecia, and poliosis) involvement. Although the pathogenesis of VKH disease is not well understood, an autoimmune T-cell response to a melanocyte-associated antigen is considered to be a cause of VKH disease. The complex immunological response to interferon and ribavirin may induce or exacerbate the autoimmune condition; however, VKH disease is a very rare complication associated with interferon therapy in chronic hepatitis C. We report a case of VKH disease occurring during pegylated interferon-α2b and ribavirin combination therapy for chronic hepatitis C.

Sudden Sensorineural Hearing Loss as Prodromal Symptom of Anterior Inferior Cerebellar Artery Infarction.
ORL J Otorhinolaryngol Relat Spec. 2011 Apr 14;73(3):137-140. [Epub ahead of print]
Martines F, Dispenza F, Gagliardo C, Martines E, Bentivegna D.

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Sudden sensorineural hearing loss is a clinical condition characterized by a sudden onset of unilateral or bilateral hearing loss. In recent years sudden deafness has been frequently described in association with anterior inferior cerebellar artery (AICA) infarction generally presenting along with other brainstem and cerebellar signs such as ataxia, dysmetria and peripheral facial palsy. The authors report a rare clinical case of a 53-year-old man who suddenly developed hearing loss and tinnitus without any brainstem or cerebellar signs. Computed tomography of his brain was normal, and the audiological results localized the lesion causing deafness to the inner ear. Surprisingly, magnetic resonance imaging showed an ischemic infarct in the right AICA territory. This case represents the fifth in the literature to date but it confirms that AICA occlusion can cause sudden deafness even without brainstem or cerebellar signs. Therefore, we recommend submitting the patient for neuroimaging, as an emergency, in order to exclude infarction of the AICA territory. By doing this, it may be possible to limit the extent of the lesion by commencing early therapy.

Meningioma of the internal auditory canal with rapidly progressive hearing loss.
Ishikawa T, Kawamata T, Kawashima A, Yamaguchi K, Kubo O, Hori T, Okada Y.

Department of Neurosurgery, Tokyo Women's Medical University.

A 38-year-old male presented with a meningioma within the internal auditory canal (IAC) manifesting as rapidly progressive hearing loss over a period of one month. He had a 2-year history of tinnitus. Magnetic resonance imaging revealed a 10-mm intracanalicular tumor, which was surgically resected.
by a retrosigmoid lateral suboccipital approach. The histological findings showed meningothelial meningioma. The patient had no facial palsy after surgery, but his cochlear function did not recover. Common symptoms of IAC meningiomas are tinnitus and hearing loss, but rapidly progressive hearing loss is very rare. IAC meningioma is rare but should be taken into consideration as a cause of rapidly progressive hearing loss.

**Tympanic paraganglioma with extension into the Eustachian tube and nasopharynx: a case report.**

[Article in English, Spanish]

Acta Otorrinolaringol Esp. 2011 Mar 16. [Epub ahead of print]

Portero de la Torre M, Sánchez Gutiérrez R, Gallardo Muñoz I, Bravo Rodríguez FA.

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Tympanic paragangliomas usually present as a vascular middle ear mass, with the most common presenting symptoms being pulsatile tinnitus and hearing loss. We report an unusual case of a recurrent tympanic paraganglioma extending along the Eustachian tube and nasopharynx, presenting with recurrent epistaxis. Copyright © 2010 Elsevier España, S.L. All rights reserved

**Calcifying Pseudoneoplasm of the Cerebellopontine Angle: Case Report.**

Neurosurgery. 2011 Mar 15. [Epub ahead of print]

Hodges TR, Karikari IO, Nimjee SM, Tibaleka J, Cummings TJ, Friedman AH.

Dept of Surgery, Division of Neurosurgery and Dept of Pathology, Duke University Medical Center, Durham, North Carolina.

BACKGROUND AND IMPORTANCE: Calcifying pseudoneoplasms are rare tumors of the neuraxis. To our knowledge, this is the second reported case in the literature of calcifying pseudoneoplasm of the cerebellopontine angle. The etiology and natural history of these neoplasms are not well understood. A thorough review of the histology and potential origins of calcifying pseudoneoplasm are provided in this case report. CLINICAL PRESENTATION: A 34 year old previously healthy male presented with a 6 month history of progressive worsening headaches, fatigue, tinnitus, dizziness, and blurry vision. Neurological examination was notable for tongue deviation, tongue atrophy, and left uvula deviation. Computer tomography (CT) scan showed a 3.3 x 3.5 cm densely calcified posterior fossa mass appearing to arise from the occipital bone. Magnetic Resonance Imaging (MRI) revealed a 4.3 X 2.9 X 2.9 cm left posterior fossa enhancing mass with the margin tip from the left occipital condyle. A transcondylar approach was used to resect the lesion. The mass was found to have eroded through the bone into the foramen magnum. Histopathological examination confirmed the diagnosis of calcifying pseudoneoplasm of the cerebellopontine angle. CONCLUSION: Calcifying pseudoneoplasms should be considered in the differential diagnosis of calcified cerebellopontine angle tumors. Histopathologic diagnosis is extremely important in the characterization of these lesions in order to direct the course of appropriate management. An inaccurate diagnosis of a malignant tumor can result in potentially harmful and unnecessary therapies, as prognosis for these lesions is generally favorable.
Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) secondary to epidermoid cyst in the right cerebellopontine angle successfully treated with surgery.

Jiménez Caballero PE, Portilla Cuenca JC, Casado Naranjo I.
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Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome is a rare headache syndrome classified among the trigeminal autonomic cephalalgias. It is usually idiopathic, although infrequent secondary forms have been described. Recently, the term short-lasting unilateral headache with cranial autonomic symptoms (SUNA) has been defined by the International Headache Society (ICHD-2) as similar to SUNCT with less prominent absent conjunctival injection and lacrimation. We report a patient with paroxysmal orbito-temporal pains, phenotypically suggesting SUNA, secondary to epidermoid cyst in the cerebellopontine angle which disappeared after tumor resection. Neuroimaging should be considered in all patients with SUNA, notably in those with atypical presentation as our patient who presented on examination trigeminal hypoesthesia and tinnitus. Realization of a brain MRI would rule out injuries that causes this type of syndrome.

