

RESEARCH HIGHLIGHTS December 2011

Sedley W, Teki S, Kumar S, Overath T, Barnes GR, Griffiths TD. Gamma band pitch responses in human auditory cortex measured with magnetoencephalography. Neuroimage. 2011 Sep 8. [Epub ahead of print]. Auditory Group, Institute of Neuroscience, Newcastle University Medical School, Newcastle Upon Tyne, Tyne and Wear, NE2 4HH UK.

This study demonstrates that magnetoencephalography can be used in a comparable way for assessing pitch responses like recordings via implanted electrodes.

Brozoski TJ, Wisner KW, Sybert LT, Bauer CA. Bilateral Dorsal Cochlear Nucleus Lesions Prevent Acoustic-Trauma Induced Tinnitus in an Animal Model. J Assoc Res Otolaryngol. 2011 Oct 4. [Epub ahead of print]

By demonstrating that bilateral lesions of the dorsal cochlear nucleus (DCN) prevent acoustic trauma induced tinnitus, this study sheds further light on the role of the DCN in the pathophysiology of tinnitus.

Schaette R, McAlpine D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. J Neurosci. 2011 Sep 21;31(38):13452-7. University College London Ear Institute, London WC1X 8EE, United Kingdom.

This study demonstrates abnormal activity in the auditory nerve in tinnitus patients with normal hearing thresholds. This indicates that damage to the cochlea is not always reflected by threshold shifts. Furthermore this study shows that the abnormal input leads to a compensatory increase of central gain in the brainstem and that a computational model that is based on mechanisms of homeostatic plasticity can predict these compensatory changes.

Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, Myers PJ, Newman CW, Sandridge S, Turk DC, Folmer RL, Frederick EJ, House JW, Jacobson GP, Kinney SE, Martin WH, Nagler SM, Reich GE, Searchfield G, Sweetow R, Vernon JA. The Tinnitus Functional Index: Development of a New Clinical Measure for Chronic, Intrusive Tinnitus. Ear Hear. 2011 Dec 12. [Epub ahead of print]. ¹Oregon Health & Science University, Portland, Oregon; ²VA National Center for Rehabilitative Auditory Research, Portland, Oregon; ³Bay Pines VA Healthcare System, Bay Pines, Florida; ⁴James A. Haley Veterans' Hospital, Tampa, Florida; ⁵Cleveland Clinic, Cleveland, Ohio; ⁶University of Washington, Seattle, Washington; ⁷Balance and Hearing Center Northwest, Portland, Oregon; ⁸The House Ear Institute, Los Angeles, California; ⁹Vanderbilt University, Nashville, Tennessee; ¹⁰Atlanta Medical Consultants, Atlanta, Georgia; ¹¹University of Auckland, Auckland, New Zealand; and ¹²University of California at San Francisco, San Francisco, California.

The Tinnitus Functional Index is the first tinnitus questionnaire that has been especially developed and validated for detecting changes of tinnitus severity by treatment interventions.

(articles of authors who are funded by TRI are marked in blue)

Gamma band pitch responses in human auditory cortex measured with magnetoencephalography.

Neuroimage. 2011 Sep 8. [Epub ahead of print]

Sedley W, Teki S, Kumar S, Overath T, Barnes GR, Griffiths TD.

Auditory Group, Institute of Neuroscience, Newcastle University Medical School, Newcastle Upon Tyne, Tyne and Wear, NE2 4HH UK.

We have previously used direct electrode recordings in two human subjects to identify neural correlates of the perception of pitch (Griffiths, Kumar, Sedley et al., Direct recordings of pitch responses from human auditory cortex, Curr. Biol. 22 (2010), pp. 1128-1132). The present study was carried out to assess virtual-electrode measures of pitch perception based on non-invasive magnetoencephalography (MEG). We recorded pitch responses in 13 healthy volunteers using a passive listening paradigm and the same pitch-evoking stimuli (regular interval noise; RIN) as in the previous study. Source activity was



reconstructed using a beamformer approach, which was used to place virtual electrodes in auditory cortex. Time-frequency decomposition of these data revealed oscillatory responses to pitch in the gamma frequency band to occur, in Heschl's gyrus, from 60Hz upwards. Direct comparison of these pitch responses to the previous depth electrode recordings shows a striking congruence in terms of spectrotemporal profile and anatomical distribution. These findings provide further support that auditory high gamma oscillations occur in association with RIN pitch stimuli, and validate the use of MEG to assess neural correlates of normal and abnormal pitch perception. Copyright © 2011 Elsevier Inc. All rights reserved.

Bilateral Dorsal Cochlear Nucleus Lesions Prevent Acoustic-Trauma Induced Tinnitus in an Animal Model.

J Assoc Res Otolaryngol. 2011 Oct 4. [Epub ahead of print]

Brozoski TJ, Wisner KW, Sybert LT, Bauer CA.

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Animal experiments suggest that chronic tinnitus („ringing in the ears“) may result from processes that overcompensate for lost afferent input. Abnormally elevated spontaneous neural activity has been found in the dorsal cochlear nucleus (DCN) of animals with psychophysical evidence of tinnitus. However, it has also been reported that DCN ablation fails to reduce established tinnitus. Since other auditory areas have been implicated in tinnitus, the role of the DCN is unresolved. The apparently conflicting electrophysiological and lesion data can be reconciled if the DCN serves as a necessary trigger zone rather than a chronic generator of tinnitus. The present experiment used lesion procedures identical to those that failed to decrease pre-existing tinnitus. The exception was that lesions were done prior to tinnitus induction. Young adult rats were trained and tested using a psychophysical procedure shown to detect tinnitus. Tinnitus was induced by a single unilateral high-level noise exposure. Consistent with the trigger hypothesis, bilateral dorsal DCN lesions made before high-level noise exposure prevented the development of tinnitus. A protective effect stemming from disruption of the afferent pathway could not explain the outcome because unilateral lesions ipsilateral to the noise exposure did not prevent tinnitus and unilateral lesions contralateral to the noise exposure actually exacerbated the tinnitus. The DCN trigger mechanism may involve plastic circuits that, through loss of inhibition, or upregulation of excitation, increase spontaneous neural output to rostral areas such as the inferior colliculus. The increased drive could produce persistent pathological changes in the rostral areas, such as high-frequency bursting and decreased interspike variance, that comprise the chronic tinnitus signal.

Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model.

J Neurosci. 2011 Sep 21;31(38):13452-7.

Schaette R, McAlpine D.

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Ever since Pliny the Elder coined the term tinnitus, the perception of sound in the absence of an external sound source has remained enigmatic. Traditional theories assume that tinnitus is triggered by cochlear damage, but many tinnitus patients present with a normal audiogram, i.e., with no direct signs of cochlear damage. Here, we report that in human subjects with tinnitus and a normal audiogram, auditory brainstem responses show a significantly reduced amplitude of the wave I potential (generated by primary auditory nerve fibers) but normal amplitudes of the more centrally generated wave V. This provides direct physiological evidence of „hidden hearing loss“ that manifests as reduced neural output from the cochlea, and consequent renormalization of neuronal response magnitude within the brainstem. Employing an established computational model, we demonstrate how tinnitus could arise from a homeostatic response of neurons in the central auditory system to reduced auditory nerve input in the absence of elevated hearing thresholds.

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The Tinnitus Functional Index: Development of a New Clinical Measure for Chronic, Intrusive Tinnitus.

Ear Hear. 2011 Dec 12. [Epub ahead of print]

Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, Myers PJ, Newman CW, Sandridge S, Turk DC, Folmer RL, Frederick EJ, House JW, Jacobson GP, Kinney SE, Martin WH, Nagler SM, Reich GE, Searchfield G, Sweetow R, Vernon JA.

