



**Fifth International  
TRI Tinnitus Conference  
The Neuroscience of Tinnitus**

**Hosted By:  
The Center for Hearing & Deafness  
State University of New York at Buffalo  
and the  
Tinnitus Research Initiative**

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

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*Center for Hearing & Deafness, State University of New York at Buffalo:*

Richard J. Salvi, Ph.D.

Carol M. Altman (Conference Administrator)

Brian Allman, Ph.D.

Edward Lobarinas, Ph.D.

*Tinnitus Research Initiative:*

Berthold Langguth, M.D.

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The State University of New York at Buffalo:

- Center for Hearing & Deafness
- Dept. of Communicative Disorders and Sciences
- School of Medicine and Biological Sciences

## **Conference Venue:**

The Holiday Inn Grand Island Resort and Conference Center

100 Whitehaven Road

Grand Island, New York 14072

Phone: (716) 773-1111

Alternate Conference Hotel:

Hotel Indigo

10 Flint Road

Amherst, NY 14226

Phone: (716) 689-4414

## **Post-Conference Contact Information:**

Richard J. Salvi, Ph.D. (716-829-5310; [salvi@buffalo.edu](mailto:salvi@buffalo.edu))

Carol Altman (716-829-5291; [caltman@buffalo.edu](mailto:caltman@buffalo.edu))

Brian Allman (716-829-5306; [brianall@buffalo.edu](mailto:brianall@buffalo.edu))

Edward Lobarinas (716-829-5302; [el24@buffalo.edu](mailto:el24@buffalo.edu))

Center for Hearing and Deafness

State University of New York at Buffalo

137 Cary Hall

Buffalo, NY 14214

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## TRI Tinnitus Conference: Program Overview

On Friday August 19<sup>th</sup>, the conference will open with two invited talks. To accommodate the overwhelming number registrants who requested to give talks, the Organizing Committee has scheduled two concurrent speaker sessions (The Neuroscience of Tinnitus, and Clinical Strategies) to be held in separate ballrooms throughout Saturday August 20<sup>th</sup> and Sunday August 21<sup>st</sup>. Attendees will be free to attend talks in either room. Also, we are requesting that posters be hung on Friday and left up for the duration of the conference. We will devote time for poster viewing on Friday evening, and both Saturday and Sunday afternoon.

Following the Gala Banquet dinner on the evening of Sunday August 21<sup>st</sup>, we will enjoy “A Night at the Opera.” Accompanied by **Pim van Dijk** on piano, distinguished vocalist, **Jinsheng Zhang**, will perform:

- “E Lucevan e Stelle” from Puccini’s Tosca
- “La Donna e Mobile” from Verdi’s Rigoletto
- “How can I help not thinking of her” Chinese classical by Yuanren Zhao

(Piano from Illos Piano Rebuilders LLC 2940 Main Street, Buffalo, NY 14214 (716) 832-0013)



## SCHEDULE

Friday, August 19 <sup>th</sup> : Opening Talks (Ballroom East/Center)				
Time	Speaker	Session Moderator	Title	Abstract Page #
3:45 PM	Richard Salvi	Richard Salvi	Opening Remarks	n/a
4:00 PM	Josef Rauschecker	Richard Salvi	Auditory and Limbic Components of Tinnitus Revealed by Functional Imaging in Humans	30
4:45 PM	Fan-Gang Zeng	Richard Salvi	Sound Diagnosis and Sound Therapy for Tinnitus: Lessons Learned from Cochlear Implants	38
5:30 PM	Poster Session (Settlement Room & Ballroom East/Center )			
7:00 PM	Dinner (Riverview Patio)			

### Please Note:

**Continental Breakfast** will be available for registrants in the Settlement Room from 7:15 to 8:00 a.m. on Saturday and Sunday morning.

**Neuroscience of Tinnitus Session** schedules are in blue and sessions take place in the Ballroom East/Center.

**Clinical Session** schedules are in purple and sessions take place in the Ballroom West.

<b>Saturday, August 20<sup>th</sup>: Neuroscience Sessions (Ballroom East/Center)</b>				
Time	Speaker	Session Moderator	Title	Abstract Page #
8:00 AM	Kurt Yankaskas	Richard Salvi	Operational Readiness: The Role of Tinnitus Research	38
8:30 AM	Berthold Langguth	Richard Salvi	Neuroimaging and Neuromodulation: Complementary Approaches for Identifying the Neuronal Correlates of Tinnitus	23
9:00 AM	Sven Vanneste	Richard Salvi	Tinnitus as an Emergent Property of Multiple Parallel Dynamically Changing and Partially Overlapping Brain Networks: The Role of the Emotional Network	37
9:30 AM	Dirk De Ridder	Richard Salvi	The (Para)hippocampus as the Central Hub in Tinnitus: Binding Intensity, Mood, Cognition and Distress	15
10:00 AM	Coffee Break (Settlement Room)			
10:30 AM	Carol Bauer	Sylvie Hébert	The Cerebellum as a Novel Tinnitus Modulator	12
11:00 AM	Larry Roberts	Sylvie Hébert	Electrophysiological Imaging in Tinnitus, Recruitment, and Auditory Attention	31
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Saturday, August 20 <sup>th</sup> : Clinical Sessions (Ballroom West)				
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9:30 AM	Craig Formby	Craig Formby	Design of the Tinnitus Retraining Therapy Trial (TRTT)	17
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3:00 PM	Robert Sweetow	Robert Sweetow	Effects of Fractal Tones on Tinnitus and Relaxation	34
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6:00 PM	Free Time			
6:45 PM	Appetizers / Gala Banquet 7:30 PM (Riverview Room)			
	Entertainment: "A Night at the Opera"			
	Awards Ceremony (Advocacy, Leadership and Commitment)			

<b>Sunday, August 21<sup>st</sup>: Clinical Sessions (Ballroom West)</b>				
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5:30 PM				
6:00 PM	Free Time			
6:45 PM	Appetizers / Gala Banquet 7:30 PM (Riverview Room)			
	Entertainment: "A Night at the Opera"			
	Awards Ceremony (Advocacy, Leadership and Commitment)			

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## **The Cerebellum As A Novel Tinnitus Modulator**

*Carol A. Bauer, M.D. \* and Thomas J. Brozoski, Ph.D.  
Southern Illinois University School of Medicine, Springfield, Illinois, USA*

Chronic tinnitus may develop because peripheral insults to the auditory system produce maladaptive changes in susceptible brain areas that serve as trigger zones. Trigger zones may produce a cascade of events affecting other brain areas that then serve as more permanent generator sites [Brozoski & Bauer, 2005]. The role of the cerebellum in auditory processing is unknown, although auditory afferents to the cerebellum, in particular the paraflocculus (PFL), have been reported [Morest et al., 1998]. Recently it was shown that the PFL had greatly elevated neural activity, as indicated by manganese-enhanced magnetic resonance imaging, in rats with psychophysical evidence of tinnitus [Brozoski et al., 2007]. It was further shown that PFL activity was not elevated in normal rats listening to a tinnitus-like sound. This suggests that slowly-emerging plastic changes in the PFL may underpin chronic tinnitus, i.e., it may serve as a tinnitus generator. To test this hypothesis, rats with psychophysical evidence of chronic tinnitus induced by high-level sound exposure, had one of the following manipulations: Group A. surgical ablation of the PFL with pre-existing tinnitus established; Group B. surgical ablation of the PFL before induction of tinnitus; Group C. chronic infusion of 2% lidocaine into the subarcuate fossa with pre-existing tinnitus. Post-treatment psychophysical testing indicated that PFL ablation eliminated existing tinnitus (Group A) without altering auditory discrimination; PFL ablation before tinnitus induction (Group B) attenuated, but did not eliminate development of tinnitus; PFL lidocaine treatment variably reduced existing tinnitus (Group C). It was concluded that in a rat model of noise-induced chronic tinnitus, the cerebellar PFL may serve as a non-obligatory but sufficient generator of tinnitus. Loss of, or pathological alteration of this modulatory influence may constitute a tinnitus signal. Supported by NIDCD grant # RO1DC009669-03.

## **The Use Of Real Ear Measurements In Tinnitus Clinics**

*Dr. Natan Bauman,\* Ed.D., Eng., M.S., F-AAA  
New England Tinnitus and Hyperacusis Clinic, Hamden, Connecticut, USA*

Real Ear Measurements are widely used to verify hearing aid fittings. Bauman (1999) proposed the use of REMs in aiding tinnitus clinicians in the management of tinnitus devices. Five areas were identified: (1) Aiding tinnitus patients in identifying the correct way of “setting” the level of the tinnitus device. (2) Use of REMs in counseling. (3) Verifying progress of habituation. (4) Verifying proper function of the tinnitus devices. (5) Verifying correct frequency range of audibility for optimal sound therapy. Recently a new application was investigated. In addition to the aforementioned applications, a pseudo-objective way of tinnitus identification will be presented.

## Are All (Customized) Sounds Therapeutic? - The Soundscape Architecture System, SSAS"

*\*Mikael Bergholm, Jarmo Lehtimäki, Ulla Pirvola, Jyri Sariola, Rami Kaalamo, Jukka Ylikoski, TinnOff Inc., Helsinki, Finland*

For decades tinnitus patients have been treated with masking therapy (MT). Results of MT have been modest, but have improved when individual counseling was included into the therapeutic program. Today, sound therapy (ST) is an important part of the tinnitus treatment. The reported overall efficacy of STs seems to be relatively good but most ST materials either represent standard products (white noise generators, CDs) or are not easily available. Standardized ST-solutions may not be therapeutically optimal because persons seeking help for tinnitus represent a heterogeneous group of individuals. Subsequently, the needs of tinnitus patients show large individual variations. Also, the optimal form of ST may vary over time even in the same individual. Therefore, therapeutic ST-program should be individually tailored, interactive and easily adjustable. The leading principle of our ST strategy has been individual authority, which often is contrasting product efficacy. This means, firstly, that the goal of ST should be defined in detail. In acute tinnitus masking-type of ST may be useful to prevent worsening of tinnitus annoyance and subsequent stress reaction. In chronic tinnitus the primary target is often the tinnitus-triggered stress reaction. Next step might be the specific ST for tinnitus mitigation or habituation. Secondly, appropriate type of ST should be selected based on each patient's individual needs, soundscape (tinnitus and hearing profiles) and likings. One individual may want enrichment of acoustic environment only, another masking of tinnitus, management of tinnitus-triggered stress reaction, or customized, possibly notched ST for tinnitus mitigation/habituation. In our ST strategy, on the basis of each persons soundscape an individual ST paradigm is architected interactively with the patient. All the steps from diagnostic procedures to therapeutic ST material and its possible changes with changes overtime can best be performed via the internet.

## Neurobiochemical And Psychometric Correlates Of Noise-Induced Tinnitus Following Low Frequency *rTMS* Over The Left Temporal Lobe In Humans

*Anthony T. Cacace<sup>\*</sup>, Jiani Hu, Stephen Romero, Yang Xuan  
Wayne State University, Detroit, Michigan, USA*

Based on a single-blinded sham-controlled cross-over design, we evaluated the efficacy of low frequency (1-Hz) repetitive transcranial magnetic stimulation (*rTMS*) to suppress chronic tinnitus in individuals with an etiology of occupational, recreational, or military related noise exposure and associated hearing loss. *rTMS* was applied to the left hemisphere over the posterior temporal area (T3/T5, International 20-10 System) at 110% of motor threshold. Differential pre-post outcome measures for sham and actual *rTMS* conditions evaluated for changes in specific metabolites (*N*-acetyl aspartate, choline, creatine, and glutamate) obtained from left and right auditory cortical areas using magnetic resonance spectroscopy; tinnitus-loudness levels, based on a magnitude estimation procedure; perceived psychometric changes in social, emotional, behavioral, hearing, and tinnitus impact areas using the Tinnitus Handicap Questionnaire (THQ); and, structural changes in brain anatomy using voxel-based morphometry (see Romero et al., poster at this meeting). While no subject had complete cessation of the tinnitus percept, in comparison to sham stimulation, actual *rTMS* significantly reduced tinnitus-loudness levels, improved scores in all content areas of the THQ, and down regulated glutamate concentrations in auditory cortical areas of the left temporal lobe. Significant pair-wise correlations were also observed among questionnaire-questionnaire variables, questionnaire-metabolite variables, metabolite-metabolite variables, and metabolite-loudness variables. The implications of these findings will be discussed in the context of current models and theories of tinnitus generation and its persistence. The specificity of the results and generalizability of these findings is limited to individuals with a common etiology of noise exposure and the expression of noise induced hearing loss. Also discussed are instrumental limitations associated with both sham and actual *rTMS* conditions.

## **Amygdala In Tinnitus Generation**

*Guang-Di Chen\*, Daniel Stolzberg, Senthilvelan Manohar, and Richard Salvi  
Center for Hearing & Deafness, University at Buffalo, Buffalo, New York, USA*

The amygdala, linking the classical auditory system to the limbic system, has been hypothesized to play a pivotal role in tinnitus severity by linking the aberrant neural activity in the classical auditory pathway to neural structures associated with fear and emotion. In support of this view, drug-induced inactivation of the amygdala and surrounding brain regions has been reported to suppress tinnitus in some patients. However, to our knowledge no study has directly assessed pathophysiological alterations that occur in the amygdala during tinnitus and linked these to occurring in the classical auditory pathway. To address this issue, we induced tinnitus in rats by administering a high dose of sodium salicylate (300 mg/kg, i.p.) which induces behavioural evidence of tinnitus with a pitch in the 10-20 kHz range. Afterwards, we recorded from the lateral amygdala (LA), auditory cortex (AC) and medial geniculate body (MGB). Systemic salicylate injection caused an about 20-dB threshold elevation of auditory evoked potential of the amygdala, but enhanced the evoked potential at high stimulation levels. Interestingly, as in the AC, the salicylate injection induced a massive shift of frequency receptive fields (FRF) of neurons in the LA into the 10-20 kHz tinnitus-frequency region resulting in an expanded frequency representation at the pitch of the tinnitus frequency. However, salicylate application failed to induce a significant FRF shift in the MGB. To identify changes that were mediated locally, salicylate was infused into the amygdala where it enhanced neuronal activity in the amygdala and caused a large FRF-expansion into the 10-20 kHz region in the AC. In contrast, large FRF-expansion was not observed after local salicylate application into the AC. These results suggest that the large FRF-shifts observed in the AC following systemic salicylate application may be mediated through the amygdala. These are the first physiological data showing that the amygdala undergoes pathophysiological alteration during tinnitus and plays a major role in re-tuning the AC neurons to the 10-20 kHz tinnitus pitch observed in behavioural studies. Supported by grants from NIH (R01DC009091; R01DC009219) and Tinnitus Research Initiative.

## **An Effort Towards Using The Auditory Brainstem Response As An Objective Indicator Of Salicylate-Induced Tinnitus In Rats**

*Xiao-Peng Liu, Jing-Tian Ni, Lin Chen\**  
*Auditory Research Laboratory, School of Life Sciences, University of Science and Technology of China  
Hefei, China*

In an attempt to look for an objective indicator of tinnitus, we have found that forward acoustic masker can surprisingly boost, rather than suppress, the auditory brainstem response (ABR) in the rat treated with sodium salicylate (NaSal), a tinnitus inducer. In our experiment, a forward narrow band noise caused a decrease in the amplitude of the ABR to tone burst in the normal rat, but would unexpectedly cause an increase in the amplitude in the rat with NaSal treatment. The observed effect could be manifested in the normal rat presented with a background tone, suggesting an underlying mechanism associated with tinnitus. We propose that in NaSal-treated rats, the induced tinnitus can internally mask the ABR as an external background sound does, and a forward acoustic masker can temporarily silence tinnitus to result in a rebound of the otherwise masked ABR. Our study indicates a feasibility of using the ABR as an objective measure of subjective tinnitus. Supported by the National Basic Research Program of China (Grants 2011CB504506 and 2007CB512306), the National Natural Science Foundation of China (Grants 30970977 and 30730041) and the CAS Knowledge Innovation Project (Grant KSCX1-YW-R-36).

### **Double-Blind Assessment Of Tinnitus Relief Induced By Chronic Electrical Stimulation Of Auditory Cortex (Acousco)**

*René Dauman<sup>1</sup> (MD), Emmanuel Cuny<sup>2</sup> (MD), Damien Bonnard<sup>1</sup> (MSc.), Nicolas Dauman<sup>3</sup> (PhD)  
Dept. of Otorhinolaryngology<sup>1</sup>, University of Bordeaux, France*

Introduction: Over a period of three years, nine patients affected by a severe, unilateral (or predominantly unilateral) and intractable tinnitus received a Medtronic device on the dura of their auditory cortex. Preoperatively, individual THI scores ranged from 96 to 60% (average 71.1%). Hearing was only slightly or moderately impaired. Implantation was systematically performed on the side opposite to tinnitus perception. Methods: Baseline values of tinnitus handicap (THI, Iowa THQ, and MiniTQ), audiometric matching of tinnitus and hearing were controlled a few days before surgery. Postoperatively, devices were fitted individually on a weekly basis until an effect on tinnitus was noticeable. Then, the apparently most effective fitting (AMEF) received the attribute of active stimulation whereas the role of placebo was assigned to a randomly selected fitting which had repeatedly evidenced no effect. The two programmes were then randomly administered by periods of two weeks, each being separated by interval of same duration. Results: Preoperatively, THI scores were well correlated with MiniTQ scores. THI scores were on average 10% higher than THQ scores, the difference being attributable to relatively well preserved hearing. Postoperatively, criterion chosen to document consistent improvement was a reduction of 30% in THI score. Such a change was observable in only four patients. Furthermore, documented tinnitus relief wasn't systematically related with AMEF, suggesting that placebo effect might play a major role. The reliability of these data is supported by similar findings with THQ and MiniTQ. Conclusion: These unexpected findings suggest that, beside desirable improvements in patients' selection and device programming, more attention should also be paid to unravel unexplained neurobiological/psychological phenomena.

### **The (Para)Hippocampus As The Central Hub In Tinnitus: Binding Intensity, Mood, Cognition And Distress**

*Dirk De Ridder\*, Sven Vanneste, Kathleen Joos, P Van de Heyning  
TRI Tinnitus Clinic, BRAIN and Dept of Neurosurgery & ENT, Antwerp Belgium*

Introduction: Recent animal as well as functional and structural neuroimaging studies in humans have revealed that acoustic trauma and tinnitus are related to changes in hippocampal activity and structure. These hippocampal changes have to be evaluated in the concept of tinnitus as an emergent property of altered large-scale cortical network activity and connectivity. It has also known that severe tinnitus is characterized by both cognitive deficits, altered mood states and distress. Methods: (1) The Trail Making Test (spatial cognition) was administered to 19 tinnitus patients and correlated with source localized EEG. (2) The TQ (distress) and BI (mood) are evaluated in 65 tinnitus patients and also correlated with their source analyzed EEG. (3) Graph theoretical analysis of the brain network topology is performed on resting state EEG data in 163 healthy volunteers and 163 tinnitus patients. (4) A logistic regression is performed on the same data set to compare the 2 groups. Results: (1) Both tinnitus loudness and tinnitus duration correlate positively with the cognitive processing speed. The cognitive measure correlates with Beta1 activity in the hippocampus, pregenual and subgenual ACC. (2) Distress is correlated with beta activity of ACC and right prefrontal cortex. Mood correlates with alpha activity in the left prefrontal cortex. The parahippocampal region links both pathways. (3) Tinnitus is topologically characterized by hubs with increased connectivity in hippocampal areas (BA 27, 28 and 34). (4) The difference between tinnitus and no tinnitus is related to gamma band activity in the right parahippocampal area. Discussion and conclusions: The (para)hippocampal area is critically involved in both the tinnitus related loudness, mood, distress and cognition. Jointly they function as the major hub of multiple overlapping networks each expressing a different aspect of the unified tinnitus percept.

## **Discordance Between Behavioral Test Outcomes And Hypothesized Electrophysiological Substrates Of Tinnitus**

*Jos J. Eggermont*

*Dept. of Physiology & Pharmacology, Dept. of Psychology, Univ. of Calgary, Calgary, Alberta, Canada*

Animal studies that combine behavioral measures of tinnitus with electrophysiological data suggest some discordance between the interpretation of behavioral outcomes as reflecting tinnitus, and presumed electrophysiological substrates. In addition there appear to be opposite effects for the electrophysiological measures of spontaneous and stimulus-driven cortical activity in auditory cortex following salicylate application. This indicates two major problems for understanding tinnitus mechanisms. The first is: can we rely on current behavioral tests to assess if an animal has tinnitus? If we are confident about the behavioral test outcomes then we need to reevaluate at least one proposed cortical neural correlate of tinnitus, namely increased spontaneous firing rates (SFR). One of the underlying issues is whether cortical spike activity affects conditioned response tests and gap-startle tests, or that these tests are largely based on subcortical mechanisms and changes in neural activity. The second issue is whether SFR changes in auditory cortex are required for tinnitus perception. A third issue is whether some behavioral tests reflect increased gain in the auditory system rather than increased SFR. The second major problem is that the current neural models of tinnitus, mostly based on homeostatic mechanisms, predict gain changes in the central auditory system that should similarly affect SFR and stimulus evoked measures such as local field potentials (LFPs). Although this is the case after noise-induced hearing loss, at least up to the inferior colliculus level, following salicylate application SFR behaves differently from LFP in auditory cortex. This can be understood if there are potentially different transmitter pools or release mechanisms for spontaneous vs. stimulus driven activity, either at the hair cell or in the central auditory system. The distinction between tonic and phasic GABAergic inhibition may be relevant to solve these issues.

## **Sound Therapy In Tinnitus: What The Evidences Tell (And Don't Tell)**

*Dr. Amr El Refaie*

*Centre of Hearing and Balance Studies, Bristol University, United Kingdom*

A recent Cochrane review "Sound therapy (masking) in the management of tinnitus in adults" (Hobson, Chisholm and El Refaie, 2010) was published in December 2010 and concluded that the evidences in the literature failed to show strong evidences of efficacy of sound therapy in tinnitus management. A brief introduction to the different theories involving sound therapy in tinnitus management will be discussed. I intend to elaborate on the process that lead to such conclusion in the review, and discuss the limitation of both the available research and the review itself. I would argue that the absence of evidence does not equal the lack of clinical efficacy in this case, and suggest a way forward to guide clinical practice and conduct further research.