Perilymphatic fistula of the round window.

Service ORL et centre d'implantation cochléaire, CHU Gui-de-Chauliac, 80, avenue Augustin-Fliche, 34295 Montpellier cedex 5, France.

OBJECTIVE: To highlight diagnostic and treatment pitfalls in perilymphatic fistula. CASE REPORTS: Two cases of round-window fistula are reported, detailing clinical aspect, treatment and outcome. The triad comprising sensorineural hearing loss, tinnitus and vertigo with associated fistula sign is classical but in fact rarely encountered. Imaging is of limited contribution, but may reveal anatomic abnormalities suggestive of perilymphatic fistula. Outcome is improved by early management, especially in case of moderate hearing loss. DISCUSSION/CONCLUSION: Diagnosis of perilymphatic fistula is challenging, but enables effective treatment. On any suspicion, surgical exploration should be undertaken, being the only reliable guide to diagnosis and etiologically adapted management. Copyright © 2011 Elsevier Masson SAS. All rights reserved.

Association between Cogan's syndrome and inflammatory bowel disease: a case series.

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BACKGROUND AND AIMS: Cogan's syndrome (CS) is a rare autoimmune disease with less than 250 cases reported. It mainly affects the audiovestibular system and the eyes frequently resulting in deafness. Inflammatory bowel disease (IBD) consists of two subtypes, Crohn's disease (CD) and ulcerative colitis (UC), and represents a common form of chronic intestinal inflammation. Here, we report an association between CS and IBD in four patients. METHODS: Patient data were collected using a questionnaire that was sent to one of our outpatients and three of the 13 members of the German CS self-help group. RESULTS: In all Cogan patients with IBD (3 female with UC, 1 male with CD), intestinal disease was diagnosed years before the onset of CS. After suffering from a complicated IBD disease course, they suddenly developed CS-related symptoms, such as hearing loss, tinnitus or eye inflammation. Three of them went deaf within a few years after diagnosis. Although all of them had been on immunosuppressive IBD therapy, these treatment regimens did not prevent the onset of CS.
CONCLUSIONS: Our data suggest a strong association of IBD and CS. Since CS rapidly leads to bilateral deafness, it seems to be a rare, but nevertheless important disease that can occur in association with IBD. However, neither an early diagnosis nor an immunosuppressive therapy seems to efficaciously prevent disease progression. Copyright © 2010 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

XV Specific Forms of Tinnitus

Primary spontaneous cerebrospinal fluid rhinorrhea: a symptom of idiopathic intracranial hypertension?
J Neurosurg. 2011 Apr 8. [Epub ahead of print]

Department of Neurosurgery, Beijing Neurosurgical Institution of Capital Medical University.

Object: The authors aim to identify the characteristics of primary spontaneous CSF rhinorrhea and propose a hypothesis for its pathogenesis. Methods: Between 2003 and 2009, 21 patients diagnosed with primary spontaneous CSF rhinorrhea underwent surgery in the authors’ hospital. The clinical aspects were retrospectively reviewed, and their characteristics were analyzed. Results: There were 18 women and 3 men, whose ages ranged from 37 to 74 years (mean 53 years). Body mass index (BMI) ranged from 22 to 58.8 kg/m(2) (mean 31.2 kg/m(2)). Eighteen patients (85.7%) were overweight, and 18 (85.7%) suffered from headache or tinnitus before rhinorrhea. Radiological images revealed fully or partially empty sellae in 14 patients (66.7%). The preoperative intracranial pressure (ICP) ranged from 11 to 28 cm H(2)O (mean 17.6 cm H(2)O), while the postoperative ICP ranged from 21 to 32 cm H(2)O (mean 25.5 cm H(2)O, \( p < 0.01 \)). An endoscope-assisted transnasal approach was chosen for the repair. Postoperatively, in 95.2% of patients a cure was achieved. Rhinorrhea recurred in only 1 patient, and a leakage from a new defect occurred in another patient 4 years after the operation. Both patients underwent additional surgery, which was successful. The follow-up period varied from 5 to 75 months with a mean of 34 months. Conclusions: All patients had direct or indirect evidence of elevated ICP, most patients presented with symptoms of idiopathic intracranial hypertension (IIH), and most patients were women and obese. Primary spontaneous CSF rhinorrhea may be due to IIH, and it is a rare symptom of IIH. When treating or monitoring these patients during follow-up, ICP should be controlled, and other symptoms of IIH should be noted.

Ménière’s Disease: A Challenging and Relentless Disorder.

Semaan MT, Megerian CA.
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Ménière’s disease (MD) is characterized by episodic vertigo, fluctuating hearing loss and tinnitus, and by the presence of endolymphatic hydrops on postmortem examination. This disease continues to be a diagnostic and therapeutic challenge. Patients with MD range from minimally symptomatic, highly functional individuals to severely affected, disabled patients. Current management strategies are designed to control the acute and recurrent vestibulopathy but offer minimal remedy for the progressive cochlear dysfunction. Recent research highlights the role of neurotoxicity in the pathogenesis of the cochleovestibular deterioration. This article discusses a patient with MD, and provides an algorithm for the management of this disease.
Proteomics in Ménière disease.


