



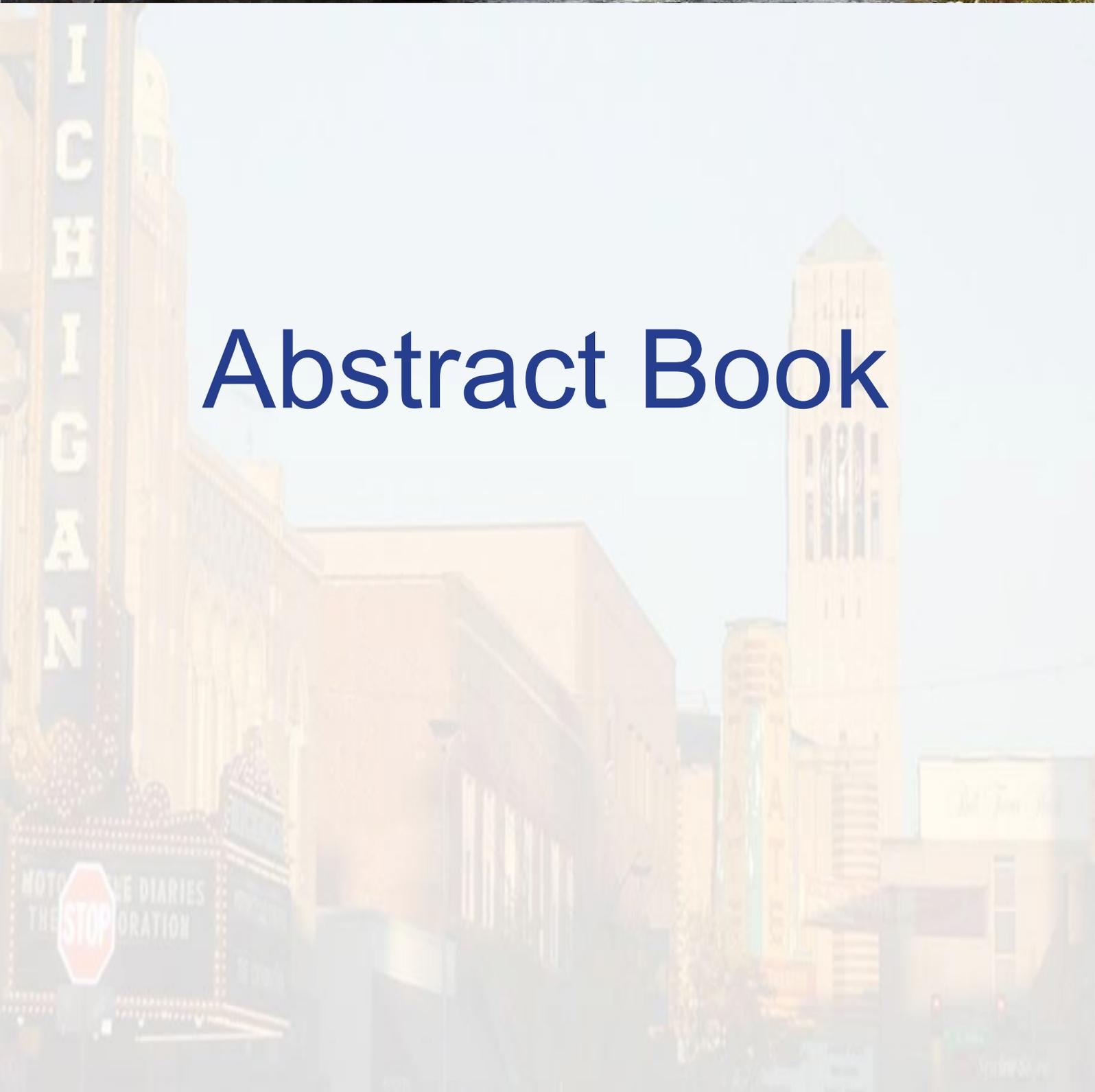
9th INTERNATIONAL

TRI Tinnitus Conference

TINNITUS: FROM COCHLEA TO BRAIN AND BACK

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Abstract Book

**TRI 2015
PROGRAM ABSTRACTS**

PODIUM SESSIONS

MONDAY, JUNE 8, 2015

**FEATURED SPEAKER
MOLECULAR UNDERPINNINGS OF TINNITUS**

Knipper, M

*Department of Otolaryngology, Head and Neck Surgery, Hearing Research Centre Tübingen,
Molecular Physiology of Hearing, University of Tübingen, Elfriede-Aulhorn-Straße 5, 72076
Tübingen, Germany*

Hearing disorders (Age- and Noise dependent hearing loss, Tinnitus or Hyperacusis) are expected to increase over the next decades due to demographic changes and altered leisure behavior. We here summarize the current knowledge of different cochlear damage profiles in the context of different brain responses and possible resulting auditory disorders. On the basis of this current knowledge new possible research directions and requests for future medical and industrial research profiles are suggested.