## **Tinnitus: Pharmacological Intervention, What Should We Target?**

*Ana Belén Elgoyhen*

*Instituto de Investigaciones en Ingeniería Genética, CONICET. Buenos Aires, Argentina*

One in 10 adults has clinically significant subjective tinnitus, and for 1 in 100, tinnitus severely affects their quality of life. Despite the significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA-approved drug on the market. Since in some individuals, tinnitus causes irritability, agitation, stress, depression, insomnia and interferes with normal life, even a drug that produces a small but significant effect would have a huge therapeutic impact. The search for drugs that target tinnitus is hampered by the lack of a deep knowledge of the underlying neural substrates of this pathology. Initially considered an inner ear pathology, it is now clear that at least chronic tinnitus is a central nervous system disorder. Based on recent progress in the understanding of tinnitus, I will focus my talk on a brief overview of the pharmacotherapies that have been used, on the challenges faced when designing a tinnitus pharmacotherapy, on potential neural substrates as targets for pharmacological intervention and on the approach followed by the TRI Pharma Workgroup.

## Design Of The Tinnitus Retraining Therapy Trial (TRTT)

Craig Formby\* and Roberta W. Scherer  
\* University of Alabama, Tuscaloosa, Alabama, USA

The Tinnitus Retraining Therapy Trial (TRTT), designed to investigate the efficacy of tinnitus retraining therapy (TRT) and its component parts, directive counseling (DC) and sound therapy (ST), is a multi-center randomized controlled trial, enrolling individuals with subjective debilitating tinnitus to one of 3 treatment groups: (1) DC and ST achieved with conventional sound generators (SG); (2) DC and placebo SG; or (3) Standard of Care (SC) as usually administered in the military. We will enroll 76 participants per group using a treatment allocation ratio of 1:1:1 for a total of 228 participants. A standardized protocol for treatment and data collection will be used by all centers. The primary outcome is change in Tinnitus Questionnaire (TQ) score assessed longitudinally at follow-up, taking place at 3, 6, 12, and 18 months following the initial treatment session. Secondary outcomes include change in TQ sub-scores, in Tinnitus Handicap Inventory and Tinnitus Functional Index scores, and in the visual analogue scale of the TRT Interview. Other secondary outcomes include audiometric measures, psychoacoustic measures, and change in quality of life. The primary objective of the study is to evaluate the efficacy of TRT (DC and conventional SG) compared with SC. Secondary objectives are to evaluate (1) the efficacy of DC plus placebo SG versus SC, and (2) the efficacy of conventional versus placebo SG in study participants assigned to DC. We hypothesize that (1) full TRT will be more efficacious than SC, (2) DC + placebo SG will be more efficacious than SC, and (3) conventional SG will be more efficacious than placebo SG, in habituating the tinnitus awareness, annoyance, and impact on the study participant's life. Study centers include a Study Chair's Office, Data Coordinating Center, and 6 Military Clinical Centers, which offer a rich and diverse population for the study of primary tinnitus in the TRTT.

## A Potential Novel Tool To Objectively Assess Tinnitus Frequency And Intensity

Longenecker R.J, Galazyuk A.V.\*  
Dept. of Anatomy and Neurobiology, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio, USA

Progress in the field of tinnitus would benefit from a reliable and objective method for measuring tinnitus. An ideal method should not only detect the presence of tinnitus but also to measure its spectrum and intensity. It would be even more beneficial for the field if such a method was capable of assessing tinnitus both in humans and in animal models. Existing methodologies have been proven to detect tinnitus in animal models but have yet to demonstrate a capacity to fully estimate all tinnitus parameters. This study was conducted on 12 experimental and 8 control CBA/CaJ mice. In the experimental group, tinnitus was induced by an exposure to a loud (116 dB SPL) narrow band noise (centered at 16 kHz). Mice responses to startle stimuli (broad band noise, 110 dB SPL, 20ms duration) were recorded and measured. Startle stimuli were presented in a random fashion in combination with a continuous background of narrow band noise centered at different frequencies (4.0 - 31.5 kHz) and intensities (40 - 80 dB SPL). All tested mice exhibited suppression of their startle responses in the presence of the background. The magnitude of this suppression depended on both background frequency and intensity. The maximum suppression was observed at frequencies of 12 or 16 kHz. At the lowest (4 kHz) and highest (31.5 kHz) frequencies used such suppression was minimal. Furthermore, suppression increased with background intensity. In the control group of mice these frequency- and intensity-dependent changes were monotonic. In the group of mice exhibiting tinnitus this systematic change was noticeably altered at a particular (mouse specific) intensity/frequency combination. The frequency of this combination matched the mouse tinnitus frequency identified using pre-pulse inhibition of the acoustic startle reflex. We believe that our method is capable of identifying both tinnitus frequency and intensity. Studies on humans will confirm whether our method can assess tinnitus intensity. This study was supported by a Research Incentive Grant from NEOMed.

## **Change In Patients' Perception And Reaction To Tinnitus From Screening To Baseline In Randomized Controlled Trials (RCT) For Subjective Tinnitus. An Approach To Define Predictors For Treatment Outcome**

*Bankstahl, Ulli S.; Schmidt, Bernd; Görtelmeyer, Roman\**  
Merz Pharmaceuticals GmbH, Clinical R&D CNS/ SM&E, 60318 Frankfurt, Germany

Background: In order to better understand the highly variable treatment responses in subjective tinnitus it is urgently needed to characterize patients according to etiology (e.g. hearing loss, noise induced tinnitus (Sindhusake et al, 2003; Nicolas-Puel et al, 2006)), tinnitus characteristics, suffering and other features (Tyler et al, 2007). Furthermore significant treatment effects may be achievable in subgroups rather than in heterogeneous total populations. There is little quantitative research on factors and predictors for impact of tinnitus on Health-Related Quality of Life (Bartels et al, 2010; Kamalski et al, 2010). Current treatments attempt to interfere with pathophysiological cortical networks involving various approaches (Fioretti et al, 2011; Langguth et al, 2009; Argstatter et al., 2009). Finding predictors of treatment success is challenging. One way is to analyze status and run-in behavior of patients during screening and inclusion phase of RCTs. Methods: The data from several RCTs with neramexane is used to characterize patients based on tinnitus characteristics, etiology, distress, anxiety, depression, sleeping problems, emotional reactions and impairments. Sequential correlation and regression methods, and common factor analysis followed by non-parametrical classification procedures are used to detect subpopulations and defining types of run-in behavior. Results: The analysis set comprised N=1220 patients suffering from subjective tinnitus for 3-12 months, mean age: 47.8 yrs (SD: 12.8), 35% female. 56% of the patients do not know the reason for their tinnitus, 16% indicate noise trauma, 10% stress and 7% sudden hearing loss to be the main reason of their tinnitus. Classification procedures revealed six to ten groups for which we observed differences with regard to distress, anxiety, depression and sleep problems as well as heterogeneity in change scores on THI-12 (Greimel et al., 1999) total score and response patterns during the RCT run-in phase.

## **Neural Correlates Of Tinnitus Related Distress - An fMRI -Study**

*Dennis Golm\*, Carsten Schmidt-Samoa, Peter Dechent, Birgit Kroener-Herwig*  
\*University of Goettingen, Department of Clinical Psychology and Psychotherapy, Germany

Approximately 5% of the population is affected by chronic tinnitus. However, only 20% experience severe distress due to the phantom noise. This distress cannot be predicted by psychoacoustic features of tinnitus. It is commonly assumed that negative cognitive emotional evaluation of tinnitus and its expected consequences is a major factor determining the impact of tinnitus related distress. The neurophysiological model proposes differences of limbic activation levels between high and low distressed tinnitus patients. As an extension aglobal brain model proposes a top-down-modulation of a fronto-parietal-cingulate network on the excitability of the auditory cortices, mediated by the amount of tinnitus related distress. An experimental paradigm using semantic material to stimulate cognitive emotional processing of tinnitus related information was conducted. High and low distressed tinnitus patients and healthy controls (n=16, N=48) underwent fMRI while sentences with neutral, negative or tinnitus related content were presented. A random effects group analysis was performed on the basis of the general linear model. Tinnitus patients showed stronger activations to tinnitus related sentences in comparison to neutral sentences than healthy controls in various limbic/ emotion processing areas, such as the ACC, MCC, PCC, RSC and insula and also in frontal areas. High and low distressed tinnitus patients differed in terms of activation of the left middle frontal gyrus. These results and correlational analysis between the beta-values of relevant contrasts and tinnitus related distress support the idea of a fronto-parietal-cingulate network, which seems to be more active in highly distressed tinnitus patients.

## **Stress And Hearing Problems**

*Dan Hasson, Associate Professor  
Karolinska Institutet , Department of Physiology and Pharmacology , Stockholm, Sweden*

The associations between stress and hearing problems have not been previously reported in a human population. This presentation will review a recently completed study demonstrating associations between stress and hearing problems (hearing loss, tinnitus and hyperacusis) in 350 individuals with different levels of burnout scores (normal vs. medium and high long-term stress). Hearing tests (pure tone, speech in noise, uncomfortable loudness) was obtained before and after an acute stress challenge (cold pressor in combination with emotional stroop and social stress). Preliminary results indicate that those who have symptoms of long-term stress have increased hearing sensitivity after acute stress. This was in contrast to the normal subjects whose hearing sensitivity adaptively decreased after acute stress. Moreover, it was found that long-term stress and coping strategies (only in men) were the strongest predictors of tinnitus, even stronger than traditional risk factors (i.e., hearing loss, age, sex, hyperacusis). These findings are highlighting the importance of including burnout as a risk factor for hearing problems.

## **In Search Of An Objective Measure Of Tinnitus: The Acoustic Startle Paradigm And Psychoacoustic Parameters**

*Sylvie Hébert  
École d'orthophonie et d'audiologie, Université de Montréal  
& BRAMS, International Laboratory for Brain, Music, and Sound Research, Montréal, Canada*

The search for an objective measure of tinnitus that could be used before and after treatments to assess their effectiveness is an important issue in tinnitus research. Recently such an approach based on an acoustic startle paradigm has been proposed in an animal model of tinnitus. Acoustic startle is a primitive reflex produced by a sudden and unexpected loud sound. In normal-hearing rodents, a silent gap inserted amidst a background noise presented a few milliseconds before the loud sound stimulus was shown to inhibit the startle reflex. In contrast, in rodents with salicylate- or noise- induced tinnitus, the startle reflex was obtunded, presumably because the gap was filled by the tinnitus sound. Such inhibition was specific to background noise similar to the tinnitus frequency. Therefore, this approach may be useful to objectively demonstrate the presence of tinnitus. We applied this paradigm to human participants with high-frequency tinnitus. Preliminary results indicate that animal findings can be replicated in human subjects, suggesting that the startle reflex may be a promising approach from which an objective measure of tinnitus may be derived. However, it will be necessary to further address caveats such as selection of adequate frequency background noise with reference to the specific tinnitus frequency and loudness, as well as test-retest reliability. Therefore, carefully characterization of adequate tinnitus parameters using appropriate methods is needed, in particular at high frequencies (above 8kHz). I will introduce two novel participant-controlled methods (touch-screen and frequency slider selection) that were tested and compared in our laboratory to assess the psychoacoustic parameters of tinnitus.

## **Auditory Perceptual Learning At Normal Hearing Frequencies Affects Changes In Tinnitus Intrusiveness And Percept**

*Derek J Hoare<sup>\*</sup>, Victoria L Kowalkowski, and Deborah A Hall  
NIHR National Biomedical Research Unit in Hearing, Nottingham, United Kingdom*

That auditory training may have efficacy for tinnitus draws on observations that link tinnitus and hearing loss with altered activity at different levels of the auditory system, and that auditory perceptual training affects neural plasticity in the auditory cortex. We present a double-blind randomised trial of frequency discrimination training involving 42 participants who had chronic subjective tinnitus. Participants were randomly assigned to train at a pure tone whose frequency was either within the region of normal hearing or in the region of hearing loss, or a harmonic complex tone made up of four components spanning the region of hearing loss. Participants did 20 training sessions of 30 minutes over 4 weeks. Only groups trained on pure tone frequencies showed significant perceptual learning on the training task. Outcome measures were the Tinnitus Handicap Questionnaire, a Visual Analogue Scale of tinnitus loudness, and psychoacoustic measures of tinnitus pitch and loudness. Previous studies suggest that training which provides sound enrichment for hearing loss frequencies has benefit for tinnitus. However, we found that the group to show a significant reduction in tinnitus handicap was that trained at frequencies in the region of normal hearing, and not either group trained at hearing loss frequencies. This benefit was maintained at one month follow-up. Furthermore, the same group also showed notable changes in both the frequency of the dominant tinnitus pitch and matched tinnitus loudness after training. We conclude that frequency discrimination training at normal hearing frequencies which results in perceptual learning has potential benefit for tinnitus. The mechanism of benefit will require functional studies.

## **Noise-Induced Hyperactivity In The Inferior Colliculus And Its Relationship With Hyperactivity In The Dorsal Cochlear Nucleus**

*James A. Kaltenbach<sup>\*</sup> and Nauman Manzoor  
Department of Neurosciences, Lerner Research Institute/Head and Neck Institute  
Cleveland Clinic, Cleveland, Ohio, USA*

Hyperactivity after intense sound exposure has been identified at several levels of the auditory system, including the dorsal cochlear nucleus (DCN), inferior colliculus (IC) and auditory cortex. The means by which these auditory centers become hyperactive is unclear but one possibility is that they acquire their hyperactivity independently via shifts in the balance of excitation and inhibition or other plastic changes. Another possibility is that hyperactivity at some levels of the auditory system might be driven by input from other hyperactive centers via a bottom-up or top-down mechanism. Recently, we showed that noise-induced hyperactivity at selected recording sites in the IC could be abolished by ablating the contralateral DCN, providing evidence for a bottom-up mechanism in the IC. However, because the recording site was limited to a single locus in each animal, the data could not rule out the possibility that hyperactivity might have persisted in other parts of the IC or may have been an artifact of tissue movement caused by the ablation. To test these possibilities, we performed a more in-depth study examining how DCN ablation affects noise-induced hyperactivity across the full tonotopic range of the IC. Hyperactivity was induced in the IC of hamsters by exposure to an intense (115 dB SPL) 10 kHz tone for 4 hours. After 1-4 weeks post-exposure, we performed electrophysiological recordings as a function of depth through the central nucleus of the IC. Complete ablation of the DCN resulted in a nearly complete loss of hyperactivity in the contralateral IC across the entire tonotopic range. Incomplete lesions of the DCN lead to only a partial loss of hyperactivity in the IC. These findings suggest that the DCN plays a supporting role in driving hyperactivity at the IC level via a bottom up mechanism. We discuss the implications of these findings and what they suggest about possible neural mechanisms of tinnitus. (This work was supported by NIDCN grant R01 DC009097).

## Directing Cortical Plasticity To Understand And Treat Tinnitus

*Michael P. Kilgard\*, Sven Vanneste, Dirk De Ridder, William A. Vrana, Navzer D. Engineer, Michael S. Borland, Justin A. Nichols, Marco Atzori, Andrew M. Sloan, Robert L. Rennaker  
University of Texas at Dallas, Richardson, Texas, USA*

Many studies have documented that tinnitus is associated with hearing loss and changes in neural activity. The prevailing hypothesis is that hearing loss leads to pathological brain changes that are directly responsible for tinnitus. This hypothesis has proven difficult to test. Correlation alone does not imply causation and there are few methods available to direct the long lasting brain changes that might reverse tinnitus. We have developed a novel method to direct highly specific and long lasting neural plasticity and used it to test the hypothesis that abnormal neural activity (and not hearing loss per se) can be responsible for chronic tinnitus. Our method involves repeated delivery of brief bursts of vagus nerve stimulation paired with different pure tones. The idea is that pairing release of neuromodulators (such as acetylcholine and norepinephrine) with tones that are distant from the tinnitus frequency will reverse the frequency map distortion and reduce the pathological activity patterns associated with tinnitus. The results of our animal study are consistent with the hypothesis that reversing the abnormal activity in the central auditory system can eliminate tinnitus. We have begun a series of human and animal studies to better understand how to optimize VNS-tone pairing as a therapy for chronic tinnitus. We are examining the mechanism of action and the factors that are predictive of treatment efficacy. We have begun a pilot trial and initial results are encouraging.

## Electric Stimulation Of The Basal Cochlear Turn And Electric Acoustic Stimulation As Treatment Of Tinnitus

*Andrea Kleine Punte\*, Ellen Cochet, Marc De Bodt, Paul Van de Heyning  
Univ. Dept. Otorhinolaryngology and Head and Neck Surgery, Antwerp University Hospital,  
University of Antwerp, Antwerp, Belgium*

Background: Electrical stimulation (ES) of the cochlea via cochlear implantation (CI) has been reported as a successful tinnitus treatment in patients with single-sided deafness (SSD) (Van de Heyning et al. 2008, Kleine Punte et al. 2011). Severe steep sloping high frequency hearing loss (HFHL) is also often accompanied by tinnitus and can be treated with electric acoustic stimulation (EAS). Aim: To report on the treatment of tinnitus with electric stimulation of the basal part of the cochlea via CI and electric acoustic stimulation (EAS). Methods: 7 patients with SSD were implanted with a Med-EL SonataTI 100 CI. All patients suffered from severe incapacitating tinnitus. In the first four weeks of CI activation electrodes 1-4 were subsequently activated. After 4 weeks all 12 electrodes were activated. 3 patients with HFHL were treated with EAS with ES in first 18mm of the cochlea. Tinnitus analysis was performed and tinnitus loudness (TL) was measured with the Visual Analogue Scale (VAS (0-10)) before treatment and after implantation with and without electrode activation. Results: In SSD, ES of the first basal cochlear turn reduced tinnitus in one patient. The other 6 patients did not experience a significant decrease with ES of the 1<sup>st</sup> basal turn of the cochlea. After activation of all inserted electrodes the remaining 6 patients also reported a significant reduction of tinnitus, TL decreased acutely from 8.25/10 on the VAS to 4.6/10, and after 6 months of ES TL decreased further to 3.2/10. In HFHL EAS could significantly reduce tinnitus in all 3 patients. Conclusions: ES of the complete cochlea seems more effective to treat tinnitus than ES of the basal part of the cochlea in patients with profound hearing loss. However, in patients with residual low frequency hearing ES over a reduced cochlear length may be effective in reducing tinnitus when combined with acoustic stimulation of the low frequencies.

## **Efficacy Of Different Protocols Of Repetitive Transcranial Magnetic Stimulation (rTMS) For The Treatment Of Tinnitus: A Randomized Controlled Study**

*Tobias Kleinjung\*, Michael Landgrebe, Elmar Frank, Martin Schecklmann, Philipp G Sand, Veronika Vielsmeier, Goeran Hajak, Berthold Langguth*  
*Interdisciplinary Tinnitus Clinic, University of Zurich, Dept. of Otorhinolaryngology, Zurich, Switzerland*

Background: Tinnitus affects the quality of life severely in 1-3% of the population and is related to alterations in neuronal activity of auditory and non-auditory brain areas. Targeted modulation of the auditory cortex and the frontal cortex by repetitive transcranial magnetic stimulation (rTMS) has been proposed as a new therapeutic approach for chronic tinnitus. Methods: We undertook a randomized, double-blind, parallel-group, sham-controlled clinical study for investigating different rTMS protocols for the treatment of tinnitus. 192 adults aged 20-79 years, suffering from chronic tinnitus were randomly allocated to receive 10 stimulation sessions of either sham rTMS, PET based neuronavigated 1 Hz rTMS, 1 Hz rTMS over the left auditory cortex, or combined 20 Hz rTMS over the left frontal cortex, followed by 1 Hz rTMS over the left auditory cortex. The primary outcome was the change of the Tinnitus Questionnaire (TQ) score between baseline and end of treatment. Findings: rTMS treatment was well tolerated and no severe side effects were observed. All active rTMS treatments resulted in a significant reduction of the TQ as compared to baseline, (neuronavigated: mean difference: 1.88, CI: 0.16-3.59,  $p=0.032$ ; left temporal: 2.00, 0.18-3.82,  $p=0.032$ ; combined: 3.32, 1.23-5.40,  $p=0.002$ ), whereas no such effect was observed for the sham rTMS group (0.76, -0.88-2.39,  $p=0.26$ ). The comparison between treatment groups failed to reach significant differences. The number of treatment responders was higher for temporal rTMS (38%) and combined frontal and temporal rTMS (43%), as compared to sham (6%). Interpretation: This large study demonstrates the safety and tolerability of rTMS treatment in tinnitus patients. While the overall effect did not prove superior to placebo, secondary outcome parameters argue in favor of the active stimulation groups, and specifically the combined frontal and temporal rTMS protocol. Funded by Tinnitus Research Initiative.

## **Molecular Aspects Of Tinnitus**

*Rüttiger L, Singer W, Zuccotti A, Matsumoto M, Panford-Walsh R, Köpschall I, Rohbock K, Zimmermann U, Knipper M\**  
*University of Tübingen, Department of Otorhinolaryngology, Hearing Research Center Tübingen, Molecular Neurobiology, Tübingen, Germany*

Aberrant neuronal activity, occurring during tinnitus, is known to lead to changes in neuronal plasticity. However, molecular changes following sensory trauma and the subsequent response of the central nervous system are only poorly understood. We focused on finding a molecular tool for monitoring the features of excitability, which occur in the auditory system following acoustic trauma. In our rodent animal model, perception of tinnitus was studied by a behaviour test (Rüttiger et al., Knipper, 2003) thereby allowing to differentiate between animals which experience, and those, which do not experience, tinnitus. At different time points after tinnitus induction, the expression of several genes was analysed in the cochlea and in the central auditory system. Here, we present a summary of recent findings comparing and correlating expression of different genes with functional and physiological data after different trauma paradigms and time points. Moreover initial trials are done to pharmacologically reverse/influence changes in tinnitus behavior and in gene expression that occur after trauma, using local round window or systemic drug application. Supported by a grant from the Tinnitus Research Initiative, the Marie Curie Research Training Network CavNET MRTN-CT-2006-035367, Deutsche Forschungsgemeinschaft, grant DFG-Kni-316-4-1 and the Hahn Stiftung (Index AG).