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Ménière’s disease (MD) is a disorder of the inner ear characterized by an insidious onset and aspecific symptoms, such as dizziness, vertigo, tinnitus, and hearing loss, that may become very debilitating. The presence of endolymphatic hydrops is a common feature in MD patients, but the pathophysiology is still largely unknown. In this study, we have used a proteomics-driven approach to identify potential biomarkers of MD. To this end, plasma was obtained from whole blood of 16 individuals previously diagnosed as suffering from MD and compared to plasma from healthy donors. A depletion of the highly abundant proteins (i.e. albumin, IgG, transferrin, etc.) was performed in order to enhance the chance of detection of the less represented ones, therefore reducing the noise-background. Two-dimensional gel electrophoresis, followed by in-gel tryptic digestion of the selected spots and LC-MS/MS analysis, allowed us to identify a set of proteins whose expression appears to be differentially modulated in patients vs. controls. In particular: complement factor H and B, fibrinogen alpha and gamma chains, beta-actin and pigment epithelium derived factor are over expressed; on the other hand, the levels of beta-2 glycoprotein-1, vitamin D binding protein and apolipoprotein-1 are significantly decreased in the plasma of MD-affected individuals. Even though preliminary and not necessarily linked directly to the molecular pathogenesis of the disease, our original findings suggest that a molecular signature, represented by the plasma protein profile previously described, might represent a potentially powerful, innovative and not invasive tool for early diagnosis and clinical management of MD patients. © 2011 Wiley Periodicals, Inc.

Genetic Aspects of Familial Ménière's Disease.
Otol Neurotol. 2011 Mar 23. [Epub ahead of print]

Arweiler-Harbeck D, Horsthemke B, Jahnke K, Hennies HC.

Depts of Otorhinolaryngology, Head and Neck Surgery, and Human Genetics, Univ. Hospital Essen, Univ. Duisburg-Essen; and Cologne Center for Genomics and Center for Molecular Medicine, Univ. of Cologne, Germany.

OBJECTIVE: Ménière’s disease (MD) is a chronic illness characterized by sensorineural hearing loss, recurring vertigo attacks, and tinnitus. It is possibly of multifactorial origin, although several families with autosomal dominant inheritance and reduced penetrance have been described. To elucidate the genetic basis of MD, patients and their families were investigated, and linkage analysis was performed. STUDY DESIGN: Retrospective and prospective family survey. PATIENTS AND METHODS: Of 193 patients diagnosed with MD, 37 patients could be ascertained as having a positive family history, which means a frequency of 19.2%. Nineteen families with 81 members (52 positive for MD and 29 negative for MD) were investigated according to the guidelines of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology. Blood samples were obtained, and a genome-wide linkage analysis was performed with microsatellite markers. RESULTS: Age of onset diminished in subsequent generations. We found suggestive evidence of linkage assuming heterogeneity of MD on chromosome 5 with a maximum multipoint logarithm of the odds of linkage (LOD) score of 1.9 for 13 of 17 families and a potential region on chromosome 12 for 8 families. Of the 81 subjects, 27 (33.3%) reported MD only, 25 (30.9%) reported migraine and MD, and 7 (8.6%) reported migraine only. CONCLUSION: Family trees suggest an autosomal dominant inheritance with reduced penetrance and anticipation. A probable candidate region for MD was located on chromosome 5.
Intratympanic gentamicin for Ménière's disease or syndrome.

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BACKGROUND: Ménière's disease is characterised by three major symptoms: vertigo, deafness and tinnitus, which may be accompanied by aural fullness, all of which are discontinuous and variable in intensity. While discontinuous, these symptoms are synchronous. Intratympanic application of gentamicin, an ototoxic aminoglycoside, is a relatively new ablative treatment for vertigo in Ménière’s disease with promising results. OBJECTIVES: To assess the effectiveness of intratympanic gentamicin in the treatment of vertigo in Ménière's disease. SEARCH STRATEGY: We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ISRCTN and additional sources for published and unpublished trials. The date of the most recent search was 30 June 2010. SELECTION CRITERIA: All randomised or quasi-randomised controlled trials of intratympanic gentamicin versus placebo, or versus another treatment for Ménière’s disease. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trial quality and extracted data. We contacted study authors for further information. MAIN RESULTS: We identified two trials, involving 50 participants, which fulfilled the inclusion criteria. Both of these trials are prospective, double-blind, placebo-controlled randomised clinical trials on the effect of intratympanic gentamicin on vertigo complaints. Both of these trials found a significant reduction in vertigo complaints in the gentamicin group when compared to the placebo group. Due to clinical heterogeneity we could not perform a meta-analysis. AUTHORS’ CONCLUSIONS: Based on the results of the two included studies, intratympanic gentamicin seems to be an effective treatment for vertigo complaints in Ménière’s disease, but carries a risk of hearing loss.

Idiopathic intracranial hypertension: clinical features in Chinese patients.

Liu IH, Wang AG, Yen MY.
Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan.

PURPOSE: To describe the clinical features and visual outcomes of idiopathic intracranial hypertension (IIH) in Chinese patients. METHODS: We retrospectively reviewed the charts of patients diagnosed with IIH in Taipei Veterans General Hospital from 1981 to 2009. Demographic data, clinical features, laboratory data, treatment, and visual outcomes were analyzed. RESULTS: Twelve patients were included, seven female and five male patients. The mean age at onset was 32 (range, 13-65) years. Obesity was found in four (33%) patients. The most common clinical symptom was headache (75%), followed by transient visual obscuration (42%) and tinnitus (17%). Snellen visual acuity was equal to or better than 20/30 in 23 eyes, and the only eye with vision worse than 20/50 vision belonged to a patient who had been amblyopic since childhood. Visual field defects were detected in seven eyes by either Goldmann or automated perimetry. Generalized depression and an enlarged blind spot were the most common patterns. Ten patients were found to have bilateral disc edema. One patient with unilateral papilledema and one patient without papilledema were identified in the study. CONCLUSIONS: In IIH in Chinese, men are more likely to be affected than women, but obesity is not as frequent as reported in Western countries. Visual function outcomes are more favorable in Chinese patients.
# Tinnitus and Arterial Hypertension

<table>
<thead>
<tr>
<th>Current status</th>
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<td>Sponsors and collaborators</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01333683</td>
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**Purpose**

Many authors link tinnitus to arterial hypertension. The aim of this study is to establish a possible relationship between them, analyze the severity of tinnitus related to arterial hypertension and analyze a possible influence of ototoxic drugs used to treat arterial hypertension.