¹Oregon Health & Science University, Portland, Oregon; ²VA National Center for Rehabilitative Auditory Research, Portland, Oregon; ³Bay Pines VA Healthcare System, Bay Pines, Florida; ⁴James A. Haley Veterans' Hospital, Tampa, Florida; ⁵Cleveland Clinic, Cleveland, Ohio; ⁶University of Washington, Seattle, Washington; ⁷Balance and Hearing Center Northwest, Portland, Oregon; ⁸The House Ear Institute, Los Angeles, California; ⁹Vanderbilt University, Nashville, Tennessee; ¹⁰Atlanta Medical Consultants, Atlanta, Georgia; ¹¹University of Auckland, Auckland, New Zealand; and ¹²University of California at San Francisco, San Francisco, California.

OBJECTIVES: Chronic subjective tinnitus is a prevalent condition that causes significant distress to millions of Americans. Effective tinnitus treatments are urgently needed, but evaluating them is hampered by the lack of standardized measures that are validated for both intake assessment and evaluation of treatment outcomes. This work was designed to develop a new self-report questionnaire, the Tinnitus Functional Index (TFI), that would have documented validity both for scaling the severity and negative impact of tinnitus for use in intake assessment and for measuring treatment-related changes in tinnitus (responsiveness) and that would provide comprehensive coverage of multiple tinnitus severity domains. **DESIGN:** To use preexisting knowledge concerning tinnitus-related problems, an Item Selection Panel (17 expert judges) surveyed the content (175 items) of nine widely used tinnitus questionnaires. From those items, the Panel identified 13 separate domains of tinnitus distress and selected 70 items most likely to be responsive to treatment effects. Eliminating redundant items while retaining good content validity and adding new items to achieve the recommended minimum of 3 to 4 items per domain yielded 43 items, which were then used for constructing TFI Prototype 1. Prototype 1 was tested at five clinics. The 326 participants included consecutive patients receiving tinnitus treatment who provided informed consent-constituting a convenience sample. Construct validity of Prototype 1 as an outcome measure was evaluated by measuring responsiveness of the overall scale and its individual items at 3 and 6 mo follow-up with 65 and 42 participants, respectively. Using a predetermined list of criteria, the 30 best-functioning items were selected for constructing TFI Prototype 2. Prototype 2 was tested at four clinics with 347 participants, including 155 and 86 who provided 3 and 6 mo follow-up data, respectively. Analyses were the same as for Prototype 1. Results were used to select the 25 best-functioning items for the final TFI.

RESULTS: Both prototypes and the final TFI displayed strong measurement properties, with few missing data, high validity for scaling of tinnitus severity, and good reliability. All TFI versions exhibited the same eight factors characterizing tinnitus severity and negative impact. Responsiveness, evaluated by computing effect sizes for responses at follow-up, was satisfactory in all TFI versions. In the final TFI, Cronbach's alpha was 0.97 and test-retest reliability 0.78. Convergent validity ($r = 0.86$ with Tinnitus Handicap Inventory [THI]; $r = 0.75$ with Visual Analog Scale [VAS]) and discriminant validity ($r = 0.56$ with Beck Depression Inventory-Primary Care [BDI-PC]) were good. The final TFI was successful at detecting improvement from the initial clinic visit to 3 mo with moderate to large effect sizes and from initial to 6 mo with large effect sizes. Effect sizes for the TFI were generally larger than those obtained for the VAS and THI. After careful evaluation, a 13-point reduction was considered a preliminary criterion for meaningful reduction in TFI outcome scores.

CONCLUSIONS: The TFI should be useful in both clinical and research settings because of its responsiveness to treatment-related change, validity for scaling the overall severity of tinnitus, and comprehensive coverage of multiple domains of tinnitus severity.

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RESEARCH HIGHLIGHTS September 2011

Yang S, Weiner BD, Zhang LS, Cho SJ, Bao S. Homeostatic plasticity drives tinnitus perception in an animal model. Proc Natl Acad Sci U S A. 2011 Sep 6;108(36):14974-9. Epub 2011 Sep 6. This animal study demonstrates that hearing lesions cause specific changes in synaptic transmission in the auditory cortex with a decreased inhibitory function in the sensory deprived region and increased inhibitory and excitatory function in the nondeprived area. The reduced inhibition of the sensory deprived area is interpreted as consequence of homeostatic plasticity. Important consequences of these findings are that the reorganisation of the cortical map may not be pathological, but rather compensatory and that therapeutic efforts should aim at strengthening the deficient inhibition of the deprived area either by specific pharmacotherapy or by bringing information to the deprived region.

Van der Loo E, Congedo M, Vanneste S, De Heyning PV, De Ridder D. Insular lateralization in tinnitus distress. Auton Neurosci. 2011 Sep 1. [Epub ahead of print]. This study addresses the relevance of the autonomic nervous system for tinnitus distress and proposes an important role for the right anterior insula in mediating this effect

Larson PS, Cheung SW. Deep brain stimulation in area LC controllably triggers auditory phantom percepts. Neurosurgery. 2011 Aug 12. [Epub ahead of print]. By demonstrating that auditory perception can be modulated by deep brain stimulation in the caudate nucleus, this study highlights the gating role of the dorsal striatum for auditory information to reach perceptual awareness

(articles of authors who are funded by TRI are marked in blue)

Homeostatic plasticity drives tinnitus perception in an animal model.
Proc Natl Acad Sci U S A. 2011 Sep 6;108(36):14974-9. Epub 2011 Sep 6.

Yang S, Weiner BD, Zhang LS, Cho SJ, Bao S.

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Hearing loss often results in tinnitus and auditory cortical map changes, leading to the prevailing view that the phantom perception is associated with cortical reorganization. However, we show here that tinnitus is mediated by a cortical area lacking map reorganization. High-frequency hearing loss results in two distinct cortical regions: a sensory-deprived region characterized by a decrease in inhibitory synaptic transmission and a normal hearing region showing increases in inhibitory and excitatory transmission and map reorganization. Hearing-lesioned animals displayed tinnitus with a pitch in the hearing loss range. Furthermore, drugs that enhance inhibition, but not those that reduce excitation, reversibly eliminated the tinnitus behavior. These results suggest that sensory deprivation-induced homeostatic down-regulation of inhibitory synapses may contribute to tinnitus perception. Enhancing sensory input through map reorganization may plausibly alleviate phantom sensation.

Insular lateralization in tinnitus distress.
Auton Neurosci. 2011 Sep 1. [Epub ahead of print]

Van der Loo E, Congedo M, Vanneste S, De Heyning PV, De Ridder D.

BRAI²N & Department of Neurosurgery, University Hospital Antwerp, Belgium.

Tinnitus affects 15% of the population. Of these 1-2% are severely disabled by it. The role of the autonomic system in tinnitus is hardly being investigated. The aim of this study is to investigate the relationship between tinnitus distress and lateralization of the anterior insula, known to be involved in interoceptive awareness and (para)sympathetic changes. For this, Tinnitus Questionnaire scores are correlated to Heart Rate Variability markers, and related to neural activity in left and right anterior insula.



Our results show that tinnitus distress is related to sympathetic activation, in part mediated via the right anterior insula. Copyright © 2011 Elsevier B.V. All rights reserved.

Deep brain stimulation in area LC controllably triggers auditory phantom percepts.

Neurosurgery. 2011 Aug 12. [Epub ahead of print]

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BACKGROUND: Tinnitus is predominantly viewed as the consequence of dysfunctional hyperactivity, plastic change or synchronized oscillations in the central auditory system. An alternative to the current auditory-centric view of auditory phantom perception is the basal ganglia-centric view. Recent electrical stimulation experiments in area LC, a locus of the caudate nucleus positioned at its anterior body, has shown loudness modulation of existing tinnitus percepts.