## The Frequencies Characteristics Of Tinnitus And Its Impact On Sound Treatment

*Weijia Kong*

*Wuhan Union Hospital of Tongji Medical College, Department of Otolaryngology, Wuhan, China*

**Objectives:** Observe and analysis the effects of the Residual inhibition (RI) test and other tinnitus evaluations at different octaves or half-octaves. **Methods:** Collect 681 patients data from outpatient department, then detailly evaluation and analysis 370 patients after screening. The patients were evaluated by tinnitus tests such as sound type matching (pure tone and narrow-band noise), pitch matching, intensity matching, minimal masking level (MML), tinnitus masking curves, and residual inhibition test at different frequencies respectively with the loudness at the MML, 10dB HL less and 10 dB HL more than MML by both pure tone sound and narrow band noise for 142 ears screening from the cases, and the RI test was executed in each octave or half-octave. Then they were divided into 9 groups according to frequencies 125HZ, 250HZ, 500HZ, 1000HZ, 2000HZ, 3000HZ, 4000HZ, 6000HZ and 8000HZ in pitch match process. **Results:** The hearing loss mainly happened at high frequencies ( $p < 0.05$ ). The congruence (22.98%), convergence (32.83%) and the distance (28.28%) type of tinnitus masking curve occupied large proportion and their positive ratio is greater than others ( $p < 0.05$ ). The tinnitus intensity in high frequencies octaves is statistical significantly smaller than in low frequencies while within the low or high frequencies groups there is no statistical significant differences. After analysis of the cases which chosen for detailed tests, the frequency and loudness of inhibition sound cause different result with subgroups. **Conclusion:** 1) High frequency tinnitus may be more sensitive in perception of inhibition sounds. 2) Tinnitus masking curves have different effects. 3) How to set the mixing-point of individual tinnitus should put onto a more important position than just undergo the sound inhibition therapy. **Keywords:** tinnitus, octave, residual inhibition.

## Neuroimaging And Neuromodulation: Complementary Approaches For Identifying The Neuronal Correlates Of Tinnitus

*Langguth B<sup>1</sup>, Schecklmann M<sup>1</sup>, Poepl T<sup>1</sup>, Kreuzer P<sup>1</sup>, Landgrebe M<sup>1</sup>*

*<sup>1</sup>Department of Psychiatry, Psychosomatic Medicine and Psychotherapy and Tinnitus Center, University of Regensburg, Germany*

An inherent limitation of functional imaging studies is its correlational approach. In other words, functional imaging can only reveal alterations of neuronal activity that are related to a specific symptom, but cannot distinguish, which alterations are of causal relevance and which may just represent epiphenomena. More information about critical contributions of specific brain regions can be gained by focal transient perturbation of neural activity in specific regions with noninvasive focal brain stimulation methods. In tinnitus patients functional imaging studies have revealed alterations in neuronal activity of central auditory pathways, probably resulting as a consequence of sensory deafferentation. Modulation of neuronal activity in auditory cortical areas by repetitive transcranial stimulation (rTMS) can reduce tinnitus loudness and, if applied repeatedly, even may exert therapeutic effects, confirming the relevance of auditory cortex activation for tinnitus generation and persistence. However stimulation of auditory areas reduces tinnitus only in a subgroup of patients and the effect size is only moderate. Measurements of oscillatory brain activity before and after rTMS provide an explanation for this finding by demonstrating that the same stimulation protocol has different effects on brain activity in different patients. Moreover these measurements indicate, which changes of auditory cortex activity are related to subjective perceptual changes. In addition to alterations in auditory pathways, imaging techniques also indicate the involvement of non-auditory brain areas. These non-auditory brain areas include fronto-parietal areas representing an 'awareness' network involved in the conscious perception of the tinnitus signal as well as a non-tinnitus-specific distress network consisting of the anterior cingulate cortex, anterior insula and amygdale. Preliminary studies targeting the dorsolateral prefrontal cortex, the dorsal anterior cingulate cortex and the parietal cortex with rTMS and with transcranial direct current stimulation confirm the relevance of the mentioned non-auditory networks. Available data indicate the important added value of brain stimulation as a complementary approach to neuroimaging for identifying the neuronal correlates of the various clinical aspects of tinnitus.

## **Towards A Neural Prosthesis For Tinnitus: Understanding The Corticofugal Network Involved With Auditory Plasticity**

*Hubert H. Lim*

*Biomedical Engineering, University of Minnesota, Minneapolis, USA*

Tinnitus can be viewed as abnormal reorganization throughout the central auditory system that also extends into non-auditory brain regions. One potential treatment for tinnitus suppression involves brain stimulation to somehow reverse these abnormal changes back to a normal state. Considering that tinnitus has been associated with abnormal tonotopic reorganization, the question arises as to if and where brain stimulation can be applied to reset back the original tonotopy (as well as other tinnitus-related features). Numerous corticofugal plasticity animal studies suggest that the descending system from the auditory cortex to the inferior colliculus, including its central nucleus (ICC), plays a crucial role in the development and maintenance of tonotopic plasticity. Recent findings in patients implanted with central auditory implants further suggest that a fixed tonotopic representation exists or at least is manifested within the ICC. Whether this fixed map coexists with a reorganized map within the ICC is not yet clear. However, we have recently observed the ability to switch different ICC neurons back and forth between altered and normal coding states (i.e., spike firing patterns) by activating specific projections from the outer inferior colliculus to the ICC paired with acoustic stimuli. We can further modulate neurons within the outer inferior colliculus through electrical stimulation of the auditory cortex. These findings support the possibility that the brain may maintain both a fixed and plastic state for tonotopy, such as within the ICC, that can be modulated and switched by corticofugal projections. We are pursuing experiments to test this hypothesis in hopes of identifying specific regions (e.g., inferior colliculus, auditory cortex) that can be stimulated to reset abnormal tonotopic reorganization associated with tinnitus back to a normal state. Whether such a reset effect will lead to perceptual suppression of tinnitus remains to be tested.

## **Effects Of Cyclobenzaprine, A Muscle Relaxant, On Noise Induced Tinnitus**

*Edward Lobarinas, Caroline Shillitoe, Courtney Campbell and Richard Salvi*  
*Center for Hearing & Deafness, University at Buffalo, Buffalo, New York, USA*

Noise induced hearing loss is one of the leading causes of persistent tinnitus. However, how this occurs and how to treat this condition remains unknown. A leading hypothesis is that this form of tinnitus arises from central auditory dysfunction in response to the peripheral ear injury. There are anecdotal clinical reports that Cyclobenzaprine, a commonly prescribed muscle relaxant, may attenuate single sided tinnitus in patients with hearing loss. How Cyclobenzaprine may suppress tinnitus may be related to its pharmacological similarity to first generation tri-cyclic anti-depressants and its action on the central nervous system, where it is believed to affect the Locus caeruleus, a brainstem region associated with vigilance and anxiety. To evaluate Cyclobenzaprine's potential efficacy on tinnitus, we used Gap Prepulse Inhibition of the Acoustic Startle (GPIAS) to probe for behavioral evidence of tinnitus in noise-exposed rats. We hypothesized that unilateral noise exposure would lead to central disinhibition and increased awareness of the phantom sound of tinnitus in animals with behaviors consistent with persistent tinnitus. In the present experiment, rats were unilaterally exposed for 1 h to a 126 dB SPL, narrowband noise centered at 16 kHz. A subset of rats showed behavioral evidence of transient tinnitus at 16-20 kHz. Cyclobenzaprine showed a dose-dependent partial reversal of tinnitus 2 weeks post-exposure. These results suggest that Cyclobenzaprine may attenuate some forms of noise-induced tinnitus and that some forms of central tinnitus may be gated in part by the Locus caeruleus. *Supported by: Tinnitus Research Initiative.*

**Noise Protection For Tinnitus And Hyperacusis Patients With Stress On Teachers And Educators.  
Specific Aspects Of Noise Protection For Patients With Tinnitus  
And/Or Hyperacusis With Particular Stress On Teachers.**

*Lux-Wellenhof G.*

*Tinnitus and Hyperacusis Centre Frankfurt/Main, Frankfurt, Germany*

It is a challenge for every acoustician and ENT-doctor to provide noise protection for tinnitus- and hyperacusis patients. The problem is even more difficult for teachers and educators who work in class rooms with background noise and reverberation and at the same time their work necessitates good speech understanding. Understanding of speech in a classroom could be difficult even for a person with normal hearing, but it is especially challenging for those with hearing disorders. These people need better acoustic conditions for understanding. We developed noise protection for different professional groups working in noisy surroundings with special emphasis on persons with tinnitus and hyperacusis. Apart from improving the quality of life for the patients, these new possibilities of noise protection help to prevent loss of working hours. For these professionals we developed a special method, which in our experience proved to be very helpful. It is a combination of specially formed ear pieces, which attenuate the noise and a frequency amplifier which enhances sound in the speech range and/or compensates for hearing loss. The challenge in providing noise protection for tinnitus and hyperacusis patients is providing the balance of noise protection. Too much of protection is disadvantageous, because it increases the gain within the auditory system consequently increasing tinnitus and hyperacusis. Too small protection could annoy the patient and consequently could aggravate tinnitus and hyperacusis. Last but not least for tinnitus and hyperacusis patients it is important to assure that the perception of the patients' own voice is not too loud, because this could increase the feeling of insecurity.

**Resting-State fMRI Activity In Tinnitus**

*Audrey Maudoux, Philippe Lefebvre, Athena Demertzi, Jean-Evrard Cabay,  
Audrey Vanhauzenhuysse, Steven Laureys, Andrea Soddu*

*Coma Science Group, Cyclotron Research Centre and Neurology Dept. and Dept. of Otorhinolaryngology  
University Hospital of Liège, Belgium*

**INTRODUCTION:** Human neurophysiological and functional brain imaging studies have provided evidence for a distributed network of cortical regions associated with tinnitus. They have visualized various regions of hyperactivity in the auditory pathways as well as activation of non-auditory fronto-parietal, mnemonic and limbic structures in tinnitus patients. However, to date, few studies on tinnitus have focused on the study of functional connectivity, looking at how auditory and non-auditory emotional, mnemonic and attentional regions interact with one another. The aim of this study was to investigate auditory resting state fMRI connectivity in a cohort of patients with tinnitus. **METHODS:** We studied 13 tinnitus patients and 15 age-matched healthy volunteers. 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). We also performed a connectivity analysis using a new methodology that build for any Independent Component a connectivity graph which summarizes the level of connectivity for a defined network of ROIs according to the time behavior described by the auditory component (Soddu et al, Human Brain Mapping 2011). **RESULTS/CONCLUSIONS:** With this experiment, we were able to study the baseline brain auditory activity using fMRI. We report modifications of brain functional connectivity in chronic tinnitus sufferers. We confirm previous evidence of a distributed network of auditory and non auditory cortical regions associated with tinnitus. Regions concerned by these modifications of connectivity are located in limbic (parahippocampal gyrus, nucleus accumbens) and frontoparietal areas, previously shown to play a role in selective auditory attention, evaluation of stimuli significance (saliency) and retention of sensory information.

## The Effects Of Environmental Noise On Tinnitus Induction

*Brad May and Kerrie Tiedemann, Johns Hopkins University, Baltimore, Maryland, USA*

Sound therapy is a well established method for the treatment of tinnitus, but the mechanisms that give rise to resulting benefits are not well understood. In addition, the potential role of sound therapy in tinnitus prevention has not been adequately addressed because treatment of patient populations usually begins after individuals have endured the disorder for months or years. To explore the auditory processes by which sound therapy may influence the induction and maintenance of tinnitus, we have developed an animal model for characterizing the effects of environmental noise on tinnitus behavior and central auditory neural activity. Tinnitus is induced by exposing rats to an intense sound. Successful induction is confirmed by demonstrating behavioral deficits in a gap detection task. Sound therapy is simulated by housing the rats in a heavy-traffic institutional vivarium, where high-exchange air handlers and investigator activity create a loud, temporally complex acoustic environment. Rats express substantially lower rates of tinnitus when they are housed in this noisy environment prior to the damaging sound exposure. These results suggest that sound therapy is an effective intervention for the prevention of tinnitus induction. The treatment does not need to be maintained indefinitely. Noise-housed rats do not develop tinnitus if they are moved to quiet conditions a few weeks after the sound exposure. Work in progress suggests that quiet-housed rats continue to experience tinnitus if they are moved to the heavy-traffic vivarium after they manifest the behavioral phenotype. Consequently, current clinical practice appears to be based on the least effect method of sound therapy. These findings will be discussed in terms of the activity-dependent regulation of synaptic transmission in the central auditory pathways.

## fMRI Activation, Auditory Brainstem Responses, And The Parallel Organization Of The Central Auditory Pathway: Implications For Tinnitus And Hyperacusis

*Jennifer R. Melcher\*, Jianwen W. Gu, Inge M. Knudson, Robert A. Levine,  
Christopher F. Halpin, Barbara Herrmann  
Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston MA USA*

This talk will (1) review functional magnetic resonance imaging (fMRI) and auditory brainstem response (ABR) data for the inferior colliculi as it relates to tinnitus and hyperacusis in humans, (2) explain how the parallel architecture of the auditory pathway can resolve an apparent contradiction between fMRI and ABR data, and (3) discuss whether parallel processing of aberrant neural activity might explain some of the puzzles of tinnitus. The fMRI and ABR results are from tinnitus and non-tinnitus subjects with clinically normal or near-normal thresholds, all behaviorally tested to assess sound-level tolerance. In fMRI, subjects with diminished sound-level tolerance (i.e. hyperacusis) showed elevated fMRI activation in response to sound in the inferior colliculi, whereas there was no relationship between activation and tinnitus. In contrast to fMRI, the ABR data showed effects of tinnitus, but not hyperacusis. Specifically, subjects with tinnitus showed, on average, an elevated wave V, which likely reflects elevated input activity to the inferior colliculus from one of multiple parallel pathways originating in the ventral cochlear nucleus – the pathway arising from spherical bushy cells. The fact that fMRI shows activity elevations in inferior colliculus related to *hyperacusis* whereas ABR wave V, again reflecting inferior colliculus activity, shows elevations related to *tinnitus* is not necessarily a contradiction. Tinnitus and hyperacusis may be triggered by a common peripheral insult, but arise in parallel within the brainstem and inferior colliculi. This scenario would help explain why the two conditions do not always occur together. It is worth considering whether the foundation of this explanation - the parallel architecture of the central auditory system – underlies other seeming contradictions in tinnitus, such as the poor correlation between tinnitus loudness and distress. Funding from ATA, TRI, TRC, NIH/NIDCD.

## **Maintenance rTMS Therapy For Tinnitus: Follow-Up To A PET-Guided Clinical Trial**

*Mark Mennemeier\*, John Dornhoffer, Tiffany Munn*

*\*Department of Neurobiology and Developmental Sciences University of Arkansas for Medical Sciences.*

We completed a placebo-controlled, crossover study that applied 5 days of 1-Hz rTMS over the temporal cortex (1800 pulses per day @ 110% motor threshold) to treat chronic subjective tinnitus in 21 patients. Forty-three percent of patients in this study were designated as treatment responders, achieving a 33% reduction in tinnitus loudness from baseline in at least one ear following active but not sham treatment. We then conducted two follow-up, open-label pilot studies, using the same subjects, to learn if a tinnitus patient's response to repetitive, transcranial magnetic stimulation (rTMS) over the temporal cortex could be improved either by stimulating the hemisphere opposite the side originally targeted for treatment or by stimulating the same hemisphere at a higher frequency. Finally, seven treatment responders were enrolled in an open label study to learn if maintenance rTMS could augment and prolong the duration of rTMS effects. We found that if a subject responded to stimulation of one hemisphere, they also responded to stimulation of the opposite hemisphere in a similar fashion and if they failed stimulation of one hemisphere, they also failed stimulation of the opposite hemisphere. With two notable exceptions, patients who responded positively to 1-Hz rTMS over the temporal cortex also responded to 10-Hz stimulation, and patients who failed 1-Hz rTMS tended to fail 10-Hz stimulation. The exceptions were that 10-Hz stimulation was more beneficial than 1-Hz for tinnitus annoyance, and one patient who failed 1-Hz stimulation subsequently converted to a treatment responder after 10-Hz stimulation. The most important conclusion of this pilot study is that, in treatment responders, maintenance rTMS appears to have an additive and sustained benefit for tinnitus when compared to placebo and to the benefit achieved after a one-week course of treatment. Maintenance treatment delivered every 3 to 6 weeks would appear to be a reasonable schedule for retreatment.

## **Intratympanic Treatment For Tinnitus In The Past, Present And Future**

*Thomas Meyer*

*Auris Medical AG, Basel, Switzerland*

Since the 1940's, various attempts have been made to treat tinnitus of peripheral origin by way of intratympanic injection. This administration procedure requires only low concentrations of medication thanks to the highly targeted delivery to the site of action and comes with minimal systemic exposure. The occurrence of side effects has been an important and potentially dose-limiting factor with various experimental tinnitus drugs that are given systemically. Relatively high systemic doses may be necessary in order to overcome the blood-labyrinth barrier and achieve therapeutic concentrations within the cochlea. While different compounds have been tested with intratympanic injection for their effects on tinnitus, no breakthrough has been achieved so far. Accordingly, clinical use of intratympanic tinnitus treatments has remained limited to date. More widespread adoption of the approach will require the development of specific medications for tinnitus of peripheral origin as well as proof of safety and efficacy established in randomized controlled clinical trials.

## The Effect Of Tinted Light On Perception Of Tinnitus: A Preliminary Study

Mulheran M\*, Gaskin J, Rea P, Banerjee A.

\*Dept. Cell Physiology & Pharmacology, University of Leicester, Leicester UK.

Background: Tinnitus perception can be modulated by a range of cross sensory stimuli, although specific effects of colored (tinted) light on tinnitus have not been previously reported. This preliminary study aimed to establish if tinted light modulated tinnitus perception. Methods: Tinnitus patients (n=94) clinically screened for chronic tinnitus >6 months were recruited. Assessment employed THI scores, Likert and VAS scales. Experiments were conducted in darkened sound proof rooms. Subjects reported if their tinnitus changed whilst observing a 20x30 cm light field at 30-40 cm distance. Illumination was PC controlled and generated by three banks of tuned RGB LEDs, output re: CIE 1931 X:Y colour space (CS) co-ordinates; White=0.333:0.333; 800lx (Orthoscopes, Cambridge, UK). Under user direction for ≈5-10 mins, X:Y points in CS reported to affect tinnitus were identified and recorded re: CIE 1931. Results & Conclusion: 41/94 subjects reported acute improvement at 1 or more CS points, 6/94 reported worsening. Of the main covariates, sex (Fem) and lower median age (60 vs 50 yrs) were significantly (P<0.01) associated with reported improvement. Proportionately more reports of improvement occurred within the predominantly 'blue' CS boundaries; Blue:Red:Green = 29:8:4 ≈ 70%:20%:10%. In particular, there appeared favoured colour regions, eg. X:Y centred at ≈ 0.15:0.1; (an intense 'blue'). Of the 41 reporting improvement, 23 went on to repeat tests at 30-90 mins. All reported improvement, with 13/23 (55%) choosing at least 1 identical 'improving' X:Y CS point re:Test 1. Chronic repeat tests at 6-24 months for 15 returning 'improved' subjects, all reported improvement, with 9/15 (60%) choosing identical CS points re:Test 1. In short 3 min longevity tests by 31/41 improved subjects, median VAS score dropped by 50% from 6 (re:dark) to 3 (p<0.0001). This early study suggests tinted light may have some therapeutic potential in treating tinnitus in responsive subjects.

## Tinnitus: Radiators, Chickenpox, And Keys To Success

Stephen M. Nagler, M.D., F.A.C.S.