Acknowledgements

This work was supported by the Marie Curie Research Training Network CavNET MRTN-CT-2006-035367, the Deutsche Forschungsgemeinschaft DFG-Kni-316-4-1 and Hahn Stiftung (Index AG).

**FEATURED SPEAKER
COCHLEAR SYNAPTOPATHY OF NOISE AND AGING**

Kujawa, S

Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

Aims: The aim of this review is to summarize recent work on noise- and age-related cochlear synaptopathy and neurodegeneration, including mechanisms underlying the damage process and structural and functional consequences.

Methods: In a series of investigations conducted over the last 5 years, we have identified and begun characterization of noise-induced cochlear synaptopathy and neurodegeneration in several mammalian species. In the mouse, we have additionally followed the post-exposure

fate of hair cells, cochlear neurons and the synapses that connect them throughout the lifespan and compared changes to those observed in ears that age without intentional noise exposure. Hair cell-based (DPOAE, SP) and neural-based (ABR, CAP) responses are employed to assess function in noise-exposed and aging ears. Immunostained cochlear whole mounts and plastic-embedded sections are studied by confocal and conventional light microscopy to quantify hair cells, ganglion cells and synaptic structures: i.e. synaptic ribbons, glutamate receptors and cochlear-nerve terminals.

Effects of neurotrophins and drugs that act like neurotrophins are studied for their effects on the synaptopathy and neurodegeneration in parallel in vitro and in vivo models.

Results: Loss of inner hair cell (IHC) synapses with cochlear neurons occurs as a primary event in aging and noise-exposed ears. In unexposed ears of CBA/CaJ mice, synaptic loss is diffuse and gradually progressive, preceding hair cell and threshold sensitivity losses and reaching ~50% loss by the end of the lifespan¹. Such declines can be accelerated dramatically after noise, with up to ~50% of synapses lost within minutes of exposure, including many producing only temporary changes in thresholds and no hair cell loss². Although thresholds are quite insensitive to these diffuse losses, communications between IHCs and cochlear nerve fibers are nevertheless interrupted, reflected proportionately in reduced neural, but not pre-neural, response amplitudes. In both models, cochlear ganglion cell loss parallels the synaptic loss in magnitude and cochlear location. In ears that age after synaptopathic exposure, ongoing loss of synapses, ganglion cells and neural response amplitudes is exaggerated relative to age-only controls. Drug studies reveal more synapses, more neural sprouting and larger neural response amplitudes in treated preparations.

Conclusions: Results show that both aging and noise exposure have insidious consequences not revealed by standard threshold metrics. We hypothesize that these synaptopathic and neurodegenerative consequences of noise and aging may contribute to difficulties hearing in more challenging listening environments, i.e., in background noise and reverberation. They also may be important contributors to changes that result in tinnitus and hyperacusis.

Research supported by R01 DC 008577 and P30 DC 05029.

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PODIUM SESSION 1
MONDAY, JUNE 8, 2015

COCHLEAR PATHOLOGY UNDERLYING TINNITUS

Paul, BT¹; Roberts, LE^{1,2}; Bruce^{1,2,3}; Bosnyak, DJ¹; & Thompson, DC^{1,2}

1Department of Psychology, Neuroscience & Behaviour

2McMaster Institute for Music and the Mind

3Department of Electrical and Computer Engineering

McMaster University, Ontario, Canada

Background and Aims: Evidence from human and animal studies suggests that chronic subjective tinnitus results from forms of neural plasticity expressed in the central auditory system after deafferentation consequent on noise exposure or the aging process. However, not all cases of audiometric hearing loss lead to tinnitus, which could suggest that tinnitus is associated with cochlear damage not expressed in the audiogram. In agreement, tinnitus sufferers with normal audiograms exhibited reduced cochlear output (smaller Wave I of the ABR) to sounds of higher intensity compared to controls [1]. One explanation is that although type I auditory nerve fibers with low thresholds and high spontaneous rates (LT-HS ANFs) were normal for these subjects, relatively greater damage to high-threshold low-spontaneous rate (HT-LS) ANFs coding for suprathreshold sounds may have been present. We have been investigating whether measurement of detection thresholds for the presence of amplitude modulation (AM) in suprathreshold sounds may allow a test of the hypothesis that tinnitus subjects show evidence of greater damage to HT-LS ANFs compared to control subjects without tinnitus matched in age and hearing thresholds.