OBJECTIVE: To demonstrate auditory phantoms are gated by the dorsal striatum.

METHODS: Electrical stimulation in area LC through a DBS lead was performed in 6 interactive adult subjects (3 with and 3 without chronic tinnitus) undergoing surgery to treat movement disorders. Tinnitus loudness was rated on a 0 to 10 scale, sound quality was described and localization was referenced to one or both ears.

RESULTS: Short-term area LC stimulation triggered new phantom tones, clicks, and frequency modulated sounds in 5 subjects, and altered sound quality of an existing tinnitus in 1 subject. Results from this study indicate that perceptual awareness of auditory phantoms is contingent on satisfying a permission condition controlled by the dorsal striatum. Potential auditory phantoms are not automatically gated to reach perceptual awareness. A phantom percept gate control model is proposed.

CONCLUSION: Neuromodulation of area LC can trigger temporary gate dysfunction and reversibly release new phantoms for conscious awareness. Restoration of restrictive dorsal striatal gate function to treat problematic phantom percepts may be realized by adopting long-term area LC neuromodulation and choosing optimal stimulation parameters.

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Gouveris H, Schuler-Schmidt W, Mewes T, Mann W. Intratympanic Dexamethasone/Hyaluronic Acid Mix as an Adjunct to Intravenous Steroid and Vasoactive Treatment in Patients With Severe Idiopathic Sudden Sensorineural Hearing Loss. Otol Neurotol. 2011 Jun 3;

Wu HP, Chou YF, Yu SH, Wang CP, Hsu CJ, Chen PR. Intratympanic Steroid Injections as a Salvage Treatment for Sudden Sensorineural Hearing Loss: A Randomized, Double-Blind, Placebo-Controlled Study. Otol Neurotol. 2011 Jun 3;

Lee JB, Choi SJ, Park K, Park HY, Choo OS, Choung YH. The efficiency of intratympanic dexamethasone injection as a sequential treatment after initial systemic steroid therapy for sudden sensorineural hearing loss. Eur Arch Otorhinolaryngol. 2011 Jun;268(6):833-9
These three studies demonstrate the efficacy of intratympanic steroid therapy as add-on resp. salvage therapy in addition to systemic steroids in the treatment of sudden hearing loss.

Mulders WH, Robertson D. Progressive centralization of midbrain hyperactivity after acoustic trauma. Neuroscience. 2011 Jun 24. [Epub ahead of print]
This animal study highlights the relevance of temporal dynamics in the development of tinnitus. Whereas in the early phase increased activity in the central auditory pathways depends on auditory input, this is not any more the case at a later stage.

Figueiredo RR, Azevedo AA, Oliveira PM, Amorim SP, Rios AG, Baptista V. Incidence of tinnitus in mp3 player users. [Article in English, Portuguese]. Braz J Otorhinolaryngol. 2011 Jun;77(3):293-8.
By demonstrating an increased risk of tinnitus among mp3 users, this study highlights the relevance of prevention.

Wu C, Gopal K, Gross GW, Lukas TJ, Moore EJ. An in vitro model for testing drugs to treat tinnitus. Eur J Pharmacol. 2011 Jun 2. [Epub ahead of print]
This study proposes an in-vitro model to screen pharmaceutical compounds for the treatment of tinnitus. If this model turns out to be a valid predictor for clinical effects, it will open new dimensions in the search for a tinnitus drug.

Weisz N, Hartmann T, Müller N, Lorenz I, Obleser J. Alpha rhythms in audition: cognitive and clinical perspectives. Front Psychol. 2011;2:73. Epub 2011 Apr 26.
In this review the relevance of alpha oscillations for the pathophysiology of tinnitus is discussed in a larger context.

Vogler DP, Robertson D, Mulders WH. Hyperactivity in the ventral cochlear nucleus after cochlear trauma. J Neurosci. 2011 May 4;31(18):6639-45.
This animal study highlights the involvement of the ventral cochlear nucleus in the pathophysiology of tinnitus.

Okamoto H, Stracke H, Bermudez P, Pantev C. Sound Processing Hierarchy within Human Auditory Cortex. J Cogn Neurosci. 2011 Aug;23(8):1855-63. Epub 2010 Jun 3.
In this magnetencephalographic study the authors were able to differentiate the neuronal correlates of bottom-up and top-down processing in the auditory system.

Hoare DJ, Kowalkowski VL, Kang S, Hall DA. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. Laryngoscope. 2011 Jul;121(7):1555-64. doi: 10.1002/lary.21825 . Epub 2011 Jun 10.
Here the levels of evidence of generally recommended strategies of tinnitus management were reviewed.



Intratympanic Dexamethasone/Hyaluronic Acid Mix as an Adjunct to Intravenous Steroid and Vasoactive Treatment in Patients With Severe Idiopathic Sudden Sensorineural Hearing Loss.
Otol Neurotol. 2011 Jun 3.

Gouveris H, Schuler-Schmidt W, Mewes T, Mann W.

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OBJECTIVE: To evaluate differences in effectiveness (hearing recovery rates) between idiopathic sudden sensorineural hearing loss (ISSNHL) patients treated with intravenous therapy alone and patients treated with a combination of intravenous and intratympanic therapy. **STUDY DESIGN:** Retrospective case review. **SETTING:** Tertiary referral hospital center. **PATIENTS AND INTERVENTIONS:** Ninety-four patients with moderate ISSNHL treated with an intravenous steroid and vasoactive regimen (duration of therapy, 9 ± 2.76 d) and 76 patients with severe ISSNHL treated with a combination regimen of intravenous and intratympanic therapy (duration of therapy, 10 ± 2.71 d) were reviewed. In the latter patients' group, a series of 3 intratympanic injections of a dexamethasone/hyaluronic acid mix solution were applied every 2 days. **MAIN OUTCOME MEASURE:** Pure-tone audiometric thresholds at 0.5, 1, 2, 4, and 8 kHz were compared between groups using the Wilcoxon test. **RESULTS:** Combination therapy in severe ISSNHL did not show any statistically significant difference in effectiveness to intravenous therapy in moderate ISSNHL ($p > 0.05$). **CONCLUSION:** In patients with severe ISSNHL, starting intratympanic steroid therapy as an adjunct early in the course of intravenous steroid and vasoactive therapy improves hearing to a level which is obtained in patients with less severe (moderate) ISSNHL treated with intravenous therapy alone.

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Intratympanic Steroid Injections as a Salvage Treatment for Sudden Sensorineural Hearing Loss: A Randomized, Double-Blind, Placebo-Controlled Study.
Otol Neurotol. 2011 Jun 3.

Wu HP, Chou YF, Yu SH, Wang CP, Hsu CJ, Chen PR.

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OBJECTIVE: The purpose of this study was to determine, through a randomized, double-blind, placebo-controlled trial, whether intratympanic steroid injections (ITSIs) could improve hearing recovery in patients with sudden sensorineural hearing loss (SSHL) who did not respond to initial systemic steroid therapy. **STUDY DESIGN:** This was a prospective, randomized, double-blind, placebo-controlled study. **SETTING:** The study was conducted in 2 tertiary referral centers. **PATIENTS:** A total of 60 patients with idiopathic SSHL who did not respond to an initial round of systemic steroid therapy were included in this study. The subjects were randomized into an ITSI group and an intratympanic normal saline injection (ITNI) group, which were matched by age and sex. A total of 55 subjects completed the study. **INTERVENTION:** Participants received either ITSIs or ITNIs. Both groups received 4 injections within a 2-week period. **MAIN OUTCOME MEASURES:** Pure-tone thresholds were compared between the 2 groups 1 month after injection therapy. **RESULTS:** In the ITNI group, the pure-tone threshold was 69.9 ± 18.5 dB before intratympanic injection therapy. After therapy, the hearing threshold improved by an average of 4.5 ± 6.5 dB, and 10.7% of subjects improved by 10 dB or more. In the ITSI group, the pure-tone threshold was 64.6 ± 17.7 dB before intratympanic injection therapy. After the therapy, the hearing threshold improved by an average of 9.8 ± 8.5 dB, and 44.4% of subjects improved by 10 dB or more.