General Hearing Instruments, Inc., Atlanta, Georgia, USA

People with tinnitus do not make appointments with healthcare professionals because their ears ring. They say they do, but they are wrong. They make appointments because their ears ring AND it makes them feel bad. If their tinnitus did not in some way or another make them feel bad – if it were not to some extent or another intrusive – then they would have no need to make an appointment in the first place. This presentation examines the mechanisms involved in tinnitus intrusiveness and looks at various approaches that tinnitus clinicians can use to markedly improve the lives of their patients in a truly meaningful way by virtue of mitigating the aversive response to tinnitus and hence the very suffering that brings those patients to their clinics' doorsteps. The Neurophysiological Model of Tinnitus is invoked in the discussion, not because of its association with Tinnitus Retraining Therapy, but rather because the model can be readily employed to palpably illustrate the crucial role played by one's reaction to tinnitus regardless of which treatment approach the clinician feels might be appropriate in any given case. Various roadblocks to progress are enumerated with attention how clinicians can anticipate and effectively address these roadblocks. A clinically useful definition of tinnitus is offered, and emphasis is placed on how the manner in which tinnitus is defined can profoundly empower the tinnitus sufferer to his or her great advantage and relief. *Please note: "Tinnitus: Radiators, Chickenpox, and Keys to Success" contains a variety of highly practical counseling strategies that can be immediately instituted in the clinical setting, strategies that are applicable regardless of treatment approach (TRT, Cognitive Behavioral Therapy, Neuromonics, Progressive Tinnitus Management, Tinnitus Activities Therapy, etc.) The talk was originally designed to be 45 minutes in length; however, I have pared it down to 30 minutes by removing two sections. The thesis takes a while to develop, and I do not believe that I can effectively present the material in a shorter timeframe, nor does it lend itself to poster presentation. Thank you for your consideration.*

## Prevalence Of Intima-Media Thickness Of Carotid Arteries In Tinnitus-Alone Patients

*M.Nakagawa and H.Nakagawa*

*Department of ENT, International University Health and Welfare, Japan*

[Background] Intima-Media Thickness of carotid arteries is useful for the diagnosis of early arteriosclerosis. The examination of Color-Coded Doppler Sonography is often put into a brain-cardio-vascular screening. Japanese researchers reported that tinnitus is highly associated with increased IMT (Fukatsu et al 2011), and the age related hearing loss has also a high mutuality with IMT (Uchida et al 2004). However, the correlations or high prevalence of IMT with hearing disorders are just phenomena. How about vice versa of hearing disorders with IMT? In this study, we investigate retrospectively tinnitus-alone patients with IMT. [Subjects and methods] 42 tinnitus-alone patients older than 40 years old who visit our outdoor clinic without any symptom and were no current medication were evaluated in this study (female 20, male 22. mean age of 64.5). All subjects were performed with Pure Tone Audiometry, loudness-balance matching test, blood examination (LDL cholesterol, Triglyceride etc.), CCDS, Tinnitus Handicap Inventory, Visual analogue scale and Self Related Questionnaire for Depression. [Results] 88.1% of TAPs have mild increased IMT (>1.1mm) and 50% of them have severe (>1.4mm) on left bulbs position. Asymptomatic metabolic disorder is revealed with the blood exam in 32% of them. [CONCLUSIONS] From an oto-neurological perspective, metabolic disorders are beyond a complaint of tinnitus. Therefore, evaluation of possible involvement of the metabolic disorders seems feasible in all patients with tinnitus, as well as using CCDS. We know that the possibility of existence of IMT-related tinnitus. However, tinnitus patient with increased IMT, when it is mild or more, have to be referred to a specialist of internal medicine. All first visit tinnitus patients have to be performed when it is still controversial discussion in the oto-neurological diagnostic value of IMT for tinnitus. Keywords: IMT, tinnitus, Color Coded Doppler Sonography

## The Central Models Of Tinnitus And Their Clinical Implications

*Arnaud J. Norena*

*University of Provence and CNRS, Marseille, France*

More than 3 decades ago, tinnitus was thought to result from an “aberrant” activity in the cochlear nerve caused by cochlear damages. This hypothesis suggested implicitly that the auditory centers played only a “passive” role in the emergence of tinnitus: they were involved in the detection but not in the generation of the tinnitus-related signal. Importantly, most cochlear damages being irreversible, it was thought that no cure would suppress tinnitus. However, cochlear damages are accompanied by a decrease of firing rate in the cochlear nerve and cochlear nerve section does not always abolish tinnitus. These results suggest that tinnitus, or at least some types of tinnitus, may originate from (plastic) changes beyond the cochlear nerve, namely in the auditory centers. This hypothesis, proposed as early as 30 years ago, is now widely accepted in the tinnitus field as the most probable origin of the majority of tinnitus. I will review the models of tinnitus hypothesizing that auditory centers are involved in the generation of the tinnitus-related signal. I will especially focus on the reorganization of the cortical tonopic map, on the changes in central gain after sensory deprivation and on the putative neural correlate of tinnitus (is tinnitus related to an increase of neural synchrony or an increase in firing rate?). Finally, I will present the clinical implications of these models.

## **Methodological And Statistical Problems In Tinnitus Research: The Literature On rTMS**

*Jay F. Piccirillo\*, Andre Wineland, Joyce Nicklaus, Dorina Kallogjeri, Edward L. Spitznagel, Jr.  
Department of Otolaryngology – Head and Neck Surgery,  
Washington University School of Medicine  
St. Louis, Missouri, USA*

Repetitive transcranial magnetic stimulation (rTMS) is a relatively novel treatment for tinnitus. Numerous reports in the published literature describe the impact of rTMS in patients with tinnitus with varying reports of success. We hypothesized that the differences in outcome may be due, in part, to methodological and statistical problems in the conduct and reporting of rTMS for tinnitus research. To explore this question, a comprehensive review of the published literature on rTMS for tinnitus was conducted. The published literature was searched for all articles that included the terms “rTMS”, “tinnitus”, “human subjects”, and were published in the English language. A total of 56 articles were identified and reviewed. Standard criteria for the reporting the results of a randomized trial (*CONSORT*) and cohort studies (*STROBE*) were used to identify methodological and statistical problems. Among the clinical trials, failure to perform sample size/power calculations before conducting the trial, no definition of amount of change in tinnitus measure associated with clinically meaningful improvement, and no assessment of quality of sham were frequently identified problems. Among observational research, failure to include controls, failure to recognize potential sources of bias and control for confounding factors, and failure to adequately describe sampling techniques, which limits the ability of the reader to generalize the findings. A review of the published literature on clinical trials and observational studies of rTMS for tinnitus revealed multiple opportunities for improvement in the conduct of these studies. We present a checklist for the conduct and reporting of future clinical trials and observational tinnitus research. Improvement in the conduct of clinical research will aid in the identification of effective treatments and, ultimately, improve the lives of tinnitus patients. This research was supported by grants from the National Institutes of Deafness and Other Communication Disorders (R01 DC009095 and T32DC000022)

## **Auditory And Limbic Components Of Tinnitus Revealed By Functional Imaging In Humans**

*Josef P. Rauschecker  
Georgetown University Medical Center, Washington, DC, USA*

The mechanisms underlying subjective tinnitus, the perception of sound in the absence of a corresponding acoustic stimulus, are not well understood, which has slowed development of effective treatments. We recently proposed a model (Rauschecker et al., 2010; Leaver et al., 2011) that may open up new ways of treating tinnitus by targeting the limbic system. Like many researchers, we assume that the tinnitus signal initially arises from changes in the auditory system (distortion of tonotopic maps, hyperactivity of auditory neurons). However, these changes alone cannot explain why tinnitus does not occur in all cases of hearing loss, why it is intermittent in some patients, and why it can be modulated by non-auditory influences such as stress and fatigue. Integrating recent evidence for limbic system involvement in tinnitus, our model explains that the limbic system can suppress tinnitus-related thalamo-cortical activity, thus preventing the tinnitus signal from reaching awareness. If the limbic system is compromised, either permanently or temporarily (e.g., due to limbic-system overload from stress or fatigue), this “noise-cancellation system” fails and tinnitus is perceived. In my talk, I will describe experiments that use high-resolution functional magnetic resonance imaging (MRI) to assess changes in auditory cortex as well as in regions of the limbic system (medial prefrontal cortex and ventral striatum), which we believe are essential for causing chronic tinnitus. Identifying brain locations and biomarkers of tinnitus will help to develop effective ways for treatment.

## Targeting Inhibitory Amino Acid Neurotransmission In Animal Models Of Tinnitus

*Ben D. Richardson and Don M. Caspary  
Southern Illinois University, School of Medicine, Springfield, Illinois, USA*

The perception of tinnitus depends on its representation as a neural signal in the auditory neuraxis and associated structures. Selective targeting of specific circuits and receptors within the central nervous system to relieve the perception of the phantom sound and its impact on one's emotional and mental state has become a focus of tinnitus research. One basic approach involves upregulation of endogenous inhibitory neurotransmitter levels (e.g. glycine and GABA) or identification and activation of dysfunctional inhibitory receptors in hopes of normalizing tinnitus pathophysiology. Tinnitus-related changes in functional neurotransmission, namely inhibitory neurotransmitter systems, enhanced excitability and neural reorganization, have been described in the cochlear nuclei, inferior colliculus and/or auditory cortex of animals with tinnitus. However, little is known about tinnitus-related pathologies in the auditory thalamus – the medial geniculate body (MGB). The MGB is located in a key position to gate the passage of the tinnitus signal from auditory brainstem regions to cortex and limbic structures. Inhibitory regulation of MGB neuronal output is predominantly via IC and thalamic reticular nucleus afferents along with inhibitory interneurons in certain species. Moreover, MGB neurons express a heterogeneous population of GABA<sub>A</sub>Rs, including classical  $\alpha_1\beta_2\gamma_2$  synaptic constructs and the more recently identified  $\alpha_4\beta_3\delta$  extrasynaptic constructs, each having different temporal and pharmacologic properties. The extrasynaptic GABA<sub>A</sub>R subtype shows plastic/activity dependant changes in other pathologic systems (e.g. epilepsy) and may show tinnitus-related changes leading to altered inhibitory tone and enhanced excitability. The presence of a heterogeneous population of GABA<sub>A</sub>Rs, which could be altered in tinnitus pathology, along with its key anatomical position in the auditory CNS make MGB a viable structure for future tinnitus research and pharmacotherapy.

## Electrophysiological Imaging In Tinnitus, Recruitment, And Auditory Attention

*L.E. Roberts\* and D.J. Bosnyak  
McMaster University, Hamilton, Ontario, Canada*

Sound frequencies comprising the tinnitus spectrum track the region of hearing impairment (the tinnitus frequency region or TFR), and optimal residual inhibition (RI) is produced by band pass noise maskers when their center frequencies are in the same region. We investigated whether neural correlates of tinnitus reveal a similar frequency dependence. Neural representations measured by EEG were probed with 40-Hz AM sounds presented either to the TFR or below it (carrier frequencies of 5.0 or 0.5 Hz, respectively). Probes were presented when tinnitus subjects (n = 30) experienced their tinnitus (no-masking condition) or after a band pass noise masker (CF 5 kHz) that produced RI. Sound intensity was matched to a 1 kHz pure tone at 65 dB SL to control for possible abnormal loudness growth in the TFR. Age-matched controls with similar hearing loss but no tinnitus (n = 29) were identically studied. N1 amplitude (generators in secondary auditory cortex) was larger in tinnitus than control subjects with or without masking, and this effect was not frequency dependent. In contrast, ASSR amplitude (generators in primary auditory cortex) was larger in tinnitus subjects than in controls for probes below the TFR without masking while the reverse was true for probes in the TFR, revealing frequency dependence when tinnitus was experienced. Masking increased ASSR amplitude in tinnitus subjects in the TFR, returning it to control levels. We suggest that synchronous neural activity in the TFR of primary auditory cortex may depress synapses receiving inputs to this region from the auditory periphery. Enhancement of ASSR amplitude outside of this region (and of N1 at both probe frequencies) in tinnitus subjects may reflect decreased central inhibition, or frequency non-specific auditory attention that may be activated when corticofugal output generated by synchronous activity in the TFR is not congruent with input conveyed from the damaged ear. (CIHR and NSERC of Canada)

**Spontaneous Hyperactivity In The Auditory Midbrain: Relationship To Afferent Input.**

*Donald Robertson\* and Wilhelmina Mulders*

*The Auditory Laboratory, Physiology, School of Biomedical Biomolecular and Chemical Sciences,  
The University of Western Australia, Crawley, Australia*

Spontaneous neuronal hyperactivity develops in the central nucleus of the inferior colliculus (IC) of guinea pig within 1 week after unilateral acoustic trauma that results in restricted persistent hearing loss. These animals exhibit behavioral evidence of tinnitus. The IC neuronal hyperactivity is demonstrated by recording from large numbers of single neurons in many electrode penetrations through the IC and is most prominent in IC regions corresponding closely to frequencies at which cochlear nerve thresholds are persistently elevated. These cochlear regions do not exhibit inner or outer hair cell loss when examined 2 weeks after the acoustic trauma. Up to 6 weeks post trauma, IC neuronal hyperactivity can be immediately reversed by procedures, including acute cochlear ablation, perfusion with synaptic blockers and olivocochlear efferent stimulation, which rapidly eliminate or partially suppress afferent input to the brain from the traumatized cochlea. Hyperactivity is also observable in the ventral cochlear nucleus 2 weeks after cochlear trauma, consistent with IC hyperactivity at this time not being solely dependent on intrinsic hyperactivity in the dorsal cochlear nucleus. At longer recovery times (8 and 12 weeks) acute removal of cochlear afferent activity no longer results in a significant reduction in IC hyperactivity. These results suggest a two stage model for the development of IC hyperactivity and possibly tinnitus. In the initial stage central neurons become hyper-excitable, resulting in elevated spontaneous firing when driven by afferent input. In later stages, the central neurons themselves become more spontaneously active via intrinsic mechanisms, and hence hyperactivity loses its dependence on afferent drive from the cochlea. If correct, this model suggests future tinnitus therapies that target afferent input in early stages of tinnitus development. Supported by RNID & The Neurotrauma Research Program. The authors gratefully acknowledge the input of R. Salvi, D. Stolzberg and D. Ding.

**Long-Term Somatosensory Effects On Multiple Auditory Centers  
Prior To And Following Cochlear Damage: Implications For Tinnitus**

*Susan. E. Shore \**

*Kresge Hearing Research Institute, University of Michigan, Ann Arbor, Michigan, USA*

Robust functional connections between peripheral and brainstem somatosensory neurons to the cochlear nucleus (CN) provide the substrates for somatosensory modulation of auditory perception, real and phantom. Upregulation of these glutamatergic, excitatory connections after cochlear damage provide the substrates for both the modulation and generation of "somatosensory-based" tinnitus (Shore *et al.*, 2008; Zeng *et al.*, 2009). Using simultaneous, multi-channel recordings in guinea pig we extend our studies to provide evidence for long-term effects of somatosensory stimulation on auditory neurons in both dorsal and ventral divisions of the CN (DCN and VCN) as well as inferior colliculus (IC) and the auditory cortex (AC). Persistent bimodal suppression and enhancement are observed in the DCN, IC and AC, while only persistent bimodal enhancement is observed in VCN. Long-term synaptic plasticity is explored as a dominant underlying mechanism for persistent bimodal effects on DCN and AC neurons. Following unilateral cochlear damage, temporary threshold shifts (TTS) and behaviorally-verified tinnitus, persistent bimodal enhancement prevails over persistent bimodal suppression. The dominant bimodal enhancement likely reflects the upregulation of non-auditory, vGlut2<sup>+</sup> somatosensory innervation to the CN (Zeng *et al.*, 2009) and its subsequent effects on synaptic plasticity.

## **Strategies And Accomplishments Of The Tinnitus Research Consortium**

*James B. Snow, Jr., M.D.,\**  
*Tinnitus Research Consortium, West Grove, Pennsylvania, USA*

The Tinnitus Research Consortium (TRC) is sponsored by a philanthropist who wants to accelerate progress in basic and clinical research on tinnitus. The TRC consists of 12 distinguished auditory scientists who began meeting in 1998 twice a year for brainstorming for new research approaches to tinnitus, developing requests for applications, judging the scientific merit of the applications received and reviewing the progress of funded projects. TRC grants have been made up to \$100,000.00 per year for three years. The sponsor had provided \$600,000.00 per year; so two new grants could be made each year. The good news is that the sponsor's support has been increased by 50% for 2011 so that three grants have been awarded. Some of the landmark studies supported by the TRC over the last 14 years will be reviewed as will the changing conceptualization of the pathogenesis of tinnitus and its management. The effect of strategies of the TRC on the applicants, grantees, scientific field, scientific societies and other funding agencies will be discussed. For example, when the TRC was initiated, sessions devoted to tinnitus research at national scientific meetings were rare. Through the efforts of the TRC, organizations such as the Association for Research in Otolaryngology and the Society for Neuroscience were encouraged to hold special sessions on tinnitus research. Now such organizations have well attended sessions on tinnitus research each year. The size of the TRC grants, large enough to support a substantial research project, has caused several other voluntary agencies to increase the size of their grants toward the TRC standard. The NIDCD and other institutes at the NIH have devoted far more emphasis on tinnitus. By supporting sound research on tinnitus and recruiting world-class scientists to the field, the TRC has led in making tinnitus research respectable.

## **Current-Source Density And Multiunit Analysis Across Layers Of Primary Auditory Cortex Following Systemic Salicylate Administration In The Rat**

*Daniel Stolzberg, Richard Salvi, and Brian Allman*  
*Center for Hearing & Deafness, University at Buffalo, Buffalo, New York, USA*

Systemic salicylate administration at high doses is known to induce temporary tinnitus in rats and humans. While previous investigations have sought to characterize salicylate-induced alterations in primary auditory cortex (A1), little information currently exists regarding cortical layer-specific alterations in neural activity. In order to investigate layer-specific changes associated with pharmacologically-induced (250 mg/kg, IP Na<sup>+</sup>-salicylate) tinnitus, we used 32-channel linear array electrodes to sample sound-driven local field potential and multiunit activity simultaneously. Following salicylate, current-source density (CSD) analysis based on the noise-burst evoked translaminar local field potentials revealed significantly enhanced activation of granular and supragranular layers. Furthermore, multiunit responses to noise bursts, which were normally sparse in supragranular layers, became apparent following salicylate treatment. In addition, frequency-receptive fields were generated from multiunit activity and the average rectified current (AVREC) of the CSD profile. Multiunit receptive fields shifted and/or expanded their representation to the previously identified pitch of salicylate induced tinnitus in rats (10 – 20 kHz), indicating a disproportionately large representation of the tinnitus pitch along A1 tonotopy. Interestingly, AVREC receptive fields exhibited enhanced responses concentrated to tones near the previously estimated tinnitus pitch and near hearing threshold. Evidence from this study supports the hypothesis that salicylate directly disinhibits A1 resulting in increased sensitivity to sound near the tinnitus pitch and intensity. Furthermore, significantly altered CSD and multiunit activity in supragranular layers implicates intracortical mechanisms may be co-opted for abnormally large spectral integration tuned to the tinnitus pitch. Understanding alterations in A1 neural activity in context of its microcircuitry will hopefully lead to pharmacological interventions for chronic tinnitus in humans. Supported in part by NIH grants R01DC0090910, R01DC009219, F31DC010931-01 and 1R03DC011374-01.

### **Early Age Hearing Loss Suppresses GABA-A Receptor $\delta$ Subunits In The Inferior Colliculus And Affects Sound Tolerance**

*Wei Sun\**, Qiang Fu, Senthilvelan Manohar, Anand Kumaraguru, Aditi Jayaram, Brian Allman and Ji Li  
\* Center for Hearing & Deafness, Department of Communicative Disorders & Sciences,  
University at Buffalo, Buffalo, New York, USA

Recent clinical studies suggest that the recurrent otitis media in children may be related with hyperacusis, a marked intolerance to an otherwise ordinary environmental sound. However, it is unclear whether the hearing loss caused by otitis media in early age will affect the sound tolerance later in life and how the central auditory system is affected by early age sound deprivation. In this experiment, we studied the effects of tympanic membrane (TM) damage at postnatal 16 days on sound perception and GABA receptor expression development in rats. Two weeks after the TM perforation, more than 80% of the rats developed audiogenic seizure (AGS) when exposed to loud sound (120 dB SPL white noise, < 1 minute). The susceptibility of AGS lasted at least sixteen weeks after the TM damage, even the hearing loss recovered. The TM damaged rats also showed significantly enhanced acoustic startle responses compared to the rats without TM damage. These results suggest that the early age conductive hearing loss may cause an impaired sound tolerance during development. c-Fos staining showed a strong staining in the inferior colliculus (IC) in the TM damaged rats, not in the control rats, after exposed to loud sound, indicating a hyper-excitability in the IC during AGS. Using gene arrays and Western blotting technique, we identified a significant reduction of the mRNA and protein levels of GABA-A receptor  $\delta$  and  $\alpha 6$  subunits in the IC in the TM damage group compared to the control group. These results indicate that early age conductive hearing loss can impair sound tolerance by reducing the GABA inhibition in the IC. Supported by the Action on Hearing Loss (G42)

### **Effects Of Fractal Tones On Tinnitus And Relaxation**

*Robert W. Sweetow, Ph.D.*  
University of California, San Francisco, California, USA

The adverse relationship between stress and the ability to cope with tinnitus is noticeable. Advances in neuroscience and neuro-imaging have provided a greater understanding of the effects of various acoustical, for example, musical, stimuli on the brain and human behavior. Knowledge about site of stimulation, neural interactions, and transfer of neurotransmitters help explain the behavioral consequences, both positive and negative, of exposure to music at both high and low intensities. Studies have shown that listening to certain types of musical stimuli induces relaxation in most individuals, but that specific parameters of the music may be important. Consequently, music has recently been employed as a treatment for several physical and mental ailments. For example, many practitioners utilize filtered music with tinnitus patients because of its soothing effect on regions of the brain that are believed to be the generators for the phantom perception and the distress associated with tinnitus. In this session, a discussion of how and why certain aspects of listening to music may be applied to the management of the tinnitus patient will be discussed.

## **Counteracting Tinnitus Symptoms And Related Pathological Cerebral Synchrony By Acoustic Coordinated Reset Neuromodulation**

*Peter A. Tass<sup>\*</sup>, Ilya Adamchic, Hans-Joachim Freund, Tatjana von Stackelberg, Christian Hauptmann<sup>\*</sup>  
Institute for Neuroscience and Medicine, Research Center , Jülich, Germany*

Subjective tinnitus, the percept of sound without an objectively identifiable sound source, often emerges as consequence of a hearing loss. In cortical regions deprived of afferent input a pathologic enhanced neuronal synchronization in the  $\delta$  frequency range evolves. The loudness of tinnitus is highly correlated with abnormal neuronal synchrony in temporal brain regions. Different types of stimulation of the auditory system have been employed in an attempt to disrupt temporarily the tinnitus percept, e.g., presumed to be through inhibiting neuronal firing or reversing maladaptive structural changes. Here using acoustic coordinated reset (CR) stimulation we attempt specifically to counteract pathological, tinnitus-related neuronal synchrony by desynchronization, inducing an unlearning of pathological synaptic connectivity and neuronal synchrony. In a prospective, randomized, single blind, placebo-controlled trial in 63 patients with chronic tonal tinnitus we showed that CR treatment was safe and well-tolerated and resulted in a highly significant decrease of tinnitus loudness and symptoms as measured by VAS and TQ scores. In contrast, placebo treatment did not lead to any significant changes. Effects persisted through a preplanned 4-week therapy pause and showed sustained long-term effects after 10 months of therapy: a responder analysis revealed 75% winners and responders combined with a mean TQ reduction of 50%. Furthermore, CR therapy significantly decreased tinnitus frequency and reversed the tinnitus' characteristic EEG alterations, both indicative of therapy-induced neuroplastic changes. 15 AEs occurred in total of which 4 were judged to be treatment related; all were of mild to moderate intensity and none was permanent. Two SAEs (an abdominal pregnancy and avascular necrosis of the femoral head, not associated with treatment) were reported. CR stimulation has significant clinical therapeutic effects on tinnitus symptoms as assessed by standard clinical scores. Furthermore, with EEG recordings we show that CR stimulation specifically and significantly counteracts the pathological, tinnitus-related neuronal synchronization processes. With appropriately adapted stimuli CR stimulation might also be effective in further brain diseases characterized by abnormal synchrony, such as neurogenic pain, Parkinson's disease, or depression.