Methods: Because LT-HS ANFs saturate at levels above 40 dB SPL, HT-LS ANFs may preferentially code temporal fluctuations in suprathreshold sound in noisy environments [2]. Following this principle, we saturate HT-LS ANFs with a narrowband noise at 40 dB spectrum level centered at 5 kHz. A 5 kHz pure tone at 75 dB SPL is added, which lies in the frequency region in which tinnitus is often perceived. In our present results, we amplitude modulated the probe stimuli at 80 Hz using AM depths of 100%, 75%, and 50%, which evoked a steady-state response (SSR) in the electroencephalogram (EEG) known to arise from sources in the auditory midbrain. We correlated the slope of the function relating SSR amplitude to AM depth with the threshold of detection measured for 19-Hz AM tones using a 5 kHz pure tone presented either alone or in 40 dB spectrum level white noise, or white noise alone. In a separate procedure test-retest reliability for AM detection was also assessed.

Results and Conclusions: We will present the results for a cohort of young, normal-hearing listeners at the TRI meeting. Cohorts of tinnitus subjects matched in age and hearing thresholds to control subjects will be added. The findings may clarify whether damage to HT-LS ANFs is an underlying pathology in tinnitus.

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ON THE NEWLY-EMERGING FIELDS OF PERCEPTUAL, EMOTIONAL, AND COGNITIVE MAGNETIC RESONANCE SPECTROSCOPY

Cacace, AT¹; Galloway, MP⁴; Woodard, JL²; Sajja, VSSS³; Hu, J⁵; Ghoddoussi, F⁴; VandeVorde, .^{3,6*}; Xuan, Y⁵

*1*Departments of Communication Sciences & Disorders, *2*Psychology, *3*Biomedical Engineering, Wayne State University; *4*Departments of Psychiatry and Behavioral Neurosciences and Anesthesiology, and *5*Radiology, Wayne State University School of Medicine, Detroit, MI; *6**School of Biomedical Engineering and Sciences, Virginia Polytechnic and State University, Blacksburg, VA.

Background and objectives: In noise and blast-induced tinnitus and blast-induced neurotrauma (BINT), *in vivo* and *ex vivo* magnetic resonance spectroscopy (MRS) studies are illuminating the relationships between neurochemical constituents found in different brain areas and their perceptual, emotional, and cognitive processes. Herein, we assess the evidence for these relationships from intact brain tissue in rat and humans, both *ex vivo* and *in vivo*.

Methods:

Ex vivo studies

The *ex vivo* studies were applied using high resolution *magic angle spinning 1H-MRS* to intact tissue samples excised from rat brain after being exposed to shock-tube over-pressure blasts at the Wayne State Biomedical Engineering Research Facility. The *ex vivo* studies focused on potential relationships between behavioral phenotypes and neurochemical profiles in hippocampus, prefrontal cortex, and accumbens nuclei after exposure to a single over-pressure blast (117kPa, 7.5ms).

In vivo studies

Single-voxel 1H-MRS data were obtained from left and right auditory cortical areas in human volunteers with a history of either noise exposure or blast over pressures with concomitant hearing loss and tinnitus. A single-blinded sham-controlled cross-over design in human volunteers with noise-induced hearing loss and tinnitus used repetitive transcranial magnetic stimulation (rTMS) to assess tinnitus suppression effects where metabolites between pre/post sham and active conditions were evaluated. Volunteers with blast-induced tinnitus were assessed with a comprehensive battery of neuropsychological, audiological, and various MRI tests.

Results:

Ex vivo studies

Neurochemical responses in the hippocampus obtained from *magic angle spinning* 1H-MRS were consistent with acute neurodegeneration related to oxidative stress and mitochondrial dysfunction. These data from rats were further supported by histochemical measures confirming glial activation and apoptosis in the hippocampus. Seven days after BINT, performance on the novel object recognition test was impaired and the memory deficit was associated with increased levels of *myo*-inositol in the medial prefrontal cortex.

In vivo studies

The main finding from *rTMS* stimulation showed that decreased glutamate (Glu) was associated with a reduction in tinnitus-loudness levels. This effect was specific to the auditory cortical area treated with *rTMS* and was only evident after 5-sequential days of *active rTMS* treatment. In participants with blast-induced tinnitus, bivariate regression analyses showed that choice reaction time throughput was negatively related to left auditory cortex Glu levels; code substitution processing speed throughput was positively related to right auditory cortex Glu levels; code substitution delayed recall throughput was positively related to right auditory cortex *N*-acetyl aspartate levels; and speeded mathematical processing throughput was negatively related left auditory cortex choline levels.