**Study type and design**

Observational;  
Observational Model: Cohort  
Time Perspective: Prospective

**Official title**

Tinnitus and Arterial Hypertension: is There Any Relationship?

**Detailed Description**

Arterial hypertension has been cited as a possible tinnitus etiology. Vascular abnormalities associated with it may account for cochlear and central nervous system. However, a relationship between tinnitus and arterial hypertension has never been established. The aim of this study is to analyze this relationship, comparing groups with and without arterial hypertension and the incidence of tinnitus amongst them. Inclusion and exclusion criteria try to isolate arterial hypertension as the main etiological factor, as much as possible. Presbycusis, noise exposure, metabolical diseases and genetic factors will be ruled out. A comparison will be performed inside the arterial hypertension group between subgroups that use or not ototoxic medications, such as furosemide and beta-blockers.

**Primary Outcomes**

Incidence of tinnitus - have tinnitus x don’t have tinnitus [Time Frame: Up to 6 months] [Designated as safety issue: No]  
The purpose of this study is to compare tinnitus incidence between patients with and without arterial hypertension.

**Secondary Outcomes**

Severity of tinnitus - Tinnitus Handicap Inventory [Time Frame: Up to 6 months]  
Severity of tinnitus measured by Tinnitus Handicap Inventory, to evaluate differences between patients with and without arterial hypertension

**Expected total Enrollment**

100

**Study start**

April 2011

**Expected study completion date**

February 2012

**Expected primary completion date**

December 2011 (Final data collection date for primary outcome measure)
Groups / Cohorts
Control
Normal subjects
AH
Arterial hypertension patients

Participants (age) 40 Years to 49 Years

Gender both

Accepts health volunteers yes

Study population Patients aged between 40 and 50

Inclusion Criteria
• age between 40 and 50
• arterial hypertension for group 1
• at least 5 years standing arterial hypertension

Exclusion Criteria
• chronic noise exposure
• metabolic diseases
• family antecedents of hearing loss (except for presbycusis)
• pregnant women
• use of ototoxic drugs (except for anti-hypertensives)

Locations Faculdade de Medicina de Valença, Valença, RJ, Brazil, 27660-000

Study chairs or principal investigators Ricardo R Figueiredo, MD,MSc, Otosul, Valença Medical School

Study ID Numbers HAS

Last Updated April 11, 2011

Record first received April 7, 2011

ClinicalTrials.gov Identifier NCT01333683

Health Authority Brazil: Ministry of Health

Investigating the Neurobiology of Tinnitus

Current status not yet open for participant recruitment

Sponsors and collaborators Washington University School of Medicine
Department of Defense

Information provided by Washington University School of Medicine

ClinicalTrials.gov Identifier NCT01294124

Purpose The investigators hypothesize that individual differences exist in resting-state cortical attention, control, sensory, and emotion networks prior to noise exposure and these differences predispose some to the development of bothersome tinnitus.
Furthermore, the investigators hypothesize that these changes in functional connectivity of these vulnerable systems after noise exposure are responsible for tinnitus. The proposed study will use a case-control cohort study design. Cases will be those soldiers who develop tinnitus and controls will be those who do not. This will be the first prospective study of tinnitus and will provide important information about the neurobiology of tinnitus.

If a cortical neural network etiology for bothersome tinnitus is confirmed, it will be an astounding, powerful, paradigm shifting model for the diagnosis, prevention and, most importantly, treatment of tinnitus. Furthermore, if a battery of neurocognitive tests can identify soldiers at risk for the development of tinnitus then appropriate primary prevention strategies can be introduced.

There are three Specific Aims to this project.

Specific Aim 1. To determine if soldiers who develop tinnitus display pre-deployment differences in a set of physical, functional, cognitive, vulnerability, perpetuating factors, pre-deployment neurocognitive scores, or neuroimaging features compared to soldiers who do not develop tinnitus (“control group”).

Specific Aim 2. To determine if particular scores on neurocognitive tests or neuroimaging features of functional/structural connectivity networks are associated with the development of tinnitus.

Specific Aim 3. To identify a set of pre-deployment physical, functional, cognitive, vulnerability, and perpetuating factors, neurocognitive responses, and neuroimaging features that are associated with the development of tinnitus.

The investigators plan to recruit 200 soldiers, between the ages of 18 and 30 years who do not have hearing loss or tinnitus and have never been deployed to military theater. The soldier participants will undergo a variety of tests before and after deployment, which will include a hearing test, neurocognitive tests (i.e., brain function tests), and a variety of novel radiologic imaging studies of the brain. One of these novel radiologic imaging studies is functional connectivity Magnetic Resonance Imaging, a proven methodology that monitors changes in brain activity and connections based on blood flow between different brain areas and levels of consumption of oxygen. This information is used to describe the condition of important neural networks responsible for such things as attention, mood, sensation, vision, hearing, and introspection or self-contemplation.

---

<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>Tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Traumatic Brain Injury</td>
</tr>
<tr>
<td></td>
<td>Post Traumatic Stress Disorder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type and design</th>
<th>Observational;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observational Model: Case Control</td>
</tr>
<tr>
<td></td>
<td>Time Perspective: Prospective</td>
</tr>
</tbody>
</table>