## **Mice With Behavioral Evidence Of Tinnitus Exhibit Dorsal Cochlear Nucleus Hyperactivity Due To Decreased GABAergic Inhibition**

*Thanos Tzounopoulos  
University of Pittsburgh, Dept. of Otolaryngology and Neurobiology  
Pittsburgh, Pennsylvania, USA*

We developed an *in vitro* assay to evaluate the roles of excitation and inhibition in determining the neural correlates of tinnitus. To measure the magnitude and the 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 (DCN). FA imaging in DCN 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 in control mice. These findings suggest that DCN circuits in tinnitus mice respond to stimuli in a more robust and spatially distributed manner due to a decrease in GABAergic inhibition.

## Long-Term Tinnitus Relief After Cochlear Implantation In Single-Sided Deafness

*Paul Van de Heyning\*, Andrea Kleine Punte\*, Marc De Bodt\*, Dirk De Ridder*

*\* Univ. Dept. Otorhinolaryngology and Head and Neck Surgery, and Bra<sup>2</sup>in, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium*

**Introduction:** Severe tinnitus can seriously impair patients in their activities in daily life and reduce quality of life. In a previous study we showed tinnitus relief in single sided deafness (SSD) after cochlear implantation (CI) with a 12 month follow up. **Purpose:** The aim of this prospective clinical study was to assess the long-term effects (5 years) of CI on tinnitus and on tinnitus distress in patients with SSD and ipsilateral incapacitating tinnitus. **Material:** 29 subjects participated in this study. Patients suffered from severe tinnitus of more than 6/10 on a Visual Analogue Scale due to unilateral deafness. CI was performed with Medel Combi40+ and Sonata Ti100 implants with the M of Flex Soft electrodes fully inserted into the scala tympani. Nineteen of these subjects had normal hearing (NH-group) on the contralateral side, and ten used a hearing aid (HA-group) contralaterally. **Methods:** Tinnitus assessment consisted of a tinnitus loudness estimation by means of a Visual Analogue Scale (VAS), psycho-acoustic loudness measurement and a Tinnitus Questionnaire (TQ) that was conducted pre-implantation and at regular intervals up to 60 months post implantation (n=20). The results are compared with a delayed startgroup. Subjective improvement in speech in daily situations was evaluated using the Speech, Spatial and Qualities Hearing Scale (SSQ) and speech in noise (SPIN) tests. **Results:** All 29 patients reported a subjective benefit after CI. Tinnitus loudness reduced significantly with CI from 8.9 to 2.7 on the VAS (of 0-10). Psychoacoustically the sensation level dropped significantly. Also the TQ total score decreased significantly, the mean tinnitus degree decreasing from severe to mild. The amount of tinnitus loudness reduction continued to remain stable up to 5 years after CI. SPIN and SSQ value with CI outperform situations without CI. tinnitus and SSD. **Conclusions:** CI causes a significant and durable tinnitus relief and auditory improvement in patients with severe tinnitus and SSD. Van de Heyning et al. *Ann Otol Rhinol Laryngol* 2008;117:645-652. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation.

## Neuroanatomical Properties Of Tinnitus

*Kristiana Boyen, Dave R.M. Langers, Emile de Kleine, \*Pim van Dijk*

*Department of Otorhinolaryngology / Head and Neck Surgery, University Medical Center Groningen Groningen, The Netherlands*

The vast majority of tinnitus patients have a peripheral hearing loss. Maladaptive changes in the brain in response to the hearing loss are believed to play a key role in the pathophysiology of tinnitus. Yet, only a portion of hearing impaired subjects develop tinnitus. Apparently, the maladaptive changes in the brain only occur in a portion of the subjects. This suggests that, in addition to the peripheral hearing loss, characteristics of the brain determine whether a patient develops tinnitus. There may be neuroanatomical or neurophysiological differences between those subjects that develop tinnitus after hearing loss and those that don't. We performed an MRI study to identify tinnitus specific traits in the brain. Voxel-based morphometry (VBM) was performed in 31 subjects with tinnitus and 16 subjects without tinnitus. All these subjects had a moderate sensorineural hearing loss. The groups were matched with respect to age and hearing loss. A third group was normal hearing, had no tinnitus and was age-matched to both hearing impaired groups (n=24). VBM involves the computation of a probability that a voxel in the MRI image contains gray matter. By integrating over a region of the brain (e.g. a Brodmann area) a measure of the gray matter volume is obtained. Volume increases of gray matter associated with tinnitus were observed in the left BA 41 (primary auditory cortex). Furthermore, volume was decreased in the left frontal premotor area BA 8 and left BA 11, and was increased in the left and right BA 22 (auditory association cortex) in both hearing impaired groups. A number of small and less robust changes were observed in frontal, limbic and visual areas of the brain. These results show that hearing loss and tinnitus are associated with changes in the neuroanatomy of gray matter. Possibly, the gray matter differences that relate to tinnitus are a pre-existing condition, that make subjects susceptible to developing tinnitus. Alternatively, the differences may be the consequence rather than the cause of tinnitus, in which case they can possibly be reversed by a treatment for tinnitus. (Work supported by ATA)

## **Tinnitus As An Emergent Property Of Multiple Parallel Dynamically Changing And Partially Overlapping Brain Networks: The Role Of The Emotional Network**

*Sven Vanneste\*, Kathleen Joos, Paul Van de Heyning, Dirk De Ridder  
TRI Tinnitus Clinic Antwerp Belgium, BRAI<sup>2</sup>N and Dept of Neurosurgery & ENT, Antwerp, Belgium*

Introduction: Tinnitus is characterized by sensory discriminatory components such as the perceived loudness, the lateralization, the type (pure tone, noise-like) and an associated emotional component. For an auditory stimulus to be consciously perceived, stimulus induced auditory cortex gamma band activity needs to be embedded in a larger perceptual network. Thus the unified percept of tinnitus can be considered an emergent property of multiple parallel dynamically changing and partially overlapping networks, each with a specific spontaneous oscillatory pattern and functional connectivity signature. Therefore tinnitus can be expected to be related to spontaneous persisting auditory cortex gamma band activity embedded in a similar larger network, and each sensory discriminatory and emotional component is likely related to a specific subnetwork. Here we focus upon the emotional network. Methods: Electroencephalography can be used applying different analysis techniques such as spectral analyses, brain topography, source localization, independent component analysis, correlation analysis, connectivity analysis, and graph theory to explore this emotional tinnitus brain network. In addition invasive and non-invasive neuromodulation techniques can be used to verify the causal relationship of different brain areas delineated by EEG in the emotional tinnitus brain network. Discussion: The role of several non-auditory brain areas such as the amygdala, anterior cingulate cortex (dorsal and subgenual), dorsal lateral prefrontal cortex, insula, supplementary motor area, orbitofrontal cortex (including the inferior frontal gyrus), parahippocampus, posterior cingulate cortex and the precuneus will be discussed as well as their specific role of these brain areas within the emotional tinnitus network. It is interesting that the areas show overlap with the emotional component of the pain matrix. This emotional network will be detailed and combined into a larger conceptual model.

## **Tonic Tensor Tympani Syndrome (TTTS) In Tinnitus And Hyperacusis Patients: A Multi-Clinic Incidence Study**

*Myriam Westcott\*, Tanit Ganz Sanchez, Isabel Diges, Clarice Saba, Ross Dineen,  
Celene McNeill, Alison Chiam, Tricia Sharples, Mary O'Keefe  
Dineen and Westcott Audiologists, Melbourne, Australia*

Introduction: Tonic tensor tympani syndrome (TTTS) is an involuntary anxiety-based condition where the centrally mediated reflex threshold for tensor tympani muscle activity is reduced, causing a frequent spasm. This can trigger physiological reactions in and around the ear from tympanic membrane tension, alterations in middle ear ventilation and trigeminal nerve irritability. TTTS has been proposed as the mechanism causing the symptoms of acoustic shock (AS). AS can develop after exposure to a sudden unexpected loud sound perceived as highly threatening, with hyperacusis a dominant symptom. Aural pain and blockage without underlying pathology have been noted in tinnitus and hyperacusis patients, without wide acknowledgement. This multiclinic study aims to investigate the incidence of TTTS symptoms in tinnitus and hyperacusis patients. Method: This study included consecutive patients with tinnitus and/or hyperacusis seen in clinics in different countries. Data collected: symptoms consistent with TTTS (pain/numbness/burning in and around the ear; aural "blockage"; mild vertigo/nausea; "muffled" hearing; tympanic flutter; headache); onset or exacerbation by exposure to loud/intolerable sounds; tinnitus/hyperacusis severity; hearing loss. All patients were medically cleared of underlying pathology which could cause these symptoms. Those whose only symptoms were headache/vertigo/muffled hearing were excluded. Results: Total sample: 345 patients; 49% with tinnitus only (T group), 51% with hyperacusis (TH/H groups). 41% of T group, 80% of TH/H groups had 1 or more TTTS symptoms. 15% of T group and 63% of TH/H groups had 2 or more symptoms. 19% of total sample had AS (defined as acoustic incident trigger + TTTS), 82% of AS patients had hyperacusis. Conclusion: The high incidence of TTTS symptoms identified suggests they can readily develop in patients with tinnitus, and more particularly in those with hyperacusis. TTTS symptoms should be routinely investigated in history taking.

## **Operational Readiness: The Role of Tinnitus Research**

*Kurt Yankaskas*

*Office of Naval Research, Arlington, Virginia, USA*

Hearing is critical to Warfighter Performance and is integral to processing of information and communications. In 2006, the DoD commissioned an evidence-based study on Noise and Military Service: Implications for Hearing Loss and Tinnitus (National Academies Press, Washington, DC) which came to the conclusion that noted that “achievable attenuation values have not changed substantially since the 1970’s” in the area of hearing protection. It should be no surprise that the annual VA disability payments for tinnitus and defective hearing (hearing loss) exceed \$2 billion for 2009 and continues to increase. The military is a high noise environment, yet the Navy cannot predict who is susceptible to NIHL/tinnitus. Additionally some studies cite approximately 80% of individuals with NIHL suffer from tinnitus. Yet, there are no objective means to measure objectively measure the severity of tinnitus in those individuals. A fundamental understanding of the mechanisms of tinnitus and its relation to noise induced hearing loss is critical. Such an understanding may provide insight to who is at risk for each condition. Potentially it would allow aggressive hearing protection measures to those individuals most at risk for tinnitus/NIHL. This paper will review some of the known noise environments in Navy and Marine Corps systems. It will review some recent breakthroughs in NIHL research and pose some challenges for future research.

## **Sound Diagnosis And Sound Therapy For Tinnitus: Lessons Learned From Cochlear Implants**

*Fan-Gang Zeng\**

*\*Center for Hearing Research, Departments of Anatomy and Neurobiology, Biomedical Engineering, Cognitive Sciences, and Otolaryngology – Head and Neck Surgery, University of California, Irvine, California, USA*

Treating deafness via a cochlear implant is to give sound to those who live in a world of silence, while treating tinnitus is to restore silence to those who live in a world of too much unwanted sound. Despite this opposite research goal, there are many interesting comparisons between these two disciplines that can help us not only learn from history, but also explore future opportunities for improved diagnosis and treatment of both deafness and tinnitus. The first part of this talk will review similarities as well as differences between treating deafness and tinnitus from a historical point of view, particularly on the roles of physicians, engineers and neuroscientists and their intellectual contributions. The second part of the talk will describe recent work on using cochlear implants to suppress tinnitus. The third part of the talk will focus on sound diagnosis and sound therapy of tinnitus. Sound diagnosis deals with psychophysical characterization of tinnitus by asking questions like: What is the difference between loudness recruitment and hyperacusis? What is their relationship to tinnitus? What does tinnitus sound like to a normal-hearing listener? Sound therapy explores the interaction between tinnitus and external sounds by asking questions like: What is the difference between masking and suppressing tinnitus? What are the most effective sounds in suppressing tinnitus? Is there a relationship between the effective sound and tinnitus characteristics? The talk will end with speculations on the neural mechanisms of tinnitus generation and therapy.

**Noise-Induced Tinnitus And Its Neuromodulation**

*Jinsheng Zhang\**, Xueguo Zhang, John Moran, Edward Pace, Kelvin Kwong and Laura Lepczyk

*Department of Otolaryngology-Head and Neck Surgery,  
Wayne State University School of Medicine, Detroit, Michigan, USA*

Hyperactivity, increased bursting events, hypersynchrony and plastic reorganization in the central auditory system have been considered to represent the neural underpinnings of noise-induced tinnitus. The findings were mainly based on evidence gleaned from one auditory center at a time. It is unclear how these neural signatures of tinnitus interact among different brain centers and whether other forms of neural changes may also depict the etiology of tinnitus and its suppression. To further elucidate the mechanisms underlying tinnitus and the neuromodulation for its suppression, we set out to examine neural connectivity and interactions within and among auditory centers and search for new neural signatures of tinnitus by conducting simultaneous multistructural recordings from the dorsal cochlear nucleus (DCN), inferior colliculus (IC) and auditory cortex (AC). These structures are implicated to be related to the etiology of tinnitus. Since brain activity works within and interacts across different frequency bands, we measured coherence to evaluate neural connectivity among recording channels/sites within and among the DCN, IC and AC before and after acoustic stimulation at certain frequency bands (bottom-up modulation) and auditory cortex electrical stimulation (ACES) (top-down modulation). Our data demonstrated that, compared to tinnitus(-) animals, there was increased coherence in the AC of tinnitus(+) animals before the stimulations, supporting the notion that tinnitus percepts are of cortical origin. Acoustic stimulation and ACES suppressed behavioral evidence of tinnitus, which was accompanied by down-regulation of coherence in the AC. However, both types of modulations resulted in different changes in coherence at the brainstem level. This suggests that the induced tinnitus suppression involves adjustment of gating information throughout different brain centers and that both methods modulate tinnitus-related activity using different mechanisms.

## Treatment With Acoustic CR Neuromodulation Induces Changes Of Pathological Tinnitus-Related Oscillatory Brain Activity

*Ilya Adamchic\**, Christian Hauptmann, Peter A. Tass  
 Research Center Jülich, Institute for Neuroscience and Medicine – Neuromodulation  
 INM-7, 52425 Jülich, Germany

Introduction: It has been shown that Tinnitus is associated with an increase in delta and gamma and a decrease in alpha oscillatory activity in specific auditory and non-auditory brain areas. Here we present an EEG analysis on the neurophysiological changes in patients with subjective chronic tinnitus before and after 12 weeks treatment with acoustic coordinated reset (CR) neuromodulation. Methods: EEG recordings were performed at baseline and after 12 weeks of CR treatment. We determined oscillatory activity in predefined regions of interest: primary (AC1) and secondary auditory (AC2), orbito-frontal (OF), dorsolateral-prefrontal (DPFC) and parietal cortex (P), anterior and posterior cingulate area (ACC and PCC) by using BESA source montage and sLORETA. 28 patients with bilateral chronic tonal tinnitus were divided into 2 groups using the reliable change index (RCI) based on the Tinnitus Questionnaire (TQ) changes after 12 weeks of CR (RCI 1, TQ reduction  $\geq 12$  TQ pts; RCI 2, TQ reduction  $< 12$  TQ pts). To investigate the relationship between changes in power spectral and clinical scores we applied a partial least squares regression (PLS) for all patients. Results: In RCI 1 we observed significant decreases in gamma and delta oscillatory activity in AC1, AC2 and DPFC and significant increases of alpha in AC1, AC2, DPFC, OF and PCC. In contrast, no significant changes were observed in RCI 2. In addition we found a positive association between changes in delta and gamma oscillatory activity in AC1 and changes in TQ scores. Changes in VAS loudness and burden were positively associated with changes in delta and gamma oscillatory activity in AC1, AC2, P and cingulated areas. Conclusion: Acoustic CR neuromodulation significantly decreased pathologically elevated delta and gamma oscillatory activity and significantly increased alpha in specific auditory and non-auditory (e.g. limbic) areas. Functional impairment of these areas has been proposed to be a basis for tinnitus and many of its secondary symptoms. Hence, within a large network of auditory and nonauditory areas acoustic CR therapy counteracts pathological synchrony and enhances the physiological alpha rhythm.

## Cochlear Damage, Traumatic Brain Injury And Tinnitus Assessment In A Rat Model Of Blast Wave Exposure

*Brian Allman\**, Senthilvelan Manohar, Sneha Hinduja, Dalian Ding, Andrew Jensen Newman,  
 Joseph Mollendorf, Richard Salvi and Edward Lobarinas  
 Center for Hearing & Deafness, University at Buffalo, Buffalo, New York USA

Blast wave exposure is a major cause of hearing loss and tinnitus among military personnel. In addition to damaging the inner ear, blast wave exposure can induce traumatic brain injury (TBI). Previous studies have identified the hippocampus, one of two regions in the adult brain where neurogenesis occurs, as particularly vulnerable to TBI; however, little is known about how blast exposure affects hippocampal neurogenesis—a process strongly associated with memory function. In the present study, we exposed adult rats to repeated blast waves (3 blasts;  $\sim 187$  dB pSPL) and assessed the extent of damage in the cochlea and hippocampus at various times post-blast. The majority of hair cells survived repeated blast wave exposure, yet the distortion product otoacoustic emissions (DPOAE) were significantly reduced, indicative of impaired outer hair cell (OHC) function. Additional experiments using succinate dehydrogenase and FM-143 staining revealed that although OHCs survived they had reduced metabolic activity and permanent damage to their stereocilia transduction channel which likely contributed to their impaired function. The effect of blast wave exposure on hippocampal neurogenesis differed over time; at 7-days post-blast, double-cortin (DCX) immunolabeling was unchanged compared to age-matched controls, whereas there was suppression of neurogenesis 42-days post-blast. Given the critical role of the hippocampus in learning and memory, we speculate that suppression of neurogenesis in the weeks following blast wave exposure may contribute to the cognitive deficits common in military personnel exposed to blast trauma. Our lab is currently investigating whether the well-established paradigms for tinnitus assessment in animal models (e.g., operant conditioning and gap-startle testing) will need to be modified to accommodate the additional TBI associated with blast-induced hearing loss. Supported by NIH grants (R01DC0090910; R01DC009219-01; 1R03DC011374-01).

### **Expression Of Double Cortin In Unipolar Brush Cells Of The Dorsal Cochlear Nucleus And Cerebellum Of The Adult Rat: Evidence For Adult Neurogenesis?**

*Joan Baizer\*, Senthilvelan Manohar, Nicholas Paolone, Sarah Hayes, Marni Bleichfeld, Richard Salvi  
Center for Hearing & Deafness, University at Buffalo, Buffalo, New York USA*

Tinnitus reflects plastic processes that are hypothesized to occur in structures of the central auditory pathways. One possible mechanism for plasticity is the generation of new neurons, neurogenesis. It is well-established that there is neurogenesis in the dentate gyrus of the hippocampus and the subventricular zone of adult mammals. Neurogenesis in the adult cerebral cortex remains controversial. A number of studies have suggested that neurogenesis might also occur in the adult brainstem and cerebellum. To investigate this possibility we examined closely spaced sections through the brainstem and cerebellum of adult rats that were processed to show immunoreactivity to double-cortin (DCX) and PSA-NCAM, proteins expressed by recently generated neurons and migrating neurons. We found many DCX-immunoreactive neurons in the in the dorsal cochlear nucleus (DCN). These neurons had the appearance of unipolar brush cells (UBCs), with an oval cell body and a single dendrite ending in a "brush." Similar DCX-immunoreactive cells were seen in the flocculus and ventral paraflocculus of the cerebellum. UBCs are glutamatergic interneurons found only in the DCN and vestibulocerebellum. Double-label immunofluorescence showed colocalization of DCX with a protein expressed by UBCs, epidermal growth factor substrate 8 (Eps8). UBCs immunoreactive to PSA-NCAM were found in the same regions. We also saw DCX-immunoreactive cells with the appearance of immature neurons around the fourth ventricle and in its lateral recess. These observations suggest adult neurogenesis of UBCs around the ventricle with subsequent migration to DCN and cerebellum. These neurons in the DCN might then participate in plastic processes underlying tinnitus. Similarly, those in the vestibulocerebellum might contribute to the plastic phenomenon of vestibular compensation. Supported by NIH grants (R01DC0090910; R01DC009219-01)

### **Conservation Of Brainstem Multi-Sensory Integration In Auditory Cortex**

*Gregory J. Basura\*, Seth D. Koehler, Ishan Biswas, and Susan E. Shore  
The University of Michigan, Department of Otolaryngology/Head and Neck Surgery;  
The Kresge Hearing Institute, Ann Arbor, Michigan, USA*

Tinnitus is the perception of sound in the absence of a physical sound stimulus. It is thought to arise from aberrant neural activity within the central auditory pathways that may be influenced by multiple brain centers, including the somatosensory system. Auditory-somatosensory integration occurs in the first brainstem station, the dorsal cochlear nucleus (DCN), where somatosensory stimulation alters pyramidal cell spike-timing and rate representations of sound stimuli. Preceding a sound with spinal trigeminal nucleus (Sp5) activation alters sound-evoked first spike latencies and firing rates for the duration of the sound stimulus (Shore, EJM, 2005; Koehler et al., EJM, 2011). Furthermore, following noise damage, units with increased spontaneous firing rates (a correlate of tinnitus) are more sensitive to somatosensory stimulation (Shore et al., EJM, 2008) implicating somatosensory inputs to the DCN in somatosensory tinnitus. The aims of the present study were to determine if auditory-somatosensory integration is conserved centrally in the auditory cortex (AC), the likely site of tinnitus perception. Four-shank, 32-channel silicon electrodes were placed in guinea pig AC and DCN to simultaneously record tone-evoked unit activity in the presence and absence of electrical stimulation of Sp5. Paired Sp5-tone stimulation induced both enhancement and suppression of tone-evoked firing rates in DCN and AC with more suppression than enhancement in AC. In both DCN and AC, this integration was only evident at short stimulus pairing intervals. DCN units were more sensitive to bimodal stimulation than units in the AC; as reflected by lower thresholds and larger changes in firing rate. These data demonstrate that neuronal firing rates within the central auditory pathway are influenced by the temporal nature of multiple systems and that multimodal neuronal firing patterns exists across multiple regions which may contribute to the generation of tinnitus.