Conclusions: The *ex-vivo* data on BINT-related behavioral endophenotypes and metabolic profiles are consistent with disordered mitochondrial function as well as histological and molecular evidence of neuronal degeneration and apoptosis. *In-vivo* noise-induced tinnitus data suggest positive *rTMS* outcome associated with reduced Glu and decreased tinnitus-loudness levels; blast induced tinnitus effects suggest evidence for abnormalities in auditory cortical areas that may contribute to neuropsychological deficits on speeded and cognitively demanding tasks.

Both *in vivo* and *ex vivo* studies support a substantial translational potential for these MRS measures in the linkage among various neurochemical profiles, behavior, and physiology (tinnitus).

TINNITUS SUPPRESSION WITH LOOPED INTRACOCHELEAR ELECTRICAL STIMULATION

Arts, RAGJ¹; E.L.J. George, ELJ, A. Griessner², C. Zierhofer², R.J. Stokroos¹.

¹Department of ENT/Head and Neck Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands,

²Institute of Mechatronics, University of Innsbruck, Innsbruck, Austria

Background/aim: Earlier studies show that a Cochlear Implant (CI), capable of providing intracochlear electrical stimulation independent of environmental sounds, appears to suppress tinnitus at least short term. The current main objective is to investigate the possibility for the

development of a “Tinnitus Implant” (TI), an intracochlear pulse generator for the suppression of tinnitus. Long-term suppressive effects of looped electrical stimulation (without environmental sound perception) will be compared with the standard stimulation pattern of a CI (with environmental sound perception).

Patients and method: Ten patients with Unilateral Hearing Loss (UHL) suffering from unilateral tinnitus are fitted with a CI (MED-EL Corporation, Innsbruck, Austria). Stimulation patterns are optimized for each individual patient, after which they are compared using an AB/BA randomized crossover design, with a follow-up of six months, followed by a 3 month period using the modality of patient’s choice.

Results: This study shows that tinnitus can be suppressed with intracochlear electrical stimulation independent of environmental sounds, even long term. No significant difference in tinnitus suppression was found between the standard clinical CI and the experimental TI.

Conclusion: Coding of environmental sounds is not a requirement for tinnitus suppression using intracochlear electrical stimulation. It is therefore plausible that tinnitus suppression by CI is not solely caused by an attention shift from the tinnitus to environmental sounds. Both the standard clinical CI and the experimental TI are potential treatment options for tinnitus. These findings offer perspectives for a successful clinical application of the TI within a few years, possible even in patients with significant residual hearing.

COCHLEAR IMPLANTATION IN UNILATERAL DEAFNESS – A CURE FOR TINNITUS

G Kirkby-Strachan, C Que-Hee, B Hoddinott
Mater Adults and Children’s Hospitals, Brisbane, Australia
and Neurosensory, Brisbane, Australia.*

Background: Otolaryngologists have been placing cochlear implants (CI) into patients with unilateral sensorineural hearing loss, so called Single Sided Deafness (SSD) with a contralateral normal ear to alleviate their inability to localise sound, difficulty in speech discrimination and potentially cure associated tinnitus. Trials are needed to compare this approach to the conventional strategies for unilateral profound hearing loss and tinnitus.

Methods: Eight patients completed questionnaires regarding the pre-implant and post implant status for the following criteria: tinnitus suppression, awareness of sound in the deafened ear, hearing in noise and sound localisation. The Tinnitus Reaction Questionnaire was used to assess reduction in tinnitus perception and the Speech, Spatial and Qualities (SSQ) Questionnaire was used to assess hearing outcomes.

Results: We present eight cases of CI in Single Sided Deafness. Patients showed improvements in tinnitus suppression, hearing awareness, hearing in noise in the deafened ear after implantation, but sound localisation remained poor subjectively.

Conclusions: The cases presented suggest cochlear implantation may be superior to conventional techniques and more trials are needed to compare this approach to the traditional strategies for tinnitus in unilateral hearing loss.