| Official title | Investigating The Neurobiology of Tinnitus |

<table>
<thead>
<tr>
<th>Primary Outcome Measures</th>
<th>Development of Tinnitus [ Time Frame: Post-deployment assessment will occur no sooner than 90 days from return from active military theater. ] [ Designated as safety issue: No ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The presence of tinnitus will be based on the participants’ responses to questions 8a, 9c, and 9d of the Post-Deployment Health Assessment (PDHA).</td>
</tr>
</tbody>
</table>
| Secondary Outcome Measures | Mild Traumatic Brain Injury [ Time Frame: Post-deployment assessment will occur no sooner than 90 days from return from active military theater. ] [ Designated as safety issue: No ]
Mild Traumatic Brain Injury - Ohio State University TBI Identification Method (OSU TBI-ID version 12-10-08)(Corrigan and Bogner 2007)
Post Traumatic Stress Disorder [ Time Frame: Post-deployment assessment will occur no sooner than 90 days from return from active military theater. ] [ Designated as safety issue: No ]
Subjects whose military medical record or PDHA suggests PTSD will be asked to complete the Clinician Administered PTSD Scale (CAPS). (Blake et al. 1995; Weathers and Litz 1994) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected total Enrollment</td>
<td>200</td>
</tr>
<tr>
<td>Study start</td>
<td>March 2011</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>February 2014 (Final data collection date for primary outcome measure)</td>
</tr>
</tbody>
</table>
| Groups / Cohorts | No Tinnitus
The absence of tinnitus will be based on the participants’ responses to questions 8a, 9c, and 9d of the Post-Deployment Health Assessment (PDHA).
Tinnitus
The presence of tinnitus will be based on the participants’ responses to questions 8a, 9c, and 9d of the Post-Deployment Health Assessment (PDHA). |
| Participants (age) | 18 Years to 30 Years |
| Gender | both |
| Accepts health volunteers | yes |
| Sampling method | Non-Probability Sample |
| Study population | Active-duty or reserve United States military personnel between the ages of 18 and 30 of either sex, all races and ethnicity, who are scheduled for initial deployment to theater with a Military Occupational Specialty code (MOS) of 11B Infantryman, 11C Indirect Fire Infantryman, 19D Calvary Scout, or 19K Armor Crewman. |
| Inclusion Criteria | • Active duty or reserve military personnel with MOS job code 11B, 11C, 19D, or 19K
• Men and women between the ages of 18 and 30 years
• Scheduled for first deployment to military theater
• Must be able to read, write, and understand English
• Willing to sign Request Pertaining to Military Records (Form 180) to allow study personnel to access medical records for the purposes of this study. |
| Eligibility Exclusion Criteria | • History of hearing loss or tinnitus
• Currently taking medication for depression, anxiety, or other DSM IV Axis 1 disorder
• History of head trauma sufficient to cause loss of consciousness for 30 minutes or greater |
| **Contact** | Joyce R. Nicklaus, RN, BSN, CCRC, 314-362-7508; niklausj@ent.wustl.edu |
| **Locations** | Washington University School of Medicine, St. Louis, Missouri, United States, 63110 |
| **Principal Investigator** | Washington University School of Medicine |
| **Responsible Party** | Jay F. Piccirillo, MD, Washington University School of Medicine |
| **Study ID Numbers** | 201101920DM.INT, CDMRP |
| **Last Updated** | February 10, 2011 |
| **Record first received** | February 9, 2011 |
| **ClinicalTrials.gov Identifier** | NCT01294124 |
| **Health Authority** | United States: U.S. Army Medical Research and Materiel Command's Office of Research Protections |

### Study of BGG492 in Patients With Chronic Subjective Tinnitus

| **Current status** | currently recruiting participants |
| **Sponsors and collaborators** | Novartis |
| **Information provided by** | Novartis |
| **ClinicalTrials.gov Identifier** | NCT01302873 |
| **Purpose** | This study will assess the efficacy of a two week treatment with BGG492 in patients with chronic subjective Tinnitus. |
| **Condition(s)** | Chronic Subjective Tinnitus |
| **Intervention** | Drug: BGG492A |
| **Phase** | II |
| **Study type and design** | Interventional; Allocation: Randomized Intervention Model: Crossover Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Treatment |
## Official Title
A Multicenter, Randomized, Double-blind, Placebo-Controlled, Cross-over, Proof of Concept Study Comparing the Effects of Both Single Dose and Repeated Dosing Treatment for 2 Weeks of BGG492 in Patients With Chronic Subjective Tinnitus

## Arms
- **BGG492**: Experimental Intervention: Drug: BGG492A
- **Placebo**: Placebo Comparator Intervention: Drug: BGG492A

## Assigned Interventions
- Drug: BGG492A
- Drug: BGG492A

## Primary Outcome Measures
- Change in tinnitus loudness using a visual analogue scale (VAS) [Time Frame: after 15 days of treatment] [Designated as safety issue: No]
- Change in Clinical status of tinnitus (patients’ reaction to tinnitus) using the TBF-12 (Tinnitus Impairment Questionnaire) [Time Frame: after 15 days of treatment] [Designated as safety issue: No]

## Expected Total Enrollment
92

## Study Start
January 2011

## Estimated Primary Completion Date
October 2011 (Final data collection date for primary outcome measure)

## Participants (Age)
18 Years to 75 Years

## Gender
both

## Accepts Health Volunteers
no

## Inclusion Criteria
- Patients diagnosed with THI (Tinnitus Handicap Inventory) severity grade 3, 4 or 5 (moderate, severe or catastrophic), chronic (> 6 months and < 36 months) subjective tinnitus
- Willing to abstain from activities that require focused attention, e.g. driving a car or other vehicles, operating machines or engaging in potentially dangerous activities that require focused attention and intact physical balance
- Willing and able to refrain from engaging in activities or work involving loud noise exposure

## Eligibility Exclusion Criteria
- Patients diagnosed with tinnitus of THI severity grade equal to 2 or 1
- Patients with diagnosis of intermittent or pulsatile tinnitus
- Patients who have tinnitus as a concomitant symptom of a treatable otological disease (such as otitis media, Menière’s disease, otosclerosis), neurological tumors or/and have temporo-mandibular joint disorders
- Patients with a history of frequent middle ear infections (> 3 infections per year during the last 3 years)
- Patients with diagnosed anxiety disorders, depression, schizophrenia or other significant psychiatric diseases requiring current drug treatment or patients who required treatment in the previous 3 months for these diseases.
### Inclusion Criteria
- Patients with current unilateral or bilateral hearing loss of 75 dB or more in one or more tested frequencies (125 Hz, 250 Hz, 1 kHz, 2 kHz, 4 kHz, 6 kHz, 8 kHz)
- Patients with Vestibular Schwannoma
- Patients with a cochlear implant
- Patients with regular intake of central nervous system acting drugs for the treatment of tinnitus in the previous 6 months prior to initial dosing