## Diffusion-Tensor Imaging In Adults With Noise-Induced Tinnitus

*Randall Benson, Ramtilak Gattu, Anthony T. Cacace\**  
*Wayne State University, Detroit, Michigan, USA*

To better understand the neurobiology of tinnitus and its relationship to white matter connectivity in the brain, we used diffusion tensor-imaging (DTI) and tract-based spatial statistical analysis (TBSS) to study two groups of adults matched for etiology, degree of hearing loss, and age. Group 1: noise-induced hearing loss alone, n =13, mean age 58 yrs, range 22-88 yrs; Group 2: noise-induced hearing loss plus tinnitus, n =13, mean age 54 yrs, range 28-80 yrs. Magnetic resonance imaging (MRI) data were collected on a Siemens MAGNETOM Verio scanner at 3T using a 32 channel head coil with diffusion sensitizing gradients applied in 20 independent directions. Diffusion tensor imaging data were acquired with a diffusion weighted single shot SE-EPI sequence, where: TR/TE/FA = 7400 ms/106 ms/90°, in plane resolution = 2x2 mm<sup>2</sup>, slice thickness = 3 mm, NEX = 2. The parameters used for the TBSS analysis were fractional anisotropy (FA), where: skeleton threshold = 0.3, voxel-wise permutation-inference analysis (5000 permutations), and a cluster forming threshold of t = 3. Based on our analysis, we found that mean global white matter FA did not differ between groups. Using TBSS to compare groups, only one small region in the left parietal superior longitudinal fasciculus (SLF), showed reduced FA for the tinnitus group compared with non-tinnitus group [MNI<sub>xyz</sub> = 125,90,96]. On the other hand, there were 9 regions which showed significantly increased FA for the tinnitus group, of which 7 were left sided. These included (5) in left anterior thalamic radiations and one, each in the SLF and inferior LF. The two right sided regions were in inferior fronto-occipital fasciculus and SLF. In summary, the specificity of these DTI findings is unique because they are limited to individuals with a common etiology of noise exposure and hearing loss. The importance of these results emphasizes the application TBSS as a way to minimize variability and thereby enhance the validity of the results.

## Using The Pinna Reflex As A Behavioural Test For Tinnitus In Guinea Pigs

*Joel Berger\*, Mark Wallace and Alan Palmer*  
*MRC Institute of Hearing Research, Nottingham, United Kingdom*

Research into the correlates of tinnitus in the brains of animals requires, as a prerequisite, a means of determining which animals experience tinnitus. A simple yet effective test for tinnitus in rats was developed by Turner et al. (2006), based on a gap detection paradigm. A loud sound elicits a reflex contraction of the muscles, known as the whole body startle. When a gap in a lower-level, continuous background noise is presented just before the startling stimulus, the startle response is reduced (pre-pulse inhibition). When the background sound is adjusted to be similar to the animal's tinnitus, the tinnitus percept will fill in the gap and the startle response will not be reduced. In our laboratory, research into the auditory brain has primarily involved guinea pigs. The Turner et al. (2006) test is less reliable in the guinea pig because they rapidly habituate to the startle evoking stimulus. However, the pinna reflex appears less susceptible to habituation and we have developed a method using this pinna reflex as an alternative measure of pre-pulse inhibition. We simultaneously recorded the two reflexes to compare both methods. Pinna movement was measured using a Vicon 3-D motion tracking system with infrared cameras and reflective markers. Whole-body startle was simultaneously measured using a pressure sensitive startle platform. Early results show that there is a greater signal-to-noise ratio for the pinna reflex than the whole-body startle and the pinna reflex shows less habituation. Pre-pulse inhibition of the startle reflex is greater overall than the pinna reflex, though the whole-body startle shows greater variability. These preliminary data suggest that using a combination of the pinna reflex and the whole-body startle may be a more reliable behavioural test for tinnitus in guinea pigs than either method alone.

## **Padden-Choy Procedure**

*Daniel Choy\**

*Tinnitus Control Center, New York, New York, USA*

An FDA approved procedure was introduced in 2003 by the author utilizing self assessed tinnitus pitch and volume played back into the auditory system as sequential six (6) degree phase shifts at 30 second intervals x 360 degrees once a week. It was possible to reduce tinnitus volume by greater than 3 dB with prolonged residual inhibition in 61% of patients. The frequency of treatment was subsequently changed to three times a week, and then to three successive days x 1 week. Tinnitus volume was determined before and after treatments. METHOD: Treatment frequency was increased from: Once a week x 30 minutes x 3 (Group 1) to Once a day x 30 minutes TIW (Group 2) to Once a day x 30 minutes x 3 days in succession (Group 3) RESULTS: Based on minimum reduction of 3 dB: From 2003 to 2007: 176 patients in Group 1 had success rate of 61% with an average reduction of 8.5 dB. From 2007 to January 28, 2010: 96 patients in Group 2 had a success rate of 81% with an average reduction of 7.6 dB. From Feb 1, 2010 to June 21, 2011: 64 patients treated, 64 responded with an average reduction of 12.0 dB.

## **Distortion Product Otoacoustic Emissions (DPOAEs) Are Unaltered During Galvanic Vestibular Stimulation (GVS)**

*Daniela Cocco, M.D.\*, Michael J. Cevette, Ph.D., Gaurav Pradhan, Ph.D., Linsey Wagner, Au.D., Sarah Oakley, Au.D., Anna M. Galea Ph.D., Kenneth Brookler, M.D., Benn Smith, M.D., David Zapala, Ph.D. Jan Stepanek, M.D.*

*Aerospace Medicine and Vestibular Research Laboratory (AMVRL), Mayo Clinic in Arizona, Scottsdale, Arizona, USA*

Introduction: Recently there has been renewed interest in the application of direct current (DC) to suppress tinnitus despite earlier research that suggested DC may damage the cochlea. Level of current and manner of electrical stimulation are important aspects to study in determining any potential effect to outer hair cell function.

OBJECTIVE: The aim of the present study was to evaluate any change in DPOAEs before, during, and after DC GVS in normal hearing subjects. Methods: Fourteen subjects (13 female, 1 male; median age 26) underwent DPOAEs during several conditions of GVS stimulation. DPOAE were measured ranging from ~ 1 kHz to 8 kHz at 65/55 dB for f1/f2 with an f2/f1ratio of 1.2. Subjects were evaluated at 10 conditions of stimulation ranging from -2.0mA to 2.0mA for each frequency. Results: Data showed no statistically significant differences in DPOAE amplitude for all conditions with and without GVS. Results also showed no significant difference between DPOAE response amplitudes preceding and following GVS. Multivariate analysis showed subject variability in DPOAE amplitude which is not thought to be GVS related. Conclusions: Results indicated that GVS does not produce changes in DPOAEs and is a safe technique to investigate the potential beneficial effects of direct electrical current.

## Changes In Auditory Cortex Population Spontaneous Activity Immediately Following Intense Sound Exposure

*Brandon J. Farley and Arnaud Norena\**  
*University of Provence and CNRS, Marseille, France.*

Intense sound exposure often immediately leads to tinnitus, a spontaneous acoustic percept, with a pitch near the frequency of the exposed sound. One hypothesis is that this percept is underlied by trauma-induced changes in spontaneous activity, occurring non-uniformly across the tonotopic axis of the central auditory system. To measure activity simultaneously across the entire auditory cortex with high spatio-temporal resolution, we used voltage-sensitive dye imaging, and asked whether the pattern of spontaneous activity changes following intense sound exposure. In guinea pigs anesthetized with ketamine/xylazine, responses to pure-tone stimuli of different frequencies and levels were measured to define cortical response thresholds, and to reveal the tonotopic organization of auditory cortex. The baseline spatiotemporal pattern of spontaneous activity was then measured during several 30-second epochs of silence. Animals were subsequently exposed bilaterally to a loud (124 dB SPL) high-frequency (6 kHz) pure-tone sound for 30 minutes. Following sound exposure, cortical response thresholds increased for pure tones at the trauma frequency and above (from 20 dB to > 60 dB, in different animals). In contrast, thresholds were unchanged below the exposed sound frequency, indicating that trauma resulted in frequency-specific cortical threshold shifts. Fourier and wavelet analysis were used to compare spontaneous activity content before versus after trauma. We found a strong correlation ( $r = 0.79$ ,  $N = 10$  animals) between the cortical evoked threshold shift and a loss of spontaneous activity magnitude, considering spontaneous oscillations across the broad range of 1-20 Hz. This loss of spontaneous activity events was not restricted to the cortical region experiencing an increased threshold, but rather was present across the auditory cortex. These immediate changes may reflect neural adaptation or an acute increase of inhibition following prolonged intense sensory stimulation.

## Impact Of Sleep Disorders And Hyperacusis On Tinnitus Annoyance Evaluated With Tinnitus Questionnaires

*Alessandra B. Fioretti\*, Marco Fusetti, Alberto Eibenstein*  
*Surgical Sciences Department, ENT, University of L'Aquila, L'Aquila, Italy*

Introduction: Tinnitus is a symptom that approximately affects 15% of the world population. Patients with tinnitus are heterogeneous and several factors influence the impact of this symptom on the quality of life. The aim of the study is to evaluate the relationship of age, gender, sleep disorders and hyperacusis to tinnitus annoyance. Methods: 37 patients (18 males and 19 females) with unilateral or bilateral subjective tinnitus lasting over 3 months were evaluated with a complete interview, otological examination, pure tone audiometry, italian version of Tinnitus Sample Case History (TSCH) and Tinnitus Handicap Inventory (THI). Exclusion criteria were acute or chronic pathology of the external auditory canal or middle ear, Eustachian tube dysfunction, sleep breathing disorders like obstructive sleep apnea syndrome and abuse of caffeine (more than 3 cups of tea/coffee per day). Discussion: Age varied from 34 to 81 (mean=57.2±14.1); the mean THI value was 37.9± 22.2 (females: 41.1± 22.9; males: 34.7±21.7). THI grades were slight (16 %), mild (32 %), moderate (30 %), severe (19%) and catastrophic (3%). Based on the answers to TSCH 20 patients reported sleep disorders (54%) and 20 patients reported hyperacusis (54%). 11 patients (30%) reported sleep disorders and hyperacusis. It was not possible to find any correlation between the severity of tinnitus and the age and gender of the patients. High significant correlation was found between sleep disorders ( $p=0.0009$ ) and tinnitus annoyance and between hyperacusis ( $p=0.03$ ) and tinnitus annoyance. Conclusion: no significant relation was found between age, gender and tinnitus annoyance while a high level of annoyance was associated with hyperacusis and sleep disorders. TSCH and THI may be considered as screening tools in the clinical practice to evidence sleep disorders and hyperacusis which subsequently will be investigated with specific questionnaires and clinical assessment.

### **Loudness Functions In Tinnitus: Disentangling Loudness Recruitment From Hyperacusis**

*Fournier, P. \*, Hébert, S.*

*École d'orthophonie et d'audiologie, Université de Montréal  
and International Laboratory of Brain, Music and Sound Research (BRAMS)  
Montreal, Quebec, Canada*

Hyperacusis is estimated to prevail in about 80% of tinnitus patients. However, whether or not hyperacusis can be measured psychoacoustically remains largely unknown. In addition, it is unclear whether or not hyperacusis can be distinguished from loudness recruitment, which is an abnormal growth of loudness associated with elevated hearing thresholds. The main purpose of our study was to investigate the loudness functions of tinnitus sufferers' ears, and to compare them with control ears without tinnitus but with similar hearing loss in order to distinguish hyperacusis from loudness recruitment. A total of 126 ears from tinnitus participants and 106 ears from control participants without tinnitus were tested monaurally, for a total of 232 ears. Hearing thresholds (250Hz to 8kHz by ½ Octave steps) and loudness discomfort levels (1kHz, 2kHz, 4kHz) were assessed. Loudness growth' functions were assessed (1kHz, 4kHz) with a procedure of categorical loudness scaling. All ears (control, experimental) were divided into five groups according to their degree of hearing loss. LDLs did not differ between tinnitus and control ears. LGOB data, however, showed significantly lower sound levels in tinnitus ears compared to control ears in almost all loudness categories at both 1kHz and 4kHz, and only when the absolute hearing thresholds were normal. Loudness recruitment was observed in the control ears' group: The difference in loudness levels was significant in all hearing loss groups for lower loudness categories but disappeared for louder categories. In contrast, loudness levels were significantly lower for all loudness categories in the tinnitus ears. These findings reveal a greater sensitivity to sounds in tinnitus sufferers' ears with normal thresholds, suggesting the presence of neural degeneration in the auditory nerve. The role of central auditory gain in loudness recruitment and hyperacusis will be further discussed.

### **Treatment Of Chronic Tinnitus With Repeated Sessions Of Prefrontal Transcranial Direct Current Stimulation: Outcomes From An Open-Label Pilot Study**

*Elmar Frank, Peter Kreuzer, Michael Landgrebe, Julia Burger, Timm Pöppel, Martin Schecklmann\*,  
Tobias Kleinjung, Berthold Langguth.  
University of Regensburg; Regensburg, Germany*

Abnormal activity in central auditory pathways is considered as the neuronal correlate of tinnitus. However, there is increasing evidence from neuroimaging studies for an additional involvement of the frontal cortex in the pathophysiology of tinnitus, especially concerning its attentional and emotional aspects. Recently in a subgroup of tinnitus patients temporary reduction of tinnitus intensity and tinnitus related distress has been reported after bifrontal tDCS with the anode over the right and the cathode over the left dorsolateral prefrontal cortex (DLPFC). The aim of this study was to investigate whether repeated application of bifrontal tDCS results in longer lasting reduction of tinnitus and may represent a potential treatment approach. 32 patients with chronic and treatment resistant tinnitus received 6 sessions of bifrontal tDCS (1 mA, 30 min, 2 sessions per week) with the anode over the right and the cathode over the left DLPFC. Treatment outcome was assessed with several standardized tinnitus questionnaires, numeric rating scales, and a depression scale. In the entire group beneficial effects of bifrontal tDCS on tinnitus were found for numeric rating scores of loudness, unpleasantness, and discomfort, but not in tinnitus or depression scales. Exploratory analysis revealed an effect of gender on treatment effects with female patients demonstrating a better response in several scores. Our open label pilot study suggests some beneficial effect of bifrontal tDCS (anode right and cathode left) in the treatment of severe tinnitus, warranting further controlled studies.

## Long Lasting Change Of The Spontaneous Activity Rate In Dorsal Cochlear Nucleus Of Hamster In Response To Acoustic Stimulation *In Vivo*

Yuan Gao\* and James Kaltenbach  
Cleveland Clinic Foundation; Cleveland, Ohio, USA

Inputs that are carried by auditory nerve fibers and parallel fibers in the dorsal cochlear nucleus (DCN) are integrated by fusiform cells. Although the acoustic response properties of the parallel fibers are not known, their main targets, the cartwheel cells, have high thresholds, and are activated only at high levels of stimulation *in vivo*; suggesting that parallel fibers may also have high thresholds of activation. In contrast, fusiform cells respond over a broad range of intensities, and *in vitro* studies in mouse indicate that these cells may exhibit long-term plasticity when auditory nerve stimulation is coincident with excitation of parallel fiber inputs. Protein plasticity in DCN of rats provides a further suggestion that long-lasting changes in signal processing in response to high level acoustic stimulation may occur in fusiform cells, *in vivo*. By using multiple unit recordings on the DCN surface, which reflect largely fusiform cell activity, we find that a short period of intense sound exposure can induce a long lasting change in spontaneous activity in anesthetized hamsters. After a 2 minute exposure to a 10 kHz tone at a level of 109dB, the corresponding frequency region of the DCN (character frequency (CF) = 10 kHz) shows a significant increase of spontaneous activity (ratio=2.25 at 10 minutes after exposure, ratio=2.75 at 20 minutes after exposure,  $n=5$ ,  $P<0.05$ ). The same exposure condition significantly decreases spontaneous activity at frequency loci below (CF = 6 kHz) and above (CF =16 kHz) the 10 kHz locus (ratio=0.88 at 10 minutes after stimulation, ratio=0.83 at 20 minutes after stimulation,  $n=4$ ,  $P<0.05$ , CF = 6 kHz). One explanation of our data is that input onto fusiform cells basal dendrites from auditory nerve fibers may at high sound levels be coincident with inputs from high threshold parallel fibers, which could, in turn, induce long lasting plasticity *in vivo*. Here we also report that unlike the finding from a tinnitus animal model, a significant increase of spontaneous activity rate on the DCN surface is not associated with a shift of the threshold of tuning curves ( $n=5$ ). Thus, *in vivo* long lasting plasticity in DCN varies with the interaction of different synaptic inputs onto fusiform cells. Our study also raises a possibility that fusiform cells at different regions of DCN may show a different temporal pattern in response to a sound stimulation, which results in the different plasticity is measured in our experiments.

## No Detectable Cochlear Dead Regions In Non-Pulsatile Tinnitus Patients: An Assessment With The TEN(SPL) Test

Annick Gilles\*, Paul Van de Heyning, MD, Ph.D; Andrea Kleine Punte;  
Anouk Hofkens, Marc De Bodt Ph.D, Dirk De Ridder. \*

University Department of Otorhinolaryngology and Head and Neck Surgery, Tinnitus Research Initiative Centre (TRI), Brai<sup>2</sup>n, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium

**Introduction:** One of the hypotheses on the etiology of non-pulsatile tinnitus in normal or near normal hearing patients is the existence of sharp edged cochlear dead regions flanking normal functioning hair cells. The lack of inhibition of dead regions on the neighboring neurons may lead to hyperactivity. Previously the detection of dead regions with the Threshold Equalizing Noise (TEN) test was reported in 8/11 subjects with normal hearing and non-pulsatile tinnitus (Weisz et al, 2006). Currently the TEN(SPL) is the reference test to clinically assess cochlear dead regions. **Aim:** To identify cochlear dead regions in patients with non-pulsatile tinnitus in subjects with and without hearing loss using the TEN(SPL)-test. **Methods:** Data were obtained from adult patients with non-pulsatile tinnitus visiting the TRI Tinnitus Clinic of the University Hospital Antwerp. The TEN(SPL)-test was performed to assess the presence of cochlear dead regions for test frequencies ranging from 0.5 to 8 kHz (Moore et al. 2004). A noise level of 70dB SPL was the standard. In cases where the hearing loss exceeded 60 dB SPL, a noise level of 10 dB SPL above the threshold was used. **Results:** A total of 50 ears of 33 subjects (15 male; 18 female) with non-pulsatile tinnitus were included in the study. Subjects were divided into subgroups based on the audiometric configuration of hearing loss: flat configuration (N= 23), high-frequency gentle slope (N=10), high-frequency steep slope (N= 22). In forty-eight ears there was no evidence of cochlear dead regions. In 7 ears the results could not be reliably interpreted. This occurred in patients with high-frequency steeply sloping audiogram configurations. **Conclusions:** In our study population of subjects with non-pulsatile tinnitus no cochlear dead regions were detected with the TEN(SPL) test. This discrepancy with the report of Weisz et al. (2006) needs to be further investigated. **Acknowledgments:** We thank the Stavros Niarchos Foundation.

### **Noise-Induced Tinnitus In Adolescents: A Frequent But Underestimated Phenomenon**

*Annick Gilles\*; Paul Van de Heyning, MD, Ph.D; Andrea Kleine Punte;*

*Guido Van Hal, Ph.D; Dirk De Ridder, MD, Ph.D,*

*University Dept. of Otorhinolaryngology & Head & Neck Surgery, Antwerp University Hospital, Antwerp, Belgium*

**Introduction:** Listening to loud music has become a natural part of our society. We hypothesize that many are unaware of the possible risks of frequent exposure to excessive noise levels. **Aim:** To evaluate the prevalence of tinnitus due to recreational noise and the use of personal listening devices (PLD) in adolescents. The use of hearing protection (HP) and the attitude towards noise was also questioned. **Methods:** A 19-question survey was designed to target adolescents from the age of 15 to 20 years old. The survey contained questions about the presence and loudness of tinnitus after parties or PLD use, and the use of HP in recreational noise. The attitude of youngsters towards noise was evaluated by the Youth Attitude to Noise Scale (YANS). A total of 429 adolescents were questioned. The results of 15- to 18 year-olds were compared with those of 19- to 20 year-olds. Sixteen questionnaires were excluded due to incomplete response. **Results:** Permanent tinnitus was experienced by 20.3% of all 15 to 18-year olds and by 15.8% in the older age group. Moreover, 82.9% of the younger group experienced transient tinnitus after exposure to loud music with a mean tinnitus loudness of 3.13 (SD=2.35) on the Visual Analogue Scale (VAS), while this was respectively 91.2% for the 19- to 20 year-olds with a mean VAS score of 3.6 (SD=2.18). Prevalence of transient tinnitus increased with age. Under the age of 19 years old only 2.8% use HP. This number increases significantly in the older group (15.8%). Most 19-20-year-olds had a 'neutral' attitude towards noise. **Conclusions:** A trend of increasing prevalence of temporary tinnitus after loud music with age was revealed. Although tinnitus is a frequent phenomenon among adolescents and young adults, few precautions are taken to protect their hearing. Most adolescents and young adults have a positive attitude towards loud music and are insufficiently aware of the consequences of loud music. **Acknowledgments:** We thank the Stavros Niarchos Foundation.