Both the response rate and the level of hearing improvement were significantly greater in the ITSI group than in the ITNI group. **CONCLUSION:** These results demonstrate that ITSIs are beneficial as a salvage therapy for the treatment of patients with idiopathic SSHL who fail to respond to initial systemic steroid therapy.

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The efficiency of intratympanic dexamethasone injection as a sequential treatment after initial systemic steroid therapy for sudden sensorineural hearing loss.

Eur Arch Otorhinolaryngol. 2011 Jun;268(6):833-9.

Lee JB, Choi SJ, Park K, Park HY, Choo OS, Choung YH.

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The effect of intratympanic steroid injection is controversial as salvage or initial treatment option for sudden sensorineural hearing loss (SSNHL) and almost unknown if it is consecutively to use after initial systemic steroids. This study aimed to analyze the efficiency of intratympanic dexamethasone injection (ITDI) as a sequential treatment in the patients who failed initial systemic steroid treatments for SSNHL. Forty-six patients with SSNHL who did not respond to initial systemic steroids were prospectively included in the study. The patients were randomly classified into two groups; the ITDI group (21 patients) did not take four sequential ITDI within 2 weeks after systemic steroids, and the control group (25 patients) took any more medications. Hearing improvement was defined as a 10 dB or more decrease in the pure tone average (PTA) of the four-frequencies (0.5, 1, 2, and 3 kHz). Hearing improvement was observed in 10 (47.6%) of 21 ITDI patients and in 4 (16.0%) of 25 control patients ($P = 0.027$). An improvement of the mean PTA was 11.4 dB in the ITDI group and 1.7 dB in the control group ($P = 0.004$). The ITDI group showed significant hearing improvement at low frequency (500 Hz) than the control group. The patients with 70 or more dB in PTA before ITDI showed significant hearing improvement than the other patients with better PTAs ($P = 0.038$). The sequential ITDI, which is performed immediately after initial systemic steroid therapy, may be a simple, effective second-line treatment of choice for the patients who show poor response to initial treatments for SSNHL.

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Progressive centralization of midbrain hyperactivity after acoustic trauma.

Neuroscience. 2011 Jun 24. [Epub ahead of print]

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Partial hearing loss is known to cause increased spontaneous activity at several stages of the central auditory pathways, and this phenomenon has been suggested as a possible neural substrate for tinnitus, a phantom hearing sensation. One recent study in guinea pig has suggested that approximately 6 weeks after acoustic trauma, the increased spontaneous activity in inferior colliculus is not intrinsically generated in the central nucleus but is dependent on afferent input from the cochlea. This was unexpected in view of the fact that tinnitus in human patients can persist after severing of the auditory nerve. In this study, we show that when recovery time after acoustic trauma is extended to 8 and 12 weeks, cochlear ablation does not significantly decrease the increased spontaneous activity measured in the inferior colliculus. This result demonstrates for the first time that central hyperactivity that develops after acoustic trauma transitions from an early stage when it is dependent on continued peripheral afferent input to a later stage in which the hyperactivity is intrinsically generated within the central nervous system. Copyright © 2011. Published by Elsevier Ltd.

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Incidence of tinnitus in mp3 player users.

[Article in English, Portuguese]

Braz J Otorhinolaryngol. 2011 Jun;77(3):293-8.

Figueiredo RR, Azevedo AA, Oliveira PM, Amorim SP, Rios AG, Baptista V.

area of concentration - ENT, Rio de Janeiro Federal University.

Exposure to loud noise is one of the main causes of tinnitus. AIM: To analyze the incidence of tinnitus in mp3 player users and non-users. MATERIAL AND METHOD: One hundred subjects aged from 15 to 30 years were enrolled, 54 of them were regular mp3 player users and 46 were not. Patients with continuous tinnitus for at least 6 months completed the Tinnitus Handicap Inventory (THI) and were tested with high frequency audiometry and transient-evoked otoacoustic emissions (TAOE). STUDY DESIGN: A cross-sectional cohort study. RESULTS: The incidence of tinnitus in non-users was about 8 %; in mp3 player users it was about 28 %, a statistically significant difference. Hearing thresholds at 8kHz were significantly higher in tinnitus patients that used mp3 portable players. TAOE were reduced at 2 kHz in the users group. No statistically significant difference was found in the THI scores between the two groups. CONCLUSION: Tinnitus was more frequent in teenagers and young adults who regularly listen to mp3 music in players. Moreover, the incidence of tinnitus among mp3 player users was associated with higher hearing thresholds at 8 kHz and lower TOAE at 2 kHz.

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An in vitro model for testing drugs to treat tinnitus.

Eur J Pharmacol. 2011 Jun 2. [Epub ahead of print]

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Tinnitus affects approximately 50million people in the USA alone, with 10million being highly debilitated. Pharmacotherapy for tinnitus is still in emerging stages due to time consuming clinical trials and/or animal experiments. We tested a new cellular model where induced rapid neuronal firing or spiking was used as a mimic for the type of aberrant activity that may occur in tinnitus. Spontaneously active auditory cortical networks growing on microelectrode arrays were exposed to pentylenetetrazol (PTZ), a proconvulsant and an antagonist of GABA(A) receptor, which is implicated in tinnitus. Auditory cortical networks were then exposed to experimental tinnitus drugs linopirdine (Dup966, a potassium channel blocker), l-carnitine (an antioxidant), or selective Ca(2+) channel antagonists pregabalin (Lyrica), or gabapentin (Neurontin) at various concentrations. PTZ increased spike rate by 139.6±27% and burst rate by 129.7±28% in auditory cortical networks with a phenotypic high firing of excitable neurons. Reductions of increased activity were observed to varying degrees using the experimental tinnitus drugs. The potency of the drugs was linopirdine (EC(50): 176±7.0µM)>l-carnitine (EC(50): 1569±41µM)>pregabalin (EC(50): 8360±340µM), >gabapentin, with 34.2±7.5% efficacy (EC(50): 2092±980µM). These studies provide proof of principle for the use of auditory cortical networks on microelectrode array as a feasible platform for semi-high throughput application for screening of drugs that might be used for the treatment of tinnitus. Copyright © 2011 Elsevier B.V. All rights reserved.

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Alpha rhythms in audition: cognitive and clinical perspectives.

Front Psychol. 2011;2:73. Epub 2011 Apr 26.

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Like the visual and the sensorimotor systems, the auditory system exhibits pronounced alpha-like resting oscillatory activity. Due to the relatively small spatial extent of auditory cortical areas, this rhythmic activity is less obvious and frequently masked by non-auditory alpha-generators when recording non-invasively using magnetoencephalography (MEG) or electroencephalography (EEG). Following stimulation with sounds, marked desynchronizations can be observed between 6 and 12 Hz, which can be localized to the auditory cortex. However knowledge about the functional relevance of the auditory alpha rhythm has remained scarce so far. Results from the visual and sensorimotor system have fuelled the hypothesis of alpha activity reflecting a state of functional inhibition. The current article pursues several intentions: (1) Firstly we review and present own evidence (MEG, EEG, sEEG) for the existence of an auditory alpha-like rhythm independent of visual or motor generators, something that is occasionally met with skepticism. (2) In a second part we will discuss tinnitus and how this audiological symptom may relate to reduced background alpha. The clinical part will give an introduction into a method which aims to modulate neurophysiological activity hypothesized to underlie this distressing disorder. Using neurofeedback, one is able to directly target relevant oscillatory activity. Preliminary data point to a high potential of this approach for treating tinnitus. (3) Finally, in a cognitive neuroscientific part we will show that auditory alpha is modulated by anticipation/expectations with and without auditory stimulation. We will also introduce ideas and initial evidence that alpha oscillations are involved in the most complex capability of the auditory system, namely speech perception. The evidence presented in this article corroborates findings from other modalities, indicating that alpha-like activity functionally has an universal inhibitory role across sensory modalities.