**PIRIBEDIL, MEMANTINE AND ACEMG PRETREATMENT REDUCES NOISEINDUCED
LOSS OF INNER HAIR CELL - AUDITORY NERVE RIBBONS AND
REDUCES INCIDENCE OF TINNITUS**

*Altschuler R, Halsey K, Kanicki A, Prieskorn D, Martin C, DeRemer S, Shore S, Miller J,
Dolan D, Kresge Hearing Research Institute, University of Michigan, Ann Arbor,
Michigan*

Recent studies show noise induced loss of Inner Hair Cell - Auditory Nerve (IHC-AN) connections can lead to decreased Gap Inhibition of the Acoustic Startle Reflex (Hickox and Liberman, 2014). We therefore tested whether preventing noise induced loss of connections would result in reduced loss of Gap Detection, without loss of Pre-Pulse Inhibition (PPI) of the Acoustic Startle reflex, which has also been associated with Tinnitus. We tested a combination of Piribedil, previously shown to reduce noise-induced dendritic damage (d'Aldin et al., 1995) and Memantine, an anti-excitotoxicity agent blocking the NMDA receptor. We also tested adding an anti-oxidant mixture of Vitamins A, C and E plus magnesium (ACEMg).

Piribedil and Memantine were given i.p. starting 3 days before the noise exposure and continued for 3 days thereafter. Another group also had ACEMg added to their diet before noise and continuing until termination. Rats were given sham noise or a small arms fire – like noise (50 biphasic impulses over 2.5 minutes at 152 dB SPL) presented unilaterally. Animals were tested for Gap Inhibition and PPI of the Acoustic Startle reflex prior to the noise exposure and 2-3 times a week until termination. Animals were also tested for Auditory Brain Stem Response prior to noise exposure and prior to termination. Animals were terminated 12 weeks following noise. Cochleae were then assessed for hair cell loss and for CTBP2 immunolabeling of IHC ribbons, as a marker for IHC-AN connections in three regions of the cochlear spiral, 3.25, 5.0 and 6.5 mm from the apex, respectively.

Approximately one third of the untreated rats receiving the small arms fire – like noise developed reduced Gap Inhibition of the Acoustic Startle Reflex (reduced Gap Detection) without reduced PPI (often considered a marker for tinnitus). Treatment with Piribedil and Memantine or treatment with Piribedil and Memantine plus ACEMg resulted in significantly less noise-induced loss of IHC-AN ribbons in the region 6.5 mm from the apex (24 kHz region) and

significantly fewer animals developing reduced Gap Detection without reduced PPI following noise compared to animals receiving the noise exposure and no preventive treatments.

In a parallel study, the effect of sarcosine (a glycine reuptake inhibitor) was tested. Sarcosine was given i.p. immediately following the small arms fire like noise and then in drinking water. This treatment did not change the incidence of reduced Gap Inhibition without reduced PPI during the 2 week period after the noise but reduced the incidence by ~50% during the remaining 6 week period of assessment, suggesting potential for improving recovery.

These studies were supported by DOD grant W81XWH-11-1-0414 and NIH grants R01 DC011294 and P30 DC05188

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FEATURED SPEAKER

NEUROTROPHIN-3 REGULATES RIBBON SYNAPSE DENSITY IN THE COCHLEA AND INDUCES SYNAPSE REGENERATION AFTER ACOUSTIC TRAUMA

G Wan^{1,2}, ME Gómez-Casati¹, MC Liberman^{3,4}, G Corfas^{1,2,3}

1 F.M. Kirby Neurobiology Center, Boston Children's Hospital, Boston, MA 02115.

2 Kresge Hearing Research Institute, Department of Otolaryngology - Head and Neck Surgery, University of Michigan, Ann Arbor, MI 48109.

3 Department of Otology and Laryngology, Harvard Medical School, Boston, MA 02115.

4 Eaton Peabody Laboratories, Massachusetts Eye & Ear Infirmary, Boston, MA 02114.

Aims/Objectives: Noise exposure induces damage to the inner ear, in many cases primarily to the synapses between inner hair cells (IHCs) and spiral ganglion neurons. This synaptopathy leads to permanent hearing impairment, even if it only transiently elevates threshold, and has been suggested to contribute to the pathogenesis of tinnitus, likely by initializing the over-adaptive responses of the central auditory pathway. Understanding the mechanisms that regulate the formation of IHC synapses could help in the development of approaches to protect or regenerate these synapses in the damaged ear. The aims of this study were to test the roles of the neurotrophins Ntf3 and Bdnf in the formation and maintenance of IHC synapses, and their ability to influence the noise-induced synaptopathy.

Methods: We used cell-specific inducible gene recombination in mice to knockout or over-express either Ntf3 or Bdnf in either IHCs or supporting cells in either neonatal or adult mice

and analyzed the effect of these manipulations on IHC synapse development and their loss after noise exposure.