Other protocol-defined inclusion/exclusion criteria may apply

### Contact
Novartis Pharmaceuticals, +41-61-324-1111

### Locations
- Novartis Investigative Site, Berlin, Germany, 10117, active, not recruiting
- Novartis Investigative Site, Groningen, Netherlands, 9700, recruiting

### Principal Investigator
Novartis Pharmaceuticals

### Responsible Party
Novartis Pharmaceuticals (External Affairs)

### Study ID Numbers
CBGG492A2210, 2010-022166-27

### Last Updated
February 22, 2011

### Record first received
February 7, 2011

### Health Authority
- Germany: Federal Institute for Drugs and Medical Devices
- Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
- Switzerland: Swissmedic

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### A Trial of Magnesium Dependent Tinnitus

#### Current status
not yet open for participants recruitment

#### Sponsors and collaborators
Mayo Clinic

#### Information provided by
Mayo Clinic

#### ClinicalTrials.gov Identifier
NCT01302873

#### Purpose
Descriptions of tinnitus date back to the time of ancient Egypt, yet science has failed to unravel the mysterious underlying mechanisms that produce these subjective auditory perceptions of sound. These perceptions may be manifestations of damage resulting from noise exposure, ototoxicity, or other abnormal conditions of the auditory system. However, many individuals have idiopathic tinnitus for which no specific cause can be determined. Although often presenting in conjunction with hearing loss, the magnitude of hearing loss does not necessarily correspond with the severity of tinnitus. In addition, some individuals reporting tinnitus experience concomitant hyperacusis.
This relationship suggests these processes may be linked by underlying imbalances at the level of the hair cell. The possible influence of magnesium and its antagonist, calcium, has been discussed in the literature as a contributing factor in the mitigation of noise-induced hearing loss, ototoxicity, and the hyperexcitability of the auditory system (Cevette et al, 2003). Permanent and temporary changes in auditory function have been linked to nutritional deficiencies of magnesium. Magnesium deficiency has resulted in increased susceptibility to noise-induced hearing loss (Ising et al, 1982; Joachims et al, 1983; Joachims et al, 1987; Scheibe et al, 2000), ototoxicity (Vormann and Gunther, 1993), and hyperexcitability (Kruse et al, 1932; Cevette et al, 1989; Bac et al, 1994) of the auditory system.

The recommended daily allowance (RDA) for magnesium in adults is 4.5 mg/kg (Saris et al, 2000); however, all age groups of Americans fall short of the RDA for magnesium by 100 mg daily (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 1997). This lack of appropriate magnesium intake may have negative consequences. For example, the putative magnesium mechanism within the auditory system involves a metabolic cellular cascade of events. Specifically, magnesium deficiency leads to increased permeability of the calcium channel in the hair cells with a consequent over-influx of calcium, an increased release of glutamate via exocytosis, and overstimulation of N-methyl-D-aspartate receptors on the auditory nerve fibers. Recent studies of both noise-induced hearing loss and idiopathic sensorineural hearing loss have suggested that magnesium supplementation may lessen the severity of tinnitus in patients. Magnesium improved hearing recovery and lessened tinnitus in patients with idiopathic sudden hearing loss (Gordin et al, 2002). More recently, Nageris et al (2004) showed in a well-controlled study that magnesium was a relatively safe and convenient adjunct to corticosteroid treatment for enhancing the improvements of hearing in acute-onset sensorineural hearing loss at a dose of 4 g. The protective effect of magnesium in noise-induced hearing loss has been previously reported (Ising et al, 1982; Scheibe et al, 2000).

Despite these encouraging findings, no controlled study has examined the effect of magnesium supplementation for patients with moderate to severe tinnitus. Additionally, no study to date has examined self-reported tinnitus severity before and after magnesium supplementation.

<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>Tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Dietary Supplement: Magnesium Other: Placebo</td>
</tr>
<tr>
<td>Phase</td>
<td>III</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Interventional; Allocation: Randomized Intervention Model: Crossover Assignment Masking: Double Blind (Subject, Investigator)</td>
</tr>
<tr>
<td>official title</td>
<td>A Phase III Trial of Magnesium Dependent Tinnitus</td>
</tr>
<tr>
<td>Arms</td>
<td>Magnesium: Experimental Intervention: Dietary Supplement: Magnesium Placebo (Sugar pill): Placebo Comparator Intervention: Other: Placebo</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Assigned Interventions</td>
<td>Dietary Supplement: Magnesium Magnesium 532 mg a day Other: Placebo matching form/dosage</td>
</tr>
<tr>
<td>Primary Outcome Measures</td>
<td>magnesium dependent tinnitus [Time Frame: 3 months] [Designated as safety issue: No] The purpose of this study is to examine any change in the perception of tinnitus in patients supplemented with magnesium (535 mg daily).</td>
</tr>
<tr>
<td>Expected total Enrollment</td>
<td>40</td>
</tr>
<tr>
<td>Study start</td>
<td>February 2011</td>
</tr>
<tr>
<td>estimated study completion date</td>
<td>December 2012</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>December 2012 (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>Inclusion Criteria</td>
<td>Normal Kidney function (last checked within 6 months)</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>- Any participant with decreased kidney function within past 6 months - Current treatment with Lithium - Tinnitus rating with 0, 1, or 2 on the 0-10 Tinnitus scale</td>
</tr>
<tr>
<td>Locations</td>
<td>Mayo Clinic in Arizona, Scottsdale, Arizona, United States, 85259</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Michael Cevette PhD</td>
</tr>
<tr>
<td>Responsible Party</td>
<td>Mayo Clinic (Michael Cevette, PhD)</td>
</tr>
<tr>
<td>Study ID Numbers</td>
<td>09-008292</td>
</tr>
<tr>
<td>Last Updated</td>
<td>January 10, 2011</td>
</tr>
<tr>
<td>Record first received</td>
<td>January 7, 2011</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01273883</td>
</tr>
<tr>
<td>Health Authority</td>
<td>United States: Institutional Review Board</td>
</tr>
</tbody>
</table>
**Comparison of Single Versus Repeat Doses of AM-101 in the Treatment of Acute Inner Ear Tinnitus (TACTT1)**