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Hyperactivity in the ventral cochlear nucleus after cochlear trauma.

J Neurosci. 2011 May 4;31(18):6639-45.

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The emergence of hyperactivity in the form of elevated spontaneous firing rates after cochlear trauma has been well documented in a number of central auditory structures, including the auditory cortex, inferior colliculus, and dorsal subdivision of the cochlear nucleus. This hyperactivity is of interest as a possible neural substrate of tinnitus. Whether the ventral subdivision of the cochlear nucleus shows hyperactivity has never been investigated despite the fact that, like the dorsal division, it also receives direct input from the damaged cochlea and supplies major ascending inputs to brainstem and midbrain auditory centers. We investigated spontaneous neuronal firing rates in the ventral cochlear nucleus in a guinea pig model of cochlear trauma in which we have shown that hyperactivity consistently develops in the inferior colliculus (Mulders and Robertson, 2009). The mean spontaneous firing rates of ventral cochlear nucleus neurons was significantly elevated compared to sham controls. This hyperactivity was more evident in primary-like and onset categories of neurons. Hyperactivity in the ventral subdivision of cochlear nucleus therefore needs to be considered in relation to neural models of the genesis of tinnitus.

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Sound Processing Hierarchy within Human Auditory Cortex.

J Cogn Neurosci. 2011 Aug;23(8):1855-63. Epub 2010 Jun 3.

Okamoto H, Stracke H, Bermudez P, Pantev C.

University of Muenster, Germany.

Both attention and masking sounds can alter auditory neural processes and affect auditory signal perception. In the present study, we investigated the complex effects of auditory-focused attention and the signal-to-noise ratio of sound stimuli on three different auditory evoked field components (auditory steady-state response, N1m, and sustained field) by means of magnetoencephalography. The results indicate that the auditory steady-state response originating in primary auditory cortex reflects the signal-to-noise ratio of physical sound inputs (bottom-up process) rather than the listener's attentional state (top-down process), whereas the sustained field, originating in nonprimary auditory cortex, reflects the attentional state rather than the signal-to-noise ratio. The N1m was substantially influenced by both bottom-up and top-down neural processes. The differential sensitivity of the components to bottom-up and top-down neural processes, contingent on their level in the processing pathway, suggests a stream from bottom-up driven sensory neural processing to top-down driven auditory perception within human auditory cortex.

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Systematic review and meta-analyses of randomized controlled trials examining tinnitus management.

Laryngoscope. 2011 Jul;121(7):1555-64. doi: 10.1002/lary.21825 . Epub 2011 Jun 10.

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SourceNational Institute for Health Research National Biomedical Research Unit in Hearing, Nottingham; School of Clinical Sciences, The University of Nottingham, Nottingham. derek.hoare@nottingham.ac.uk.

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 behavioral therapy were numerous and similar enough to perform meta-analysis, from which the efficacy of cognitive behavioral 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 tinnitus retraining therapy needs to be performed. Copyright © 2011 The American Laryngological, Rhinological, and Otological Society, Inc.

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Bernhardt O, Mundt T, Welk A, Köppl N, Kocher T, Meyer G, Schwahn C. Signs and symptoms of temporomandibular disorders and the incidence of tinnitus. J Oral Rehabil. 2011 Apr 23. doi: 10.1111/j.1365-2842.2011.02224.x. [Epub ahead of print]

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 somatosensory input in the etiology of tinnitus.

De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: Tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci U S A. 2011 Apr 18. [Epub ahead of print].

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.

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

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 evidence of tinnitus.

Zhou X, Henin S, Long GR, Parra LC. Impaired cochlear function correlates with the presence of tinnitus and its estimated spectral profile. Hear Res. 2011 Mar 2. [Epub ahead of print].

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 treatment induced 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-auditory 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 into 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 covariates 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 covariated 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, Vanhauzenhuysse 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 parahypocampal 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.



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.

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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.

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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.

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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.

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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 ($r = 0.83 \pm 0.09$, $N = 19$). 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

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

J Oral Rehabil. 2011 Apr 23. doi: 10.1111/j.1365-2842.2011.02224.x. [Epub ahead of print]

Bernhardt O, Mundt T, Welk A, Köppl N, Kocher T, Meyer G, Schwahn C.

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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.

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RESEARCH HIGHLIGHTS January 2011

Kaltenbach JA. Tinnitus: Models and mechanisms. Hear Res. 2010 [Epub ahead of print]. A comprehensive review covering the cellular and molecular mechanisms underlying tinnitus generation.

Noreña AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. Neurosci Biobehav Rev. 2010 Nov 19. [Epub ahead of print]. Integrating findings from basic and clinical research Arnaud Noreña proposes a testable model for tinnitus generation.

Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringings ears: the neuroscience of tinnitus. J Neurosci. 2010;30(45):14972-9. Reviewing the neuroscience of tinnitus the latest findings from various methods are presented.

Leaver AM, Renier L, Chevillet MA, Morgan S, Kim HJ, Rauschecker JP. Dysregulation of limbic and auditory networks in tinnitus. Neuron. 2011;69(1):33-43. This imaging study highlights the importance of audio-limbic interactions in the pathophysiology of tinnitus.

Ortmann M, Müller N, Schlee W, Weisz N. Rapid increases of gamma power in the auditory cortex following noise trauma in humans. Eur J Neurosci. 2010 Dec 29 [Epub ahead of print]. Rock musicians after band practice were investigated with MEG to identify the neuronal correlates of transient tinnitus following noise trauma.

Gu JW, Halpin CF, Nam EC, Levine RA, Melcher JR. Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity. J Neurophysiol. 2010;104(6):3361-70. This fMRI study differentiates tinnitus- and hyperacusis related abnormalities of sound evoked auditory pathway activity.

Muehlmeier G, Biesinger E, Maier H. Safety of Intratympanic Injection of AM-101 in Patients with Acute Inner Ear Tinnitus. Audiol Neurootol. 2011;16(6):388-397. First results from a pilot trial investigating topical administration of a NMDA receptor antagonist for the treatment of acute tinnitus.

Suckfuell M, Althaus M, Ellers-Lenz B, Gebauer A, Goertelmeyer R, Jastreboff PJ, Moebius HJ, Rosenberg T, Russ H, Wirth Y, Krueger H. A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus. BMC Ear Nose Throat Disord. 2011;11(1):1. Neramexane, an antagonist at $\alpha 9\alpha 10$ cholinergic nicotinic receptors and N-methyl-D-aspartate receptors shows efficacy in the treatment of tinnitus in this phase II study.

Bauer CA, Brozoski TJ. Effect of Tinnitus Retraining Therapy on the Loudness and Annoyance of Tinnitus: A Controlled Trial. Ear Hear. 2010 Sep 30. [Epub ahead of print]. This controlled clinical demonstrated that both TRT and general counseling without additional sound therapy are effective in reducing the annoyance and impact of tinnitus.