Results: Supporting cell-derived Ntf3 is required for the formation and maintenance of hair cell ribbon synapses in the postnatal cochlea, while Bdnf is necessary for the formation of vestibular HC synapses. Moreover, supporting cell-derived Ntf3, but not Bdnf, promotes recovery of cochlear function and ribbon synapse regeneration after acoustic trauma.

Conclusions: These results indicate that supporting cells of the sensory epithelia are the key source of these neurotrophins in the postnatal inner ear and that these trophic factors play critical roles in the formation of HC synapses. Importantly, we show that increasing the availability of Ntf3, but not Bdnf, promotes recovery of both cochlear responses and IHC synapses after acoustic trauma, even when Ntf3 expression is induced after noise exposure. These results point to Ntf3 as a promising target for the treatment of noise-induced hearing loss, which could be also beneficial for tinnitus.

Supported in part by R01 DC 004820 (to G.C.) and P30 DC 005209 (to M.C.L.), P30-HD 18655 (to G.C.) and the Hearing Health Foundation (to G.W.).

PODIUM SESSION 2 MONDAY, JUNE 8, 2015

DEEP BRAIN STIMULATION OF THE INFERIOR COLLICULUS REDUCES TINNITUS IN A VALIDATED ANIMAL MODEL FOR TINNITUS

Smit JV¹, Janssen MLF², Jahanshahi A³, Temel Y³, Stokroos RJ¹

*1Departments of Ear, Nose and Throat / Head and Neck Surgery, 2Neurology, 3Neurosurgery
Maastricht University Medical Center, Maastricht, The Netherlands*

Background: Tinnitus can cause a serious burden on patients and remains often treatment resistant. Up to date no effective treatments are available. Deep brain stimulation (DBS) has been widely applied for various neurological disorders, most often in patients with Parkinson's disease. DBS interferes with pathological neuronal activity. The inferior colliculus (IC) shows increased neuronal firing and bursting activity in animal models of tinnitus. We therefore hypothesized that tinnitus can be treated by DBS of the IC.

Objective: In this study we assessed treatment of experimental tinnitus with DBS in the IC in an animal model with behavioral signs of tinnitus in an intra-individual controlled experimental design.

Methods: In nine Sprague Dawley rats the startle reflex using the pre-pulse inhibition (PPI) paradigm was measured as a pretest. Tinnitus was defined as an increase in gap:no-gap ratio. After bilateral DBS implantation in the IC the sham situation was assessed including screening of hearing using the auditory brainstem response (ABR). Unilateral tinnitus was induced using a 16 kHz octave-banded noise and the PPI and ABR were again measured. DBS in the IC was then applied at 100 Hz at 100 μ A.

Results: Histological examination showed that the electrodes were positioned within the IC. After noise trauma the rats showed an increase of gap:no gap ratio at 16 and 20 kHz ($p=0.01$). Hearing in the contralateral ear was not impaired by noise trauma as measured by the ABR. During DBS the gap:no gap ratio returned back to baseline ($p=0.01$).

Conclusion: This study shows that DBS of the IC is effective in reducing experimental tinnitus in a validated animal model for tinnitus. Further studies are needed to validate this finding and other more accessible brain structures for human application need to be studied.

AUDITORY MIDBRAIN IMPLANT (AMI): IMPLICATIONS FOR TINNITUS TREATMENT

S. J. Offutt¹, R. J. Hughes¹, H. H. Lim^{1,2,3}

- 1. Department of Biomedical Engineering, University of Minnesota, USA*
- 2. Department of Otolaryngology - Head and Neck Surgery, University of Minnesota, USA*
- 3. Institute for Translational Neuroscience, University of Minnesota, USA*

Objectives: One potential option for tinnitus treatment is to use deep brain stimulation of non-lemniscal and modulatory auditory nuclei to alter tinnitus-related activity within the auditory system. The AMI is currently being implanted into the inferior colliculus in deaf patients to restore hearing. Many eligible candidates also have tinnitus, and thus the AMI could be used to stimulate the non-lemniscal outer region of the inferior colliculus (ICD) to modulate the auditory system and potentially treat tinnitus. To guide tinnitus testing in future AMI patients, we performed experiments in animals to identify ICD electrical stimulation paradigms that produce the greatest amount of neural suppression, which may counteract the central hyperactivity linked to tinnitus.