<table>
<thead>
<tr>
<th>Current status</th>
<th>currently recruiting participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Auris Medical, Inc.</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Auris Medical, Inc.</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01270282</td>
</tr>
<tr>
<td>Purpose</td>
<td>The purpose of the study is to evaluate the therapeutic benefit of intratympanic AM-101 injections in comparison to placebo in the treatment of persistent acute inner ear tinnitus following acute sensorineural hearing loss.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>drug: AM-101</td>
</tr>
<tr>
<td>Phase</td>
<td>II</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Interventional; Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) - Primary Purpose: Treatment</td>
</tr>
<tr>
<td>Primary Outcome Measures</td>
<td>Change in the minimum masking level in dB from Baseline to Day 90 [Time Frame: 90 days] [Designated as safety issue: No]</td>
</tr>
<tr>
<td>Secondary Outcome Measures</td>
<td>- Standard audiological evaluations [Time Frame: 90 days] [Designated as safety issue: No]. Pure tone audiometry, tympanometry, otoscopy, tinnitus loudness match</td>
</tr>
<tr>
<td></td>
<td>- Questionnaires evaluating the impact of tinnitus [Time Frame: 90 days] [Designated as safety issue: No]</td>
</tr>
<tr>
<td></td>
<td>- Patient global impression of change scale, subjective tinnitus annoyance and loudness, tinnitus handicap questionnaire</td>
</tr>
<tr>
<td></td>
<td>- Pharmacokinetic measures [Time Frame: 3 days] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td>Expected total Enrollment</td>
<td>24</td>
</tr>
<tr>
<td>Study start</td>
<td>February 2011</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>December 2011 (Final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td></td>
<td>Placebo: Placebo Comparator Placebo Intervention: Drug: AM-101</td>
</tr>
</tbody>
</table>
### Assigned Interventions

| Drug: AM-101 | Single intratympanic injection or triple intratympanic injection |
| Drug: AM-101 | Single intratympanic injection or triple intratympanic injection |
| Drug: AM-101 | Single intratympanic injection or triple intratympanic injection |

### Participants (age)
- 18 Years to 65 Years

### Gender
- both

### Accepts health volunteers
- no

### Inclusion Criteria
- Tinnitus following acute acoustic trauma, idiopathic sudden sensorineural hearing loss, acute otitis media, middle ear surgery or inner ear barotrauma; with onset less than three months ago.

### Eligibility Exclusion Criteria
- Tinnitus that is not completely maskable
- Fluctuating tinnitus
- Intermittent tinnitus
- Meniere’s Disease
- Ongoing acute or chronic otitis media or otitis externa

### Contact
- Thomas Meyer, PhD, ear@aurismedical.com

### Locations
- Kansas University Medical Center, Kansas City, Kansas, United States, 66160

### Responsible Party
- Auris Medical Inc. (Thomas Meyer, PhD)

### Study ID Numbers
- AM-101-CL-10-02, AM-111-CL-10-02

### Last Updated
- February 8, 2011

### Record first received
- December 2010

### ClinicalTrials.gov Identifier
- NCT01270282

### Health Authority
- United States: Food and Drug Administration

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### Phase II Clinical Trial: D-Methionine to Reduce Noise-Induced Hearing Loss (NIHL)