Hesser H, Weise C, Westin VZ, Andersson G. A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. Clin Psychol Rev. 2010 Dec 23. [Epub ahead of print]. This meta-analysis concludes that CBT is an effective treatment of tinnitus distress. However there are only few large-scale, well-controlled trials.

Hobson J, Chisholm E, El Refaie A. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst Rev. 2010 Dec 8;12:CD006371. This Cochrane meta-analysis failed to show strong evidence of the efficacy of sound therapy in tinnitus.



De Ridder D, Vanneste S, Kovacs S, Sunaert S, Menovsky T, van de Heyning P, Møller A. Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression. J Neurosurg. 2011 Jan 14. [Epub ahead of print].
Here clinical results from transcranial magnetic and intracranial electrical stimulation of the auditory cortex in a large series of 43 patients are reported.

Zhang J, Zhang Y, Zhang X. Auditory Cortex Electrical Stimulation Suppresses Tinnitus in Rats. J Assoc Res Otolaryngol. 2010 Nov 6. [Epub ahead of print].
This animal study demonstrates that auditory cortex electrical stimulation suppresses behavioural evidence of tinnitus in rats.

Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake JA, Sudanagunta SP, Borland MS, Kilgard MP. Reversing pathological neural activity using targeted plasticity. Nature. 2011 470(7332):101-104.
By combining specific auditory stimulation with vagal nerve stimulation these researchers were able to reverse both behavioural evidence and neuronal correlates of tinnitus in rats.



Tinnitus: Models and mechanisms.

Hear Res. 2010 Dec 10. [Epub ahead of print]

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Over the past decade, there has been a burgeoning of scientific interest in the neurobiological origins of tinnitus. During this period, numerous behavioral and physiological animal models have been developed which have yielded major clues concerning the likely neural correlates of acute and chronic forms of tinnitus and the processes leading to their induction. The data increasingly converge on the view that tinnitus is a systemic problem stemming from imbalances in the excitatory and inhibitory inputs to auditory neurons. Such changes occur at multiple levels of the auditory system and involve a combination of interacting phenomena that are triggered by loss of normal input from the inner ear. This loss sets in motion a number of plastic readjustments in the central auditory system and sometimes beyond the auditory system that culminate in the induction of aberrant states of activation that include hyperactivity, bursting discharges and increases in neural synchrony. This article will review what has been learned about the biological origins of these alterations, summarize where they occur and examine the cellular and molecular mechanisms that are most likely to underlie them.

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An integrative model of tinnitus based on a central gain controlling neural sensitivity.

Neurosci Biobehav Rev. 2010 Nov 19. [Epub ahead of print]

Noreña AJ.

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The purpose of the current review is to propose a model highlighting the putative connections between hearing loss and the phantom perception of tinnitus (tinnitus being accompanied by hearing loss in the majority, if not all, subjects). Sensory deprivation is followed by dramatic functional and structural changes in the auditory system. Notably, while cochlear injuries are accompanied by a reduced activity in the cochlear nerve, neural activity is increased at virtually all levels in the central auditory system. We suggest that this central hyperactivity could result from a central gain increase; the general purpose of this gain modulation being to adapt neural sensitivity to the reduced sensory inputs, preserving a stable mean firing and neural coding efficiency. However, maintaining neural homeostasis at all costs, in the event of an auditory system sensory deprivation, could be done at the price of amplifying „neural noise“ due to the overall increase of gain (or sensitivity), ultimately resulting in the generation of tinnitus. The clinical implications of this model are also presented.

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Ringling ears: the neuroscience of tinnitus.

J Neurosci. 2010 Nov 10;30(45):14972-9.

Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA.

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Tinnitus is a phantom sound (ringing of the ears) that affects quality of life for millions around the world and is associated in most cases with hearing impairment. This symposium will consider evidence that deafferentation of tonotopically organized central auditory structures leads to increased neuron spontaneous firing rates and neural synchrony in the hearing loss region. This region covers the



frequency spectrum of tinnitus sounds, which are optimally suppressed following exposure to band-limited noise covering the same frequencies. Cross-modal compensations in subcortical structures may contribute to tinnitus and its modulation by jaw-clenching and eye movements. Yet many older individuals with impaired hearing do not have tinnitus, possibly because age-related changes in inhibitory circuits are better preserved. A brain network involving limbic and other nonauditory regions is active in tinnitus and may be driven when spectrotemporal information conveyed by the damaged ear does not match that predicted by central auditory processing.

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Dysregulation of limbic and auditory networks in tinnitus.

Neuron. 2011 Jan 13;69(1):33-43.

Leaver AM, Renier L, Chevillet MA, Morgan S, Kim HJ, Rauschecker JP.

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Tinnitus is a common disorder characterized by ringing in the ear in the absence of sound. Converging evidence suggests that tinnitus pathophysiology involves damage to peripheral and/or central auditory pathways. However, whether auditory system dysfunction is sufficient to explain chronic tinnitus is unclear, especially in light of evidence implicating other networks, including the limbic system. Using functional magnetic resonance imaging and voxel-based morphometry, we assessed tinnitus-related functional and anatomical anomalies in auditory and limbic networks. Moderate hyperactivity was present in the primary and posterior auditory cortices of tinnitus patients. However, the nucleus accumbens exhibited the greatest degree of hyperactivity, specifically to sounds frequency-matched to patients' tinnitus. Complementary structural differences were identified in ventromedial prefrontal cortex, another limbic structure heavily connected to the nucleus accumbens. Furthermore, tinnitus-related anomalies were intercorrelated in the two limbic regions and between limbic and primary auditory areas, indicating the importance of auditory-limbic interactions in tinnitus. Copyright © 2011 Elsevier Inc. All rights reserved.

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Rapid increases of gamma power in the auditory cortex following noise trauma in humans.

Eur J Neurosci. 2010 Dec 29. doi: 10.1111/j.1460-9568.2010.07542.x. [Epub ahead of print]

Ortmann M, Müller N, Schlee W, Weisz N.

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Tinnitus is an auditory perception in the absence of any external sound source. It has been suggested that tinnitus is related to enhanced synchronization of neuronal activity in the auditory cortex. Usually a hearing damage can be identified suggesting auditory deprivation to central auditory regions to be fundamental for neurophysiological processes related to tinnitus. Until now, human research has been conducted on patients with chronic tinnitus (> 6 months). However, neuronal activity accompanying auditory deprivation and putatively tinnitus may not remain constant over time, making it difficult to directly relate outcomes of current animal studies (acute tinnitus) to chronic tinnitus in humans, and vice versa. We investigated 14 amateur rock musicians who frequently reported a short-term tinnitus immediately after band practice. Magnetoencephalographic resting-state recordings, audiometry and tinnitus testing were performed at two separate occasions: with and without previous exposure to loud music. Analyses revealed that transient tinnitus was accompanied by temporary hearing loss in both ears and increased gamma activity in the right auditory cortex in 13 out of 14 cases. Additionally, tinnitus frequency was strongly correlated to hearing loss. Analogous to animal studies, our results show for the first time in humans that noise trauma leads rapidly to increased neuronal synchrony in the auditory cortex. Importantly, the strongly right-lateralized effect implies that it does not reflect tinnitus percept per se. This could rather have been triggered by greater discontinuities of hearing loss at high frequencies that were particularly pronounced in the left ear.

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Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity.

J Neurophysiol. 2010 Dec;104(6):3361-70. Epub 2010 Sep 29.