Methods: Multi-site arrays were positioned in the central nucleus of the inferior colliculus (ICC; main ascending auditory portion of the midbrain) and ICD of 13 ketamine-anesthetized guinea pigs. ICC spike activity in response to broadband noise stimulation was recorded before and after each ICD electrical stimulation paradigm, which included ICD stimulation alone or ICD stimulation paired with acoustic broadband noise stimulation at specific inter-stimulus intervals (ICD pulse relative to acoustic onset: -7 to +23 ms, 5 ms steps). Acoustic stimulation alone and a control condition (no stimulation paradigm) were also presented. Immediate and residual effects were determined by comparing the changes in ICC spike activity immediately and 30 minutes after each paradigm, respectively, relative to the baseline activity.

Results and Conclusions: We generally observed more suppressive than facilitatory modulation for all paired paradigms for both immediate and residual cases. Significant residual effects were particularly observed for the +18 ms paired paradigm and the ICD stimulation alone paradigm in which there was greater suppression than facilitation and more suppression compared to the control condition. Compared to the ICD paradigms, the acoustic stimulation alone paradigm exhibited more equivalent amounts of suppressive and facilitatory effects. These findings suggest that ICD stimulation has the potential to modulate and particularly suppress ascending auditory activity, which in turn could suppress neurons driving the tinnitus percept. The ICD stimulation alone paradigm will be explored in upcoming deaf patients with tinnitus who will be implanted with the AMI. If the AMI can be implanted in tinnitus patients with hearing capabilities, specific paired paradigms may be used to optimize treatment in each patient.

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THALAMOCORTICAL RHYTHMS ARE ALTERED BY RTMS IN ASSOCIATION WITH TINNITUS IMPROVEMENT

Mennemeier, M., Carter, G., Govindan, R.B., Brown, G., Dornhoffer, J., Garcia-Rill, E., Greenfield, L.J., Hayar, A., Shihabuddin, B., Thostenson, J.
Center for Translational Neuroscience, University of Arkansas for Medical Sciences, Little Rock AR, USA (*1P30GM110702)*

Aims/Objectives: To test predictions of the thalamocortical dysrhythmia hypothesis (TCD) for tinnitus in the context of a blinded, placebo-controlled, rTMS study with subject crossover. The TCD hypothesis posits a loss of normal depolarizing sensory input from the cochlea to auditory nuclei of the thalamus that causes cells to switch to burst, rather than tonic, firing mode due to increased expression of low threshold spikes (T-type calcium channels). Burst firing slows thalamocortical rhythms; shifting spectral power from normal alpha (~10Hz) to theta (~8Hz) and delta (~4Hz) frequencies. As repetitive transcranial magnetic stimulation (rTMS) delivered at 1 and 10 Hz over the temporal cortex can reduce analogue ratings of tinnitus; we recorded the resting state EEG in tinnitus patients at baseline and after they received placebo and active rTMS at 1 and 10Hz. We hypothesized that active rTMS would decrease spectral power and coherence for low-frequency EEG bands (delta-theta) and increase that for higher frequency bands (alpha-beta) and that this change will correlate with tinnitus improvement.

Methods: Nineteen patients with subjective idiopathic tinnitus were tested. RTMS was delivered over temporal cortex at frequencies of 1 and 10 Hz (1800 pulses @ 110% of

the MT x 4 days). Ratings of tinnitus awareness, annoyance and loudness were on a 0-100 scale. Artifact free, spontaneous EEG was recorded for a minimum of 12, 10 second epochs with both eyes open and closed. EEG signals were acquired with a 64 electrodes on a NicoletOne LTM EEG system using the extended 10-20 system.

Results: Active 1 Hz rTMS (but not 10 Hz or placebo) reduced ratings of tinnitus awareness and annoyance from baseline [$F=12$, $p<.005$, observed power = .89; mean difference between placebo versus 1Hz rTMS = 9.3 (3.6) points, $p<.024$]. Whereas no significant change was observed in any frequency band of the EEG after placebo rTMS; a significant increase in alpha spectral power and a significant decrease in gamma power (30-50 Hz) was observed over temporo-parietal EEG electrodes after active rTMS at 1 and 10 Hz (both eyes open and closed). Power in the delta and theta bands were slightly increased rather than decreased after active rTMS. Analysis of coherence also revealed a significant increase in the beta range after active rTMS.

Conclusion: Active rTMS reduced tinnitus awareness and annoyance which was associated with an increase in alpha power, a decrease in gamma power, and an increase in beta coherence. No decreases in spectral power were observed in the delta or theta ranges. As beta coherence is linked to top-down modulation of sensory signals, our findings could suggest that rTMS modulates tinnitus awareness and annoyance by influencing beta frequency modulation of bottom up signals.