### **Mindfulness-Based Cognitive Behavioral Therapy For The Treatment Of Chronic Tinnitus: Outcomes From A Randomized Controlled Pilot Study**

*Monika Goetz, MS; Maria Holl; Susanne Staudinger, MA; Martin Schecklmann, PhD; Michael Landgrebe, MD;*

*Berthold Langguth, MD; Peter M Kreuzer, MD\**

*Department of Psychiatry, Psychosomatic Medicine and Psychotherapy,  
University of Regensburg, Regensburg, Germany*

**Objective:** Tinnitus, the perception of sound in absence of an external acoustic source, impairs the quality of life in 2% of the population. Causal treatment options are scarce up to now so most therapeutical attempts aim to develop and strengthen individual coping strategies. In this context a randomized controlled clinical study has been conducted to investigate the efficacy of a specific mindfulness-based cognitive behavioral therapy in patients suffering from chronic tinnitus. **Methods:** 36 Patients were enrolled in the study. Treatment was performed as group therapy at two training weekends which were separated by an interval of 7 weeks (eleven hours / weekend) and in four further two-hour sessions (week 2, 9, 18 and 22). Half of the patients randomly entered active treatment immediately whereas the other patients were assigned to a waiting list control condition. The primary study outcome was the change in Tinnitus complaints as measured by the German Version of the Tinnitus Questionnaire (TQ). **Results:** ANOVA testing for primary outcome showed a significant interaction effect time by group ( $F=8.311$ ;  $df=1$ ;  $p=0.007$ ). Post hoc t-tests indicated an amelioration of TF scores from baseline to week 9 in both groups (intervention group:  $T=6.174$ ;  $df=17$ ;  $p<0.001$ ; control group:  $T=2.494$ ;  $df=17$ ;  $p=0.023$ ), but intervention group bettered at a higher rate than control group. **Conclusion:** In conclusion mindfulness-based cognitive behavioral therapy may be considered a promising approach of treating tinnitus which merits further evaluation in clinical studies with larger sample sizes.

### **Electric Promontory Stimulation And Round Window Stimulation As Predictor For The Effectiveness Of Tinnitus Suppression With A Cochlear Implant**

*Andrea Kleine Punte\*, Anouk Hofkens, Marc De Bodt, Paul Van de Heyning  
Univ. Dept. Otorhinolaryngology and Head and Neck Surgery, Antwerp University Hospital,  
University of Antwerp, Antwerp, Belgium*

Background: Many forms of tinnitus are caused by deprivation of sounds, and electrical stimulation has been applied to the promontory for treatment of tinnitus, providing significant relief from tinnitus by supplying input to the auditory nervous system. Electrical Promontory Stimulation (EPS) can suppress tinnitus temporarily and is sometimes used as a test before placement of chronic electrical stimulation devices such as Cochlear implants (CI). Aim: to investigate the predictive value of EPS and round window stimulation (RWS) in patients with single-sided deafness (SSD) and severe ipsilateral tinnitus. Methods: 19 subjects underwent a trial with EPS prior to CI surgery. Another group of 5 patients underwent a trial with RWS prior to CI surgery. The effectiveness of EPS or RWS for tinnitus suppression was compared to the outcome of tinnitus suppression with a CI. Tinnitus loudness was assessed with the Visual Analogue Scale (VAS (0-10)). Patients suffered from severe tinnitus of more than 6/10 on a VAS (0-10) due to single-sided deafness (SSD). Results: 8/19 subjects reported significant tinnitus relief with EPS, while there was no effect on tinnitus in the remaining 11 subjects. In the case of RWS only slight improvement of tinnitus loudness (1-2 points on the VAS) was observed in 3/5 subjects. 2 subjects did not experience any tinnitus relief with RWS. All 19 EPS patients received a Med-EI CI. 2/5 subjects of the RWS trial were implanted. 2 subjects without effective tinnitus suppression with RWS declined CI treatment, and 1 subject with a low degree of tinnitus suppression was not implanted due to personal reasons. Conclusion: EPS could significantly reduce tinnitus and even completely suppress tinnitus, at least during electrical stimulation in more than 40% of the cases. However, fewer subjects experienced tinnitus relief with EPS compared to CI (90%). RWS was less effective in suppressing tinnitus than EPS. Tinnitus suppression with EPS or RWS did not reliably predict tinnitus relief obtained with a CI. Also patients with no tinnitus relief with EPS or RWS may benefit from chronic electrical stimulation of the auditory nerve with a CI.

### **Relationship Between Audiogram And Tinnitus Pitch In Unilateral Tonal Tinnitus**

*Tobias Kleinjung\*, Berthold Langguth, Michael Landgrebe, Veronika Vielsmeier, Thomas Steffens, Martin Schecklmann, Interdisciplinary Tinnitus Clinic, University of Regensburg, Germany; Department of Otorhinolaryngology, University of Regensburg, Germany; Department of Otorhinolaryngology, University of Zurich, Switzerland*

Background: There is increasing evidence that tinnitus, the phantom perception of sound is a consequence of neuroplastic alterations in the central auditory pathways. These alterations in turn result from a dysbalance of excitatory and inhibitory mechanisms on many levels of the auditory pathways which are due to disturbed auditory input. However it still remains a matter of debate, whether the main responsible mechanism for tinnitus generation is reduced lateral inhibition or feed forward inhibition. On a perceptual level these different mechanisms should be reflected by the relation between the individual hearing curve and the perceived tinnitus frequency. Whereas some studies found that the tinnitus spectrum corresponds to the hearing loss, others stressed the relevance of the edge frequency. Here we investigated in a large sample of patients with unilateral tonal tinnitus the relationship between the perceived tinnitus pitch and the individual audiogram. Subjects and Methods: 320 patients who presented at the Tinnitus Clinic at the University of Regensburg with unilateral tonal tinnitus (145 right, 175 left) were analyzed. The tinnitus frequency as determined by pitch matching was compared with audiogram of the ear where the tinnitus was perceived. Findings: The perceived Tinnitus pitch depended to a greater extent on the frequency of maximum hearing loss than on the edge frequency. Interpretation: Results of our study confirm the relevance of absolute hearing loss for tinnitus generation as compared to the edge frequency, suggesting that tinnitus is rather a fill-in phenomenon, e.g. generated by altered gain control, than the result of deficient lateral inhibition.

### **Can Temporal rTMS Be Enhanced By Targeting Affective Components Of Tinnitus With Frontal rTMS? - A Randomized Controlled Trial**

*Kreuzer PM\*; Landgrebe M; Schecklmann M; Poepl T; Vielsmeier V; Hajak G; Kleinjung T; Langguth B.  
Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany*

Objectives: Low-frequency repetitive transcranial magnetic stimulation (rTMS) of the temporal cortex has been investigated as a new treatment tool for chronic tinnitus during the last years and has shown some efficacy. However, there is growing evidence that tinnitus is not a pathology of a specific brain region, but rather the result of network dysfunction involving both auditory and non-auditory brain regions. In functional imaging and magnetencephalographic studies the right dorsolateral prefrontal cortex has been identified as an important hub in tinnitus related networks which may be particularly related to the affective components of tinnitus. Based on these findings we aimed to investigate whether the effects of left low frequency rTMS can be enhanced by antecedent right prefrontal low-frequency rTMS. Study Design: A total of 56 patients were randomized to receive either low-frequency left temporal rTMS or a combination of low-frequency right prefrontal and low-frequency left temporal rTMS. Treatment effects were assessed with a standardized tinnitus questionnaire (TQ). The study is registered with clinicaltrials.gov (NCT01261949). Results: Directly after therapy there was a significant improvement of the TQ-score for both groups, but no differences between groups. Post hoc tests indicated an amelioration of symptoms after beginning of treatment and a return to baseline levels during the last follow-up (week 12). Responder rates ranged between 37 and 40 percent in both groups (response criterion: reduction in TQ-score of at least 5 points). The combined rTMS protocol exhibited a persistent trend towards better efficacy concerning all outcome criteria with a bettering in primary outcome showing an effect size of 0.2 in group comparison. Conclusion: Additional stimulation of the right prefrontal cortex seems to be a promising strategy for enhancing TMS effects over the temporal cortex. These results further support the involvement of the right DLPFC in the pathophysiology of tinnitus. The relatively small effect sizes might be due to the study design comparing the combined treatment protocol to an active and already established control condition.

### **Salicylate-Induced Modulation Of Gene And Protein Expression In Rat Auditory Cortex: Molecular Correlates Of Neural Hyperactivity And Tinnitus**

*Senthilvelan Manohar\*, Samson Jamesdaniel, Caroline Shillitoe, Edward Lobariñas, Wei Sun, Richard Salvi, Donald Coling. Center for Hearing and Deafness, The State University of New York at Buffalo, USA*

Tinnitus, the perception of a phantom auditory sensation, can be highly disturbing causing anxiety, depression, stress, and sleep disturbance. Administering a large dose of sodium salicylate is a reliable and effective method for inducing tinnitus in humans and animals and has been used extensively to investigate neural mechanisms giving rise to tinnitus. Peripheral auditory pathologies are important to the acquisition of tinnitus. Recent research has identified central auditory pathways thought to mediate inhibition leading to neural hyperactivity in the auditory cortex and an exaggerated acoustic startle reflex. However, few studies have examined molecular mechanisms in the central nervous system. We have used an antibody microarray targeting 725 signaling proteins to screen for significant changes in protein expression related to tinnitus in the auditory cortex of Sprague-Dawley rats. Salicylate treatment induced changes in protein expression in 23 proteins. Levels of 7 proteins decreased compared to saline-treated controls while expression increased in the remaining 16. Subsequent results with a custom RT-PCR array confirmed changes in corresponding mRNA levels for 7 of the 9 largest protein changes. Salicylate-induced tinnitus was associated with significant changes in the expression of 3 functional groups of proteins; those involved with neuronal maturation (Inexa, Smn1, Rab6ip2, Hnrnpu, Cnp, Myd88), cell cycle (Cdc2, Ccna2, Prmt6, Cdc14a) and Glucose metabolism (GSK3 $\beta$ , Pdia3, Grb2). These changes in gene and protein expression may provide a molecular basis for the salicylate-induced hyperactivity observed in the auditory cortex and the hyper-active acoustic startle response.

### **Effect Of Cortical Stimulation On Neural Firing In The Inferior Colliculus: Towards A Cortical Stimulator For Tinnitus**

*Craig D. Markovitz\* and Hubert H. Lim  
University of Minnesota, Minneapolis, USA*

Introduction: Cortical electrical stimulation has been proposed as a new treatment option for patients with severe tinnitus. While clinical trials utilizing cortical stimulation have shown promise, results have been highly variable across patients. Objectives: Our goal was to determine the effect of cortical electrical stimulation on the central auditory pathway, in particular within the inferior colliculus (IC), a major convergence point of ascending and descending projections. Methods: We positioned multi-site electrode arrays into A1 and the IC of anesthetized guinea pigs. After characterizing the acoustic-driven responses on each site to confirm its location (i.e., which frequency region and sub-nuclei of A1 or IC), we electrically stimulated different layers of A1 and recorded the corresponding changes in spontaneous and acoustic-driven responses throughout the IC. Results: Stimulation of deeper A1 output layers elicited excitatory responses within the IC, especially for regions that had similar best frequencies. However, IC responses varied dramatically depending on the frequency region and layer of stimulation within A1. Along a single A1 column, stimulation of an output layer could elicit excitatory IC responses while stimulation of a more superficial site could elicit little or no effect. Furthermore, stimulation of a given A1 site could elicit strong responses in one IC region yet show no, or even a suppressive, effect in another IC region with a similar best frequency, suggesting some segregated descending projections from A1 to the IC. Conclusions: The large variation in IC responses to stimulation of A1 may partially explain how inconsistent placement of large electrode sites in the current patients can lead to variable results. More localized stimulation strategies may be required to suppress specific tinnitus-related activity in each patient.

### **The Efficacy Of A Self-Administered Self-Management Program For Acute Tinnitus: A Randomised Controlled Study**

*Nele Nyenhuis\*, Sarah Zastrutzki, Burkard Jäger, Birgit Kröner-Herwig  
Georg-August-University Göttingen, Goettingen, Germany*

Objective: Chronic tinnitus can lead to a substantial impairment in one's psychological well-being. Nevertheless, there are no investigated programs for secondary prevention. The aim of this study was to evaluate a self-management program for acute tinnitus. Methods: Applicants were included if they had suffered from subjective tinnitus for up to 6 months, were between 18 and 75 years old and were not involved in tinnitus-related psychological treatment or rehabilitation. A total of 276 participants were randomly assigned to either a self-management treatment based on cognitive behavioural therapy (presented via the Internet or a booklet) or an information group. Tinnitus distress, depressive symptoms, psychosomatic discomfort, health care utilisation and treatment satisfaction were assessed. Results: An intention-to-treat analysis revealed no distinctive group differences in tinnitus distress changes, depressive symptoms, or psychosomatic discomfort. An analysis of the clinical significance of change revealed a significantly higher improvement rate for tinnitus distress in the Internet condition than in the information condition. The effect sizes were large for the training conditions and moderate for the information condition. Treatment satisfaction was high and treatment tended to result in a lower use of health care. The dropout rate between pre- and post-training assessment was 37 %. Conclusion: This evaluation hints at the moderate efficaciousness of both training conditions. Though the main analyses were mostly insignificant, the additional analyses suggest a comparably stronger improvement in the training groups in regards to the tinnitus distress, depressiveness and the magnitude of health care use.

## Can Persistent Exposure To Moderately Loud Sound Lead To Hyperacusis And/Or Tinnitus?

*Martin Pienkowski\* and Jos J. Eggermont*

*Departments of Physiology and Pharmacology, and Psychology, University of Calgary, Calgary, Canada*

Partial loss of cochlear hair cells (OHCs or IHCs) and/or spiral ganglion cells (SGCs) leads to a number of changes in the response properties of central auditory neurons that correlate with the emergence of hyperacusis and tinnitus. Specifically, at various stages of the auditory pathway and over time scales ranging from minutes to weeks, neurons can exhibit increases in spontaneous and sound-evoked firing, and in the synchrony of firing, as well as shifts of the receptive field to sound frequencies at the edge(s) of the hearing loss. It is not yet completely clear which changes are actually causal to hyperacusis and tinnitus, and what mechanisms underlie the changes. Although hyperacusis and tinnitus are more prevalent in people with hearing loss, both can be experienced in spite of clinically normal audiograms, albeit that normal pure tone thresholds do not necessarily rule out either (small) OHC lesions or (even large) IHC/SGC lesions, and, for example, problems with speech intelligibility in noisy conditions. We have been exposing adult cats to bandlimited noise and tone pip ensembles at moderate sound levels (~70 dB SPL) for several weeks to months. Auditory brainstem response thresholds were unaffected by the exposure. However, spike and LFP activity in the region of primary auditory cortex (AI) normally tuned to the exposure band was suppressed while activity in neighboring regions was enhanced. Also, on average, AI neurons in the enhanced regions had lower response thresholds, and higher spontaneous firing rates and firing synchrony. These changes, which were slow to reverse after exposure offset, can be interpreted as electrophysiological signs of hyperacusis and tinnitus.

### ReSound Live™TTS:

#### An Innovative Tinnitus Sound Generator Device To Assist In Tinnitus Management

*Michael Piskosz, M.S. \*, Board Certified in Audiology & Snehal Kulkarni, Au.D.  
GN ReSound – Global Audiology, Coral Gables, Florida, USA*

Tinnitus is a concern for many people, and affects approximately 10-15% of the overall population, with approximately 3-5% of the population suffering from clinically treatable tinnitus (McFadden, 1982). As hearing loss is increasingly identified and diagnosed, this trend is most likely to continue and grow (Vernon, 1998). Many tinnitus sufferers, and clinicians, have struggled finding flexible tinnitus treatment devices that are suitable components of a tinnitus treatment and counseling support program. ReSound Live™TTS is an advanced combination hearing instrument and Tinnitus Sound Generator (TSG) device that provides fitting flexibility for clinicians, and an innovative TSG solution for users.

### Structural Brain Changes In Chronic Tinnitus: The Role Of Clinical Characteristics

*Timm B. Poeppel\*, Martin Schecklmann, Peter Kreuzer, Veronika Vielsmeier, Tobias Kleinjung, Berthold Langguth,  
Michael Landgrebe, University of Regensburg; Regensburg, Bavaria Germany*

Tinnitus, the phantom perception of sound, has been shown to be associated with functional as well as anatomical cerebral changes. However, knowledge about alterations of brain structure is based on relatively few studies, investigating small sample sizes and demonstrating conflicting results. Here, we compared cerebral gray and white matter in a large sample of 357 tinnitus patients and 100 matched healthy controls using voxel-based morphometry in automated whole-brain analyses. All subjects from the patient group had duration of disease more than six months. Results will be interpreted with regard to tinnitus characteristics such as laterality, distress and duration.

## **Acoustic Coordinated Reset Neuromodulation For The Treatment Of Tinnitus: A Computational Study**

*Oleksandr V. Popovych\* and Peter A. Tass*

*Institute of Neurosciences and Medicine - Neuromodulation (INM-7), Research Center Jülich, Germany*

Introduction: Tinnitus is a deafferentation-induced phantom phenomenon characterized by abnormal cerebral synchrony. In a modeling study we analyze the emergence of pathological neuronal synchronization and connectivity and their control by acoustic coordinated reset (CR<sup>®</sup>) neuromodulation and noisy acoustic stimulation. Methods: Our oscillatory neuronal population comprises spike timing-dependent plasticity (STDP) and is split into two sub-populations, receiving full and reduced afferent noisy inputs, respectively, which models a partial deafferentation. Employing the tonotopic organization of the central auditory system, the target population is stimulated by acoustic CR<sup>®</sup> neuromodulation, where different brain sites are sequentially reset by acoustically delivered tones of different pitch. Results: We show that a strong noisy input can induce an onset of synchronization in the deafferented neuronal sub-population, which mimics the effect of a noise trauma. This transition is accompanied by an up- and down-regulation of excitatory and inhibitory synaptic connections, respectively. Acoustic CR<sup>®</sup> neuromodulation can effectively desynchronize the abnormal synchronization and restore a physiological pattern of synaptic connections. It induces a long-lasting anti-kindling effect so that the desynchronized neuronal firing is maintained after the stimulation is switched off. These results are in accordance with clinical and electrophysiological findings. In contrast, noisy stimulation can induce an anti-kindling only in a small parameter range and can have adverse, synchrony-boosting effects. Conclusions: Acoustic CR<sup>®</sup> neuromodulation turned out to be superior to noisy acoustic stimulation and is a promising candidate for a reliable control of tinnitus-related synchronization.

## **The Effect Of The NMDA Channel Blocker Memantine On Salicylate-Induced Tinnitus**

*Massimo Ralli\*, Edward Lobarinas, Guan-Di Chen, Anna Rita Fetoni,*

*Diana Troiani, Gaetano Paludetti, Richard Salvi*

*Università Cattolica del Sacro Cuore; Rome, Italy*

Short-term dose-dependent tinnitus has been reported following administration of salicylate at high doses; NMDA channels seem to play a vital role in tinnitus onset by selectively amplifying NMDA-mediated responses. The aim of this study is to determine whether systemic treatment with a NMDA channel blocker can prevent the onset of salicylate-induced tinnitus in animals. Additional experiments were performed to evaluate the effect of memantine on the hearing function and on OHC alone. Thirty-six rats were divided into 3 groups and were treated daily for four consecutive days; one group (n=12) was injected IP with salicylate (300 mg/kg), the second (n=12) was with memantine at a dose of 200 mg/kg, the third group (n=12) was injected with salicylate and memantine (saline IP 300 ml/kg). All rats were tested for tinnitus and hearing loss at 2, 24, 48, 72 and 96 hours after the first drug administration; tinnitus was assessed using GPIAS, hearing function was measured with DPOAE, ABR and NBPIAS. Rats in the salicylate group showed transient tinnitus-like behavior with a pitch near 16 kHz, starting 2 h after treatment resolving spontaneously 24 h after the last day of drug administration. Animals treated with memantine did not show significant changes in GPIAS. Animals subjected to combined injection of salicylate and memantine showed a significant attenuation of tinnitus-like behavior. Hearing function was tested in all animals. No permanent shifts were found at the ABR in all animals. DPOAEs revealed a cumulative effect on DPOAEs for the salicylate group with complete reversibility 1 day after the end of treatment. No changes were reported in animals treated with memantine alone. Interestingly, animals treated with salicylate and memantine showed an alteration comparable to animals treated with salicylate alone; demonstrating no effect of memantine on OHC. The present study confirms the role of cochlear NMDA receptors in the induction of salicylate-induced tinnitus.

### **Voxel-Based Morphometric Assessment Of Neuronal Plasticity Associated With Low Frequency *rTMS* For The Treatment Of Noise-Induced Tinnitus**

*Stephen G. Romero, Lauren Laitman, Anthony T. Cacace\*, Jiani Hu, Yang Xuan  
Union College, Schenectady, New York, USA*

Voxel-based morphometry was used to evaluate structural changes in brain anatomy before and after sham and actual *rTMS* in a sample of 25 adults with an etiology of noise exposure and hearing loss. This was part of a larger study evaluating the efficacy of *rTMS* on tinnitus suppression and its neurobiochemical/psychometric correlates (see Cacace et al., this meeting). Data were collected on a 3T Siemens MAGNETOM Verio scanner using the magnetization prepared rapid gradient echo pulse sequence (TR = 1.6s, TE = 4.38 ms, TI = 800ms, FA = 8, 176 slices, matrix = 256 x 256, voxel size = 0.7 x 0.7 x 1.3 mm<sup>3</sup>, acquisition time, 5:26 min). With the MAGSTIM Rapid TMS device, sham stimulation produces an audible acoustic pulse; actual stimulation produces an acoustic + magnetic pulse. In pre-post sham conditions, reductions in grey-matter (GM) volume in the left middle frontal gyrus were found following actual *rTMS*, GM volume reductions were also found in the right inferior parietal lobe. White matter (WM) volume increased in pre-post sham conditions in the left middle temporal gyrus. In pre-post actual conditions, WM volume increased in the putamen, medial geniculate nucleus, and inferior parietal lobe all on the right side of the brain, whereas WM volume decreases were found in right superior frontal gyrus and in the left caudate. In separate analyses, reductions in loudness level and improvements in THQ scores were significantly correlated with post-*rTMS* images, indicating that brain volume in some regions other than those indicated in the pre-post image analyses have a relationship with actual symptom improvement. Taken together, these results suggest that plasticity occurs from both sham and actual *rTMS* and that actual volume in certain brain areas may be predictive of those individuals that will respond best to actual *rTMS*. The generalizability of these results is limited to individuals with a common etiology of noise exposure and hearing loss.