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Phantom sensations and sensory hypersensitivity are disordered perceptions that characterize a variety of intractable conditions involving the somatosensory, visual, and auditory modalities. We report physiological correlates of two perceptual abnormalities in the auditory domain: tinnitus, the phantom perception of sound, and hyperacusis, a decreased tolerance of sound based on loudness. Here, subjects with and without tinnitus, all with clinically normal hearing thresholds, underwent 1) behavioral testing to assess sound-level tolerance and 2) functional MRI to measure sound-evoked activation of central auditory centers. Despite receiving identical sound stimulation levels, subjects with diminished sound-level tolerance (i.e., hyperacusis) showed elevated activation in the auditory midbrain, thalamus, and primary auditory cortex compared with subjects with normal tolerance. Primary auditory cortex, but not subcortical centers, showed elevated activation specifically related to tinnitus. The results directly link hyperacusis and tinnitus to hyperactivity within the central auditory system. We hypothesize that the tinnitus-related elevations in cortical activation may reflect undue attention drawn to the auditory domain, an interpretation consistent with the lack of tinnitus-related effects subcortically where activation is less potently modulated by attentional state. The data strengthen, at a mechanistic level, analogies drawn previously between tinnitus/hyperacusis and other, nonauditory disordered perceptions thought to arise from neural hyperactivity such as chronic neuropathic pain and photophobia.

After each gentamicin application, patients were monitored for their symptoms and hearing. If symptoms persisted, they received another intratympanic injection of gentamicin. This method is referred to as the variable titration method. A retrospective chart review was performed, and questionnaires were used to assess hearing, functional status, tinnitus, ear fullness sensation, and the control of vertigo attacks in response to treatment. **RESULTS:** Nineteen patients were sampled. Eighteen patients (94%) had complete or substantial control of vertigo. Five patients (26%) had worse hearing results on their post-treatment audiogram, averaging 13 dB hearing loss (range, 5-25 dB). In response to the questionnaires, all patients reported a significant improvement in the quality of life after treatment. **CONCLUSION:** The treatment was found to be highly effective. The variable titration method of injection prevents unnecessary injections for patients whose symptoms have already subsided.

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Safety of Intratympanic Injection of AM-101 in Patients with Acute Inner Ear Tinnitus.

Audiol Neurotol. 2011 Jan 21;16(6):388-397. [Epub ahead of print]

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Effective pharmacological treatments for tinnitus have proven elusive. Emerging evidence suggests that dysregulation of cochlear N-methyl-D-aspartate (NMDA) receptors may underlie aberrant excitation of the auditory nerve, which in turn is perceived as tinnitus. The blocking of these receptors thus represents a promising therapeutic approach. In a recent phase I/II clinical trial, the safety and local tolerance of intratympanic injections of the NMDA receptor antagonist AM-101 was evaluated for the first time in humans. The results from the double-blind, randomized, placebo-controlled study show that intratympanically injected AM-101 was well tolerated by study participants, and provided the first indications of therapeutic efficacy.

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A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus.

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Suckfuell M, Althaus M, Ellers-Lenz B, Gebauer A, Goertelmeyer R, Jastreboff PJ, Moebius HJ, Rosenberg T, Russ H, Wirth Y, Krueger H.

BACKGROUND: Neramexane is a new substance that exhibits antagonistic properties at both the 9/10 nicotinic and the N methyl-D aspartate receptor, suggesting potential efficacy in the treatment of tinnitus. **METHODS:** A total of 431 outpatients with moderate to severe subjective tinnitus (onset 3-18 months before screening) were assigned randomly to receive either placebo or neramexane mesylate (25 mg/day, 50 mg/day and 75 mg/day) for 16 weeks, with assessment at four-week intervals. The primary (intention-to-treat) efficacy analysis was based on the change from baseline in Week 16 in the total score of the adapted German short version of the validated Tinnitus Handicap Inventory questionnaire (THI 12). **RESULTS:** Compared with placebo, the largest improvement was achieved in the 50 mg/d neramexane group, followed by the 75 mg/d neramexane group. This treatment difference did not reach statistical significance at the pre-defined endpoint in Week 16 ($p = 0.098$ for 50 mg/d; $p = 0.289$ for 75 mg/d neramexane), but consistent numerical superiority of both neramexane groups compared with placebo was observed. Four weeks after the end of treatment, THI 12 scores in the 50 mg/d group were significantly better than those of the controls. Secondary efficacy variables supported this trend, with p values of <0.05 for the 50 mg/d neramexane group associated with the functional-communicational subscores of the THI 12 and the assessments of tinnitus annoyance and tinnitus impact on life as measured on an 11-point Likert-like scale. No relevant changes were observed for puretone threshold, for tinnitus pitch and loudness match, or for minimum masking levels. The 25 mg/d neramexane group did not differ from placebo in respect of any of the outcome measures. Neramexane was generally well tolerated. Laboratory values, electrocardiography and vital signs revealed no relevant influence of the study medication. Dizziness was the most common adverse event and showed a clear dose-dependence. **CONCLUSIONS:** This proof-of-concept and dose-finding study demonstrated the safety and tolerability of neramexane treatment in patients with moderate to severe tinnitus. The primary efficacy variable showed a trend towards improvement of tinnitus suffering in the medium- and high-dose neramexane groups. This finding is in line with consistent beneficial effects observed in secondary assessment variables. These results allow appropriate dose selection for further studies. ClinicalTrials.gov Identifier: NCT00405886.

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Sound therapy (masking) in the management of tinnitus in adults.

Cochrane Database Syst Rev. 2010 Dec 8;12:CD006371.

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BACKGROUND: Tinnitus is described as the perception of sound or noise in the absence of real acoustic stimulation. Numerous management strategies have been tried for this potentially debilitating, heterogeneous symptom. External noise has been used as a management tool for tinnitus, in different capacities and with different philosophical intent, for over a century. **OBJECTIVES:** To assess the effectiveness of sound-creating devices (including hearing aids) in the management of tinnitus in adults. Primary outcome measures were changes in the loudness or severity of tinnitus and/or impact on quality of life. Secondary outcome measures were change in pure-tone auditory thresholds and adverse effects of treatment. **SEARCH STRATEGY:** We searched the Cochrane ENT Group Trials Register; CENTRAL (2009, Issue 3); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. The date of the most recent search was 11 September 2009. **SELECTION CRITERIA:** Prospective randomised controlled trials recruiting adults with persistent, distressing, subjective tinnitus of any aetiology in which the management strategy included maskers, noise-generating device and/or hearing aids, used either as the sole management tool or in combination with other strategies, including counselling. **DATA COLLECTION AND ANALYSIS:** Two authors independently examined the 362 search results to identify

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studies for inclusion in the review, of which 33 were potentially relevant. Both authors extracted data independently. MAIN RESULTS: Six trials (553 participants) are included in this review. Studies were varied in design, with significant heterogeneity in the evaluation of subjective tinnitus perception, with different scores, scales, tests and questionnaires as well as variance in the outcome measures used to assess the improvement in tinnitus sensation/quality of life. This precluded meta-analysis of the data. There was no long-term follow up. We assessed the risk of bias as medium in three and high in three studies. No side effects or significant morbidity were reported from the use of sound-creating devices. AUTHORS' CONCLUSIONS: The limited data from the included studies failed to show strong evidence of the efficacy of sound therapy in tinnitus management. The absence of conclusive evidence should not be interpreted as evidence of lack of effectiveness. The lack of quality research in this area, in addition to the common use of combined approaches (hearing therapy plus counselling) in the management of tinnitus are, in part, responsible for the lack of conclusive evidence. Other combined forms of management, such as Tinnitus Retraining Therapy, have been subject to a Cochrane Review. Optimal management may involve multiple strategies.

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Auditory Cortex Electrical Stimulation Suppresses Tinnitus in Rats.