| Current status | not yet open for participant recruitment |
| Sponsors and collaborators | Southern Illinois University; Department of Defense |
| Information provided by | Southern Illinois University |
| ClinicalTrials.gov Identifier | NCT01345474 |
| **Purpose** | This prospective study is a randomized, double-blind, placebo-controlled Phase II clinical Trial of oral D-met to reduce noise-induced hearing loss (NIHL) and tinnitus. The goal of the study is to develop a safe, oral pharmacological agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population is a cohort of Drill Sergeant (DS) instructor trainees during and 22 days after their 11 day weapons training. The primary objective of this study is to determine the efficacy of D-Met in preventing NIHL or reducing and tinnitus secondary to a minimum of 800 rounds of M-16 weapons training occurring over an 11 day period. |
| **Condition(s)** | Tinnitus |
| **Intervention(s)** | Drug: D-methionine, oral liquid suspension  
Other: Placebo Comparator |
| **Phase** | II |
| **Study type and design** | Interventional; Allocation: Randomized  
Endpoint Classification: Safety/Efficacy Study  
Intervention Model: Parallel Assignment  
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)  
Primary Purpose: Prevention |
| **Official Title** | Phase II Clinical Trial: D-Methionine to Reduce Noise-Induced Hearing Loss (NIHL) |
| **Primary Outcome Measures** | pure tone air conduction threshold [Time Frame: 22 days after cessation of weapons training] [Designated as safety issue: No]  
change from baseline in pure-tone thresholds as measured by absolute change and frequency of significant noise-induced threshold shift (STS) |
| **Secondary Outcome Measures** | - tinnitus scales [Time Frame: 22 days after cessation of weapons training] [Designated as safety issue: No]  
Tinnitus questionnaire report of change from baseline in scores for both loudness and annoyance  
- tympanic membrane function [Time Frame: 22 days after cessation of weapons training] [Designated as safety issue: No]  
tympanometry measurement report of change from baseline |
| **Expected total Enrollment** | 600 |
| **Study start** | September 2011 |
| **Estimated Study Completion Date** | August 2017 |
| **Estimated Primary Completion Date** | August 2016 (Final data collection date for primary outcome measure) |
| Arms | Placebo: Placebo Comparator  
Placebo contains sorbitol, orange flavor and purified water; is flavor and color matched to D-Met.  
Intervention: Other: Placebo Comparator  
D-methionine, oral liquid suspension: Experimental  
D-methionine liquid suspension also contains sorbitol, orange flavor and purified water  
Intervention: Drug: D-methionine, oral liquid suspension |
|---|---|
| Assigned Interventions | Other: Placebo Comparator  
Two daily doses of up to 100mg/kg/day of placebo for 18 days.  
Drug: D-methionine, oral liquid suspension  
Two daily doses of up to 100mg/kg/day of D-met for 18 days  
Other Name: D-Met |
| Detailed Description | Hearing loss can render a soldier less able to detect and identify the enemy, less able to understand commands, particularly in background noise typical on the battlefield, and may permanently reduce quality of life. In some cases, hearing loss may preclude redeployment or result in less optimal job assignment. Currently, no FDA approved pharmacological prevention exists for noise-induced hearing loss (NIHL). We have documented in animal studies that administration of D-methionine (D-met) can reduce or prevent NIHL. We now need to determine if it has similar efficacy in humans. Although we have not yet tested D-Met on protection from noise-induced tinnitus in animals, this clinical trial would provide us the opportunity to also test for protection from noise induced tinnitus simultaneously.  
Objective Hypotheses:  
Primary Hypothesis: Administration of oral D-methionine prior to, during and 4 days post-weapons training will reduce or prevent permanent noise-induced hearing loss.  
Secondary Hypothesis: Administration of oral D-methionine prior to, during and 4 days post-weapons training will reduce or prevent noise-induced tinnitus.  
Specific Aims:  
1. To determine whether administering oral D-met can prevent permanent NIHL after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday for first week, Monday-Thursday for second week), and 4 days after for a total of 18 days. Pure tone hearing thresholds will be assessed before and 22 days after completion of weapons training (ie: 18 days after the last day of study drug/placebo administration).  
2. To determine whether administering oral D-met can prevent tinnitus after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday for first week, Monday-Thursday for second week), and 4 days after for a total of 18 days. Tinnitus questionnaires will be assessed before and 22 days after completion of weapons training (ie; 18 days after the last day of study drug/placebo administration). |
3. To monitor for any potential side effects of D-met in human subjects. This aim will be accomplished by subject query on each day study drug is dispensed (twice daily) and at final study visit, routing of any adverse event reports to study medical personnel, statisticians and to the Food and Drug Administration (FDA).

<table>
<thead>
<tr>
<th>Participants (age)</th>
<th>21 Years to 40 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>both</td>
</tr>
<tr>
<td>Accepts health volunteers</td>
<td>yes</td>
</tr>
</tbody>
</table>

### Inclusion Criteria
- Negative pregnancy test at enrollment and prior to taking study drug; willing to use an effective method of birth control during the study (women of childbearing potential)
- Pure tone air conduction threshold average (PTA) at .5, 1 and 2 kHz of no greater than 40 dB HL bilaterally with no air bone gaps greater than 10 dB and normal otoscopy and tympanometry screens
- Ability to comply with all study requirements
- Negative pregnancy test at enrollment and willing to use an effective method of birth control (women of childbearing potential)

### Eligibility Exclusion Criteria
- Pure tone air conduction threshold average (PTA) at .5, 1 and 2 kHz of no greater than 40 dB HL bilaterally with no air bone gaps greater than 10 dB and normal otoscopy and tympanometry screens
- Inability to comply with all study requirements
- Abnormal tympanograms or other indication of middle-ear abnormality
- History of fluctuant hearing or asymmetric hearing worse than 25 dB at any test frequency
- Perilymphatic fistula
- Tumor of the auditory system
- Head injury or other CNS disorder that is likely to affect hearing
- Exposure within the previous 6 months to systemic ototoxic substances including aminoglycoside or macrolide antibiotics, or chemotherapy with carboplatin, cisplatin, vincristine, vinblastine, or difluoromethylornithine
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug
- Recent history of (within 12 months of screening) alcohol or substance abuse
- Women of childbearing age who are not using effective contraceptive methods and who may become pregnant during the course of the study
- Women who are pregnant or breastfeeding

### Contact
Kathleen CM Campbell, PhD, 217-545-7310, kcampbell@siumed.edu
Karen Hinz, RN, BS, 217-545-7579, khinz@siumed.edu

### Locations
US Army Basic Combat Training Center of Excellence, Fort Jackson, North Carolina, United States
<table>
<thead>
<tr>
<th><strong>Responsible Party</strong></th>
<th>Southern Illinois University School of Medicine (Kathleen CM Campbell, CCC-A, PhD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator</strong></td>
<td>Kathleen CM Campbell, CCC-A, PhD, Southern Illinois University School of Medicine</td>
</tr>
<tr>
<td><strong>Study Chair</strong></td>
<td>Jillyen E Curry-Mathis, Captain, AuD, MS, United States Department of Defense, US Army Ft. Jackson</td>
</tr>
<tr>
<td><strong>Study Director</strong></td>
<td>Leonard Rybak, MD, PhD, Southern Illinois University School of Medicine</td>
</tr>
<tr>
<td><strong>Study ID Numbers</strong></td>
<td>CAM-SIU-11-002</td>
</tr>
<tr>
<td><strong>Last Updated</strong></td>
<td>April 29, 2011</td>
</tr>
<tr>
<td><strong>Record first received</strong></td>
<td>April 27, 2011</td>
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<tr>
<td><strong>ClinicalTrials.gov Identifier</strong></td>
<td>NCT01345474</td>
</tr>
<tr>
<td><strong>Health Authority</strong></td>
<td>United States: Institutional Review Board; United States: US Army Medical Research and Materiel Command</td>
</tr>
</tbody>
</table>