### **TTTS (Tonic Tensor Tympani Syndrome) – Also A Tinnitus Explanation**

*Clarice Saba\*, Myriam Westcott and Thiago Alcântara  
Centro de Otorrinolaringologia da Bahia; Salvador, Bahia, Brazil*

The poster “Tonic Tensor Tympani Syndrome in Tinnitus and Hyperacusis Patients: A Multi-Clinic Incidence Study” were presented by us at the 10<sup>th</sup> International Tinnitus Seminar. A follow up is being done in some patients from this study at the Tinnitus Department of Bahiana Medical University, in Brazil, since then. The stapedius muscle (attached to the stapes or stirrup bone) and the tensor tympani muscle (attached to the malleus bone) provide protection to the inner ear from loud, potentially damaging sounds, by contracting to tighten the ossicles, limiting the transmission of these sounds to the inner ear. TTTS is an involuntary condition where the tensor tympani muscle reflex is lowered. This lowered reflex can lead to a frequent spasm. In many patients with tinnitus related anxiety, an increased, involuntary activity appears to develop in the tensor tympani muscle in the middle ear as part of a protective and startle response to intolerable sounds. This lowered reflex threshold for tensor tympani contraction can be activated by the anticipation of sudden, unexpected, loud sound, and the perception of these sounds as potentially damaging and/or likely to exacerbate symptoms such as tinnitus. This mechanism has not been definitively proven and is not widely understood yet in the medical profession. Data was already collected in 20 patients, age 22-55. They underwent medication – cyclobenzaprine hydrochloride (7), orthodontics (5), physiotherapy (3), and medication + orthodontics (5). So far, the best results are with the combination of medication and orthodontics.

### **Clinical Improvement And Normalisation Of Deviated Brain Activity By Individualized rTMS In A Patient With Chronic Tinnitus And Facial Pain**

*Martin Schecklmann\*, Sven Vanneste, Dirk de Ridder, Peter Kreuzer,  
Timm B. Pöppl, Michael Landgrebe, Berthold Langguth  
University of Regensburg; Regensburg, Germany*

Repetitive transcranial magnetic stimulation (rTMS) over auditory brain areas has been shown to reduce tinnitus, but effects are only moderate and the interindividual variability is high. Recent imaging studies indicate that tinnitus related changes are not restricted to auditory brain areas. Instead abnormal activation has been identified in different overlapping brain networks consisting of auditory and non-auditory brain areas. Moreover the specific activation pattern varies from patient to patient suggesting the need for individualized treatment approaches. In a patient suffering from severe tinnitus and facial pain we tested different stimulation protocols over temporal, temporoparietal, motor, sensory and frontal brain areas. We combined all protocols which had a beneficial immediate effect to a protocol which was applied for six weeks once or twice daily. After a stimulation free interval of two weeks the test procedure was repeated and followed by another eight weeks of individualized stimulation. At the end of treatment the patient reported a 90% reduction of his tinnitus and 20% reduction of his facial pain. EEG abnormalities detected before treatment in comparison to a normative database were largely reduced after treatment. This case indicates the potential of individualized brain stimulation treatment. Immediate effects after test stimulation may be a useful predictor of long term effects after repeated rTMS in the treatment of tinnitus.

### **Investigation Of The Cortical Tinnitus Network With Positron Emission Tomography: Identification Of Subgroups As Elicited By Cluster Analysis**

*Martin Schecklmann\*, Michael Landgrebe, Tim Pöppl, Tobias Kleinjung, Peter Männer, Jörg Marienhagen,  
David Wack, Göran Hajak, Berthold Langguth.  
University of Regensburg; Regensburg, Germany*

The aim of the investigation was the identification of subgroups of tinnitus patients as elicited by cluster analysis of metabolic brain activity measured with positron emission tomography (PET). We investigated brain activity (steady state FDG-PET) in 91 patients with subjective tinnitus (> 6 months). Subgroups of tinnitus patients were identified with Ward's hierarchical clustering method of brain activity and subsequently contrasted with Statistical Parametric Mapping (SPM). We could identify four groups based on the criterion of a minimal group size of 15 subjects. These groups differed only in spatial brain activity patterns and not in tinnitus duration, laterality, and distress and not in sample characteristics (age, gender, audiographic data, depressivity, and personality). One cluster showed main activity in the cerebellum, one in the ventromedial prefrontal cortex (VMPFC), one in the anterior cingulate cortex (ACC), and one in the superior frontal cortex. As we did not find associations of sample features and tinnitus characteristics with the clusters it can be speculated how far the identified subgroups with certain activity patterns can be linked with etiologic relevant features (VMPFC - problems in habituation and filtering; ACC - emotional processing). However, the results show the possibility to use imaging methods for the identification of brain regions that can be use for brain stimulation on an individual level.

### **Investigation Of The Cortical Tinnitus Network With Positron Emission Tomography: Impact Of Tinnitus Characteristics**

*Martin Schecklmann\*, Michael Landgrebe, Timm Pöppel, Tobias Kleinjung, Peter Männer, Jörg Marienhagen,  
David Wack, Göran Hajak, Berthold Langguth.  
University of Regensburg; Regensburg, Germany*

Cerebral <sup>18</sup>F-deoxyglucose positron emission tomography (FDG-PET) has shown altered central auditory pathway activity in tinnitus. However, the corresponding studies involved only small samples and analyses were restricted to the auditory cortex in most studies. Evidence is growing that also limbic, frontal, and parietal areas are involved in the pathophysiology of chronic tinnitus. These regions are considered to mediate perceptual, attentional, and emotional processes. Thus, the aim of the present study was the systematic evaluation of metabolic brain activity in a large sample of tinnitus patients. 91 patients with chronic tinnitus underwent FDG-PET. The effects of tinnitus severity (assessed by a tinnitus questionnaire score), duration and laterality were evaluated with statistical parametric mapping (SPM) in whole brain analyses. Tinnitus duration correlated positively with brain metabolism in right inferior frontal, right ventro-medial prefrontal, and right posterior cingulate cortex. Tinnitus distress correlated positively with activation of left and right posterior inferior temporal gyrus as well as left and right hippocampal regions. Tinnitus duration and distress were associated with areas involved in attentional and emotional processing. This is in line with recent findings indicating the relevance of higher order areas in the pathophysiology of tinnitus.

### **Paired Associative Stimulation Of The Auditory System**

*Martin Schecklmann\*, Gregor Volberg, Gabriele Frank, Julia Hadersdorfer, Thomas Steffens, Nathan Weisz,  
Michael Landgrebe, Göran Hajak, Mark Greenlee, Joseph Classen, Berthold Langguth  
University of Regensburg; Regensburg, Germany*

Paired associative stimulation (PAS) consisting of repeated application of transcranial magnetic stimulation (TMS) pulses and contingent exteroceptive stimuli has been shown to induce neuroplastic effects in the motor and somatosensory system. The objective of the present study was to investigate whether the auditory system can be modulated by PAS. Acoustic stimuli (4kHz) were paired with TMS of the auditory cortex with intervals of either 45ms (PAS(45ms)) or 10ms (PAS(10ms)). Two-hundred paired stimuli were applied at 0.1Hz and effects were compared with low frequency repetitive TMS (rTMS) at 0.1Hz (200 stimuli) and 1Hz (1000 stimuli) in eleven healthy students. Auditory cortex excitability was measured before and after the interventions by long latency auditory evoked potentials (AEPs) for the tone (4kHz) used in the pairing, and a control tone (1kHz) in a within subjects design. Amplitudes of the N1-P2 complex were reduced for the 4kHz tone after both PAS(45ms) and PAS(10ms), but not after the 0.1Hz and 1 Hz rTMS protocols with more pronounced effects for PAS(45ms). Similar, but less pronounced effects were observed for the 1kHz control tone. These findings indicate that paired associative stimulation may induce tonotopically specific and also tone unspecific human auditory cortex plasticity.

### **Dynamic Single-Subject Correlates Of The Tinnitus Percept: A MEG Study With Residual Inhibition**

*William Sedley\*, Sundeep Teki, Sukhbinder Kumar, Doris-Eva Bamiou, Gareth Barnes and Tim Griffiths  
Auditory Group, Institute of Neuroscience, Newcastle University, United Kingdom*

Background: MEG and EEG studies have identified cortical correlates of tinnitus in the form of altered oscillatory power in specific frequency bands. Most studies have been performed at group level, possibly masking individual differences, and focused on *static* correlates. Aims: We draw a distinction between correlates of tinnitus that are *static* (all abnormal activity in the brains of people with tinnitus) and *dynamic* (only activity that co-varies with the tinnitus percept). We aimed to study dynamic correlates in single subjects to obtain a specific picture of brain activity underlying tinnitus. Methods: We recorded MEG from 8 tinnitus patients using a residual inhibition paradigm. Prior to MEG subjects interactively created a sound to optimally suppress their tinnitus, and in the MEG session were presented with this, and a control sound. Between sounds they rated their current tinnitus intensity, allowing data sorting into “high” and “low” conditions. Data were projected into source space, using a beamformer approach. A Monte Carlo method was used to identify continuous clusters in 4-dimensional space (x, y, z, frequency), and a permutation approach taken to determine the significance threshold for clusters. Results: All but one subject had significant clusters of activity associated with higher tinnitus. In most of these subjects, at least one cluster was found involving increased delta, theta and/or gamma power in auditory cortex. The most consistent finding was reduced beta and/or gamma power in ventromedial prefrontal cortex. Some subjects showed significant clusters in posterior parietal cortex or cerebellum, but frequency bands and directions of power change varied between subjects. Conclusions: We have implemented a method to study dynamic tinnitus correlates in individual subjects. This has shown expected findings, in the form of increased delta/theta/gamma power in auditory cortex, but also suggests an inhibitory role for the ventromedial prefrontal cortex.

### **Acoustic CR Neuromodulation Counteracts Both Pathological Synchrony And Imbalance Of Interactions Of Brain Areas In Patients With Subjective Chronic Tonal Tinnitus**

*Alexander N. Silchenko\*, Ilya Adamchic, Christian Hauptmann, Peter A. Tass  
Institute of Neuroscience and Medicine 7 – Neuromodulation, Research Center Juelich, Germany*

Subjective tinnitus is an auditory phantom sensation, which typically evolves as consequence of damage to the peripheral auditory system and leads to characteristic changes of brain activity in the central auditory system. In a prospective, randomized, single blind, placebo-controlled trial in 63 patients with chronic tonal subjective tinnitus we used acoustic coordinated reset (CR) neuromodulation to specifically counteract tinnitus by means of desynchronization of tinnitus related neuronal synchrony. CR treatment was safe and well-tolerated and resulted in a significant decrease of symptoms, as measured by VAS and TQ scores, as well as in significant changes in the oscillatory brain activity. To study changes in effective connectivity between auditory and non-auditory brain areas, we analyzed EEG recordings from 28 patients with bilateral chronic tonal tinnitus. To this end, we performed a BESA source reconstruction and a directionality analysis using a combined empirical mode decomposition and partial directed coherence approach. Here, we show that CR therapy induces statistically significant changes of the effective connectivity in the delta, alpha and gamma frequency bands, which are significantly correlated with the changes in VAS and TQ scores. In particular, we observed a significant reduction of interaction between the primary auditory cortex (A1) and the limbic system in delta and gamma bands. Additionally, we revealed a strong enhancement of the causal interaction between the dorsolateral prefrontal cortex (DPFC) and A1 in the alpha band. We performed dynamic causal modeling (DCM) for pairs of source signals, whose change of coupling showed the largest impact on changes in VAS and TQ scores. We observed a reduction of the bi-directional excitatory interaction between A1 and the cingulate area in both delta and gamma bands together with a strong increase of a bi-directional inhibitory coupling between A1 and DPFC in the alpha band. Hence, within a large network of auditory and non-auditory areas acoustic CR therapy counteracts pathological and enhances physiological interactions.

## **New Neurons In The Cochlear Nuclei After Unilateral Cochlear Neurectomy In The Adult Cat**

*B. Tighilet, S. Dutheil, A. Norena\**

*UMR 6149 Université de Provence / CNRS "Neurosciences Intégratives et Adaptatives", Marseille, France*

We have recently evidenced in the adult cat that unilateral vestibular neurectomy induced an intense cell proliferation in the deafferented vestibular nuclei. Most of these newborn cells survived, differentiated into astrocytes and GABAergic neurons and contributed to the recovery of the vestibular functions. In this study we aimed to determine 1) whether a unilateral section of the cochlear nerve (UCN) induces a reactive neurogenesis in the auditory system, and 2) the survival, the differentiation and the phenotype of the newly generated cells. To determine the time course of cell proliferation in response to a UCN, 5-bromo-2'-deoxyuridine (BrdU), a newborn cell marker, was injected 3 h, 1, 3, 7, 15 and 30 days after UCN. We investigated the survival and differentiation in UCN cats injected with BrdU at 3 days and perfused 30 days after UCN. NeuN (neuronal nuclei marker), Glial fibrillary acidic protein (GFAP) and glutamate decarboxylase 67 (GAD67) were used to identify newly generated astrocytes and GABAergic neurons, respectively. Results showed a high number of BrdU-immunoreactive (-Ir) nuclei in the deafferented cochlear nuclei (CN) with a peak at 3 days after UCN and a decrease at 30 days. Most of the newly generated cells survived up to 1 month after UCN and gave rise to a variety of cell types. Confocal analysis revealed two cell lineages: astrocytes (GFAP /BrdU-Ir cells); and neurons (NeuN/BrdU-Ir cells). We showed that most of the newly generated neurons have a GABAergic phenotype (GAD-67/BrdU-Ir cells). Arac (an antimitotic drug) infusion in the fourth ventricle blocked totally the cell proliferation in the CN. In addition to the central plastic changes already described in the central auditory system after hearing loss, the present study shows that severe deafferentation is accompanied by neurogenesis in the CN. These structural changes may have functional implications, in particular for the generation of tinnitus.

## **Tinnitus And Temporomandibular Joint Disorders – Clinical Characteristics**

*Veronika Vielsmeier\*, Martin Schecklmann, Michael Landgrebe, Berthold Langguth  
Department of Otorhinolaryngology, University of Regensburg, Germany*

**Introduction:** Tinnitus is frequently associated with temporomandibular joint (TMJ) dysfunction. A pilot study (Vielsmeier et al. 2011) revealed that patients with TMJ disorder differ from those without TMJ disorder by younger age, better hearing function and higher proportion of female gender. By using the TRI database we here aimed to affirm these findings in a large multicenter sample. **Methods:** We explored the TRI database according to the standard operating procedures for statistical analysis (<http://database.tinnitusresearch.org/en/documents/trisa.pdf>). Patients with TMJ disorders were identified by self reported TMJ disorders in the Tinnitus sample case history. Patients with and without TMJ disorders were compared for age and hearing function by unpaired Student t-tests and for the gender distribution by a chi-square test. **Results:** Valid data for 1274 patients were available in the database. Patients with self reported TMJ disorders were more frequently female, were younger, and had better high frequency hearing. **Conclusions:** This analysis of a large patient sample affirms earlier findings by demonstrating that patients with tinnitus and TMJ disorders differ from those without TMJ disorders with respect to typical risk factors of tinnitus. These data provide further indirect evidence for a causal role of TMJ disorders in the pathophysiology of tinnitus.

## **Clinical Treatment Of Tinnitus/Hyperacusis Using Combined Modalities**

*Erin Walborn\**

*Audiologic Solutions Hearing and Wellness Center in Rensselaer, New York, USA*

The poster will focus on the work of Dr. Erin Walborn\*, owner/audiologist of Audiologic Solutions Hearing and Wellness Center in Rensselaer, NY. She has been treating tinnitus for a number of years and was trained by Pawel Jastreboff in 2008. Since then, she has combined aspects of TRT training with holistic measures for treatment of anxiety and stress. The results have been astounding with patients seeing a large improvement in their THI score pre and post treatment. The poster will include how to test for Tinnitus, Hyperacusis and Misophonia. Examples of questions that are asked during the case history will be presented along with ways to dig deeper to find out more information the patient might not even feel is necessary. The THI (Tinnitus Handicap Inventory) will be presented. Our counseling technique and explanation of the autonomic nervous system will be displayed in great detail. Next will be a flow chart of how stress affects the body and how it affects tinnitus. I teach my patients EFT (Emotional Freedom Technique), Mindfulness, and Deep Breathing. These instructions will be presented on the poster. Use of sound therapy will be discussed as well. Using the combined modalities of sound therapy and some stress management has shown great improvement of most people who follow through with the suggestions. Case studies will be presented.

## **Magnetoencephalography Changes During Residual Inhibition Of Tinnitus**

*Peter Winkler\**

*Macquarie Street Tinnitus Clinic, Sydney, Australia*

Introduction: Residual inhibition was previously a short lived clinical curiosity of unknown mechanism and of a duration too brief to be of therapeutic use. A 12 minute series of synthesised low frequency sounds (TIPA) can produce complete residual inhibition of tinnitus for extended periods. This finding was first published in 2008 at the International Tinnitus Seminars in Sweden and allows investigation of neural substrates of tinnitus by comparing the tinnitus present state with tinnitus absent (complete residual inhibition) in the same patient. Method: A pilot study was conducted on a 43 year old male patient who has had constant bilateral tinnitus for 20 years and normal hearing. He routinely experiences complete residual inhibition for more than 24 hours after listening to the 12 minute TIPA sound. Auditory Evoked Response Magnetoencephalography using 50ms tone pips at 1KHz and 4KHz was performed while the tinnitus was present and then immediately after complete residual inhibition was induced by TIPA. Results: The P50m and P100m responses were recorded while the tinnitus was present but were reduced in amplitude during the residual inhibition. While tinnitus was present there was a desynchronisation of auditory brain rhythms in a frequency range of 15 - 20Hz. After induction of complete residual inhibition this event related desynchronisation was abolished. Discussion: Prolonged residual inhibition produced by the TIPA signal has been successfully used in tinnitus treatment. However objective markers of residual inhibition have not been demonstrated prior to this study. The ability to switch tinnitus off now provides a new approach to the investigation of the neurophysiologic basis of residual inhibition as well as the source of tinnitus generation.

## First Treatment Experience With Acoustic CR Neuromodulation In 70 Patients With Chronic Subjective Tinnitus

*Hannes Wurzer and Gerrit Weimann\**  
ENT medical practice, Munich, Germany

**Introduction:** In tinnitus a pathological neuronal synchrony and synaptic connectivity can be found. The loudness and distress of tinnitus are highly correlated with abnormal neuronal synchrony in temporal and fronto-temporal brain regions. EEG changes show an increase in delta and gamma and a decrease in alpha oscillatory activity in specific auditory and non-auditory brain areas. Acoustic CR neuromodulation desynchronizes tinnitus-related neuronal synchrony inducing an unlearning of pathological synaptic connectivity. We report the treatment experience in 70 “real life” tinnitus patients treated with acoustic CR neuromodulation in an outpatient setting. **Methods:** 70 patients suffering from chronic tonal subjective tinnitus (0.2-10kHz) with a hearing loss <80dB received acoustic CR neuromodulation therapy in a specialized ENT outpatient setting. Treatment duration was ≥ 6 months. After individual adaption of the CR stimuli (pitch, loudness) adjustments were performed after 2, 4, 8, 12, 16, 20 and 24 weeks. Audiologic and psychometric measurements (German version of the TQ with max 84 points and VAS) were performed at baseline, 3 and 6 months. **Results:** 70 patients (male : female 3:1; 50% >60 years of age; duration of tinnitus >5years in more than 2/3 of patients) showed at baseline approx. 1/3 mild, 1/3 moderate and 1/3 severe/very severe TQ based tinnitus severity. After 6 months of treatment there were 40% “winners” ( $\Delta$ TQ >-15 points), 30% “responders“ ( $\Delta$ TQ -6 to -14 points) and just one “loser” ( $\Delta$ TQ >+6 points). **Conclusion:** The results presented here with 70% winners/responders after 6 months of treatment with acoustic CR neuromodulation are in line with the placebo controlled randomized RESET study showing 75% winners/responders at the end of a 40 week treatment. In the investigated cohort the strong improvement was achieved in “real life” patients with long-standing tinnitus of whom most underwent several pretreatments before without success. **Key words:** Tinnitus; Neuromodulation; Tinnitus Questionnaire; TQ; Coordinated Reset; CR

## Sound Therapy In Tinnitus

*Jukka Ylikoski\*, Mikael Bergholm, Jarmo Lehtimäki, Ulla Pirvola, Jyri Sariola, Rami Kaalamo*  
TinnOff Inc and Helsinki Ear Institute, Helsinki, Finland

**Background:** Sound therapy (ST) is a crucial component of tinnitus therapy. Most available ST materials, however, consist of standard products using noises, nature sounds or music. These may not be optimal solutions because the needs of tinnitus patients show large individual variations. Therefore, optimal therapeutic ST-program should be individually tailored, interactive and easily adjustable. The IBAT (internet based acoustic therapy) program was developed to fulfil these demands. **Methods:** We tested our ST paradigm in case studies of 54 patients with acute noise-induced-tinnitus (NIT). ST was selected according to the patient’s individual authority. They may need enrichment of acoustic environment only, masking of tinnitus, management of tinnitus-triggered stress reaction, or customized, possibly notched ST. ST materials were created individually according to the patients hearing and tinnitus profiles (= tinnitus soundscape). The patients used ST to mask their tinnitus at least two hours daily. **Results:** In 54 patients, the pre-treatment loudness (VAS) average was 45,4, annoyance 64,4 and THI 47.0. Pre-treatment THI was >50 in 24 patients and > 85 in 6 patients indicating severe distress reaction. After three months all these values had decreased at least by 20 in over 85% of patients. In about 60% of the patients tinnitus has disappeared. **Discussion:** Our therapy programs effectively reduced tinnitus-induced distress together with tinnitus loudness and annoyance in over 85 % of our patients with acute NIT. Therefore, the cost-benefit ratio of our therapy regimen was good. This preliminary case study demonstrates that customized ST might be a useful (additional) tool in treatment of patients with tinnitus. Considering the high incidence of severe stress reaction as seen in our patients with acute NIT, it may be important to initiate the ST at an early stage. In general, targeting the emotional and attentional distress network may set special demands on therapeutic ST. These demands may be best fulfilled by IBAT-like sound therapy strategy.