J Assoc Res Otolaryngol. 2010 Nov 6. [Epub ahead of print]

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Recent clinical studies have demonstrated that auditory cortex electrical stimulation (ACES) has yielded promising results in the suppression of patients' tinnitus. However, the large variability in the efficacy of ACES-induced suppression across individuals has hindered its development into a reliable therapy. Due to ethical reasons, many issues cannot be comprehensively addressed in patients. In order to search for effective stimulation targets and identify optimal stimulation strategies, we have developed the first rat model to test for the suppression of behavioral evidence of tone-induced tinnitus through ACES. Our behavioral results demonstrated that electrical stimulation of all channels (frequency bands) in the auditory cortex significantly suppressed behavioral evidence of tinnitus and enhanced hearing detection at the central level. Such suppression of tinnitus and enhancement of hearing detection were respectively demonstrated by a reversal of tone exposure compromised gap detection at 10-12, 14-16, and 26-28 kHz and compromised prepulse inhibition at 10-12 and 26-28 kHz. On the contrary, ACES did not induce behavioral changes in animals that did not manifest any behavioral evidence of tinnitus and compromised hearing detection following the same tone exposure. The results point out that tinnitus may be more related to compromised central auditory processing than hearing loss at the peripheral level. The ACES-induced suppression of behavioral evidence of tinnitus may involve restoration of abnormal central auditory processing.

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Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression.

J Neurosurg. 2011 Jan 14. [Epub ahead of print]

De Ridder D, Vanneste S, Kovacs S, Sunaert S, Menovsky T, van de Heyning P, Moller A.

Brai2n.

Object Tinnitus is a prevalent symptom, with clinical, pathophysiological, and treatment features analogous to pain. Noninvasive transcranial magnetic stimulation (TMS) and intracranial auditory cortex stimulation (ACS) via implanted electrodes into the primary or overlying the secondary auditory cortex have been developed to treat severe cases of intractable tinnitus. Methods A series of 43 patients who benefited transiently from 2 separate placebo-controlled TMS sessions underwent implantation of auditory cortex electrodes. Targeting was based on blood oxygen level-dependent activation evoked by tinnitus-matched sound, using functional MR imaging-guided neuronavigation. Results Thirty-seven

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percent of the patients responded to ACS with tonic stimulation. Of the 63% who were nonresponders, half benefited from burst stimulation. In total, 33% remained unaffected by the ACS. The average tinnitus reduction was 53% for the entire group. Burst stimulation was capable of suppressing tinnitus in more patients and was better than tonic stimulation, especially for noise-like tinnitus. For pure tone tinnitus, there were no differences between the 2 stimulation designs. The average pure tone tinnitus improvement was 71% versus 37% for noise-like tinnitus and 29% for a combination of both pure tone and noise-like tinnitus. Transcranial magnetic stimulation did not predict response to ACS, but in ACS responders, a correlation ($r = 0.38$) between the amount of TMS and ACS existed. A patient's sex, age, or tinnitus duration did not influence treatment outcome. Conclusions Intracranial ACS might become a valuable treatment option for severe intractable tinnitus. Better understanding of the pathophysiological mechanisms of tinnitus, predictive functional imaging tests, new stimulation designs, and other stimulation targets are needed to improve ACS results.

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Reversing pathological neural activity using targeted plasticity.

Nature. 2011 Jan 12. [Epub ahead of print]

Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake JA, Sudanagunta SP, Borland MS, Kingard MP.

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Brain changes in response to nerve damage or cochlear trauma can generate pathological neural activity that is believed to be responsible for many types of chronic pain and tinnitus. Several studies have reported that the severity of chronic pain and tinnitus is correlated with the degree of map reorganization in somatosensory and auditory cortex, respectively. Direct electrical or transcranial magnetic stimulation of sensory cortex can temporarily disrupt these phantom sensations. However, there is as yet no direct evidence for a causal role of plasticity in the generation of pain or tinnitus. Here we report evidence that reversing the brain changes responsible can eliminate the perceptual impairment in an animal model of noise-induced tinnitus. Exposure to intense noise degrades the frequency tuning of auditory cortex neurons and increases cortical synchronization. Repeatedly pairing tones with brief pulses of vagus nerve stimulation completely eliminated the physiological and behavioural correlates of tinnitus in noise-exposed rats. These improvements persisted for weeks after the end of therapy. This method for restoring neural activity to normal may be applicable to a variety of neurological disorders.

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Effect of Tinnitus Retraining Therapy on the Loudness and Annoyance of Tinnitus: A Controlled Trial.

Ear Hear. 2010 Sep 30. [Epub ahead of print]

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OBJECTIVES: Subjective tinnitus is the sensation of hearing a sound in the absence of an external stimulus. Although an estimated 30 million Americans experience chronic tinnitus, only a small percentage are significantly bothered by the sensation. However, this population is currently in need of effective therapy that reduces the impact of tinnitus. Tinnitus retraining therapy has been promoted as an effective intervention for treating chronic bothersome tinnitus from any etiology. The aim of this study was to compare the effect of tinnitus retraining therapy on the loudness and annoyance of tinnitus with a control group. **DESIGN:** Subjects with subjective, stable, bothersome, chronic tinnitus, and normal to near-normal hearing in the speech frequencies (average pure-tone thresholds for 0.5, 1, 2, and 4 kHz ≤ 30 dB HL) were recruited to participate in a study for the effect of tinnitus retraining therapy (TRT) on the loudness and annoyance of their tinnitus. Participants were assigned to either the TRT arm or a control arm, with assignment balanced between groups by tinnitus severity. After baseline evaluation, participants received acoustic stimulation devices and 3 mos of individual counseling. An integrated computerized test battery of questionnaires and psychophysical procedures were used to evaluate



participants at 6, 12, and 18 mos after enrollment. The primary outcome measure was the change in total score on the tinnitus handicap inventory. Secondary outcome measures were change in global tinnitus impact on a tinnitus experience questionnaire, subjective tinnitus loudness rating, and tinnitus loudness objectively measured using a psychophysical matching procedure. RESULTS: Both TRT and general counseling without additional sound therapy are effective in reducing the annoyance and impact of tinnitus. The largest effect on overall tinnitus handicap was observed in the TRT participants, with an effect size of 1.13. However, a clinically significant effect was also observed in the control group, with an effect size of 0.78. CONCLUSIONS: Individuals with moderate to severe tinnitus, without comorbidities of either depression or hearing loss in the speech frequency range, benefit from treatment with either TRT or general counseling. The global improvement in tinnitus handicap with TRT accrues over an 18-mo period and seems to be a robust and clinically significant effect.

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A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress.

Clin Psychol Rev. 2010 Dec 23. [Epub ahead of print]

Hesser H, Weise C, Westin VZ, Andersson G.

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Tinnitus is defined as a sound in the ear(s) and/or head without external origin and is a serious health concern for millions worldwide. The aim of the present study was to determine whether Cognitive Behavior Therapy (CBT) is effective in reducing distress associated with tinnitus. Randomized, controlled trials that assessed the efficacy of CBT for tinnitus-related distress in adults were identified by searching electronic databases (PsychINFO, PubMed, the Cochrane Library), and by manual searches. Fifteen studies (total of 1091 participants) were included in the meta-analysis. CBT compared with a passive and active control at post-assessment yielded statistically significant mean effect sizes for tinnitus-specific measures (Hedges'sg=0.70, and Hedges'sg=0.44, respectively). The average weighted pre-to-follow-up effect size for the CBT group suggested that these effects were maintained over time. Smaller but yet statistically significant effects of CBT were found for mood outcome measures. Characteristics of the studies were unrelated to effect sizes. Methodological rigor, publication bias, and a series of sensitivity analyses did not influence the findings. The results suggest that CBT is an effective treatment of tinnitus distress. However, caution is warranted given that few large-scale, well-controlled trials were identified.

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