TOP-DOWN AND BOTTOM-UP NEUROMODULATION TO SUPPRESS TINNITUS

J. Zhang^{1,2}

1Department of Otolaryngology-Head and Neck Surgery, Wayne State University School of Medicine, Detroit, Michigan, USA

2Department of Communication Sciences & Disorders, Wayne State University College of Liberal Arts & Sciences, Detroit, Michigan, USA

Neuromodulation is an important way to treat neurological disorders including tinnitus. It involves stimulation of a variety of peripheral and brain structures. Among these structures modulated, stimulation of the auditory structures has demonstrated robust evidence of tinnitus suppression in both human and animal studies. The first common approach is to stimulate the auditory cortex, a top-down approach, which activates corticofugal pathways. The second approach is to stimulate the cochlea or an auditory brainstem structure, commonly referred as a bottom-up approach, which mostly activates the ascending pathways. This paper will review the latest development in human and animal studies, discuss the underlying mechanisms, and address possible translational approaches towards tinnitus suppression.

**Acoustic Coordinated Reset
Neuromodulation in a Real Life Patient Population with Chronic Tinnitus**

**Langguth, B.; Ströbel, A.;*

*Williams, M.; Patel, N.; Wurzer, H.; von Stackelberg, T.; Brinkmann, U.; Tass, P.,
Germany*

Objective: To describe the quantitative treatment outcomes of patients undergoing acoustic coordinated reset (CR) neuromodulation at a single independent audiology practice over a 22 – 26 week period as part of an open label, non-randomized, non-controlled observational study.

Methods: Sixty six patients with subjective tonal tinnitus were treated with acoustic CR Neuromodulation with a retrospective review of patient records being performed in order to identify changes of visual analogue scale (VAS, n=66) and in the score of the Tinnitus Handicap Questionnaire (THQ, n =51). Patients had their tinnitus severity recorded prior to the initiation of therapy using the Tinnitus Handicap Inventory (THI) in order to categorize patients into slight up to catastrophic impact categories. THQ and VAS for tinnitus loudness / annoyance were obtained at the patient's initial visit, at 10-14 weeks and 22-26 weeks.

Results: VAS scores were significantly improved, demonstrating a 25.8% mean reduction in tinnitus loudness and a 32% mean reduction in tinnitus annoyance with a clinically significant reduction in percept loudness and annoyance being recorded in 59.1% and 72.7% of the patient group. THQ scores were significantly improved by 19.4% after 22-26 weeks of therapy compared to baseline.

Conclusion: Acoustic CR neuromodulation therapy appears to be a practical and promising treatment for subjective tonal tinnitus.

FEATURED SPEAKER

**MULTIPLE PARALLEL BRAINSTEM PATHWAYS ARE HYPER-RESPONSIVE
IN HUMAN TINNITUS: A RESULT OF TOP-DOWN NEUROMODULATION?**

Melcher, JR and Knudson, IM

Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston MA USA

Aims/ Objectives: Parallel pathways within the human auditory brainstem were tested for differential involvement in tinnitus and the lowered sound-level tolerance (i.e., loudness hyperacusis) that commonly accompanies it.

Methods: In broad outline, experiments involved comparing stringently matched subject groups on a variety of sound-evoked, brainstem-mediated responses: brainstem auditory evoked potentials, acoustic startle responses, contralateral suppression of otoacoustic

emissions, and fMRI activation. Because of sex differences suggested by the results, we focus here on the sex (men) for which we have ample data to draw firm conclusions.

Results: Every measure tested indicated elevated activity associated with tinnitus and, to varying degrees, loudness hyperacusis. Specifically, all of the following were elevated: (1) Waves of the brainstem auditory evoked potential that reflect activity in pathways originating in the anterior division of the ventral cochlear nucleus (VCN), (2) Acoustic startle response, also likely mediated through anterior VCN in humans, (3) suppression of otoacoustic emissions by the medial olivocochlear pathway, which involves the posterior division of the VCN, (4) fMRI activation of the inferior colliculi, a site of convergence for pathways from the VCN as well as a remaining major division of the cochlear nucleus, the dorsal cochlear nucleus (DCN).

Conclusions: While the human data provide evidence for hyper-responsiveness/ hyperactivity in VCN-mediated pathways, a large amount of animal tinnitus work indicates hyper-responsiveness/ hyperactivity in the DCN. Combining human and animal data, we conclude that hyper-responsiveness/hyperactivity related to tinnitus and loudness hyperacusis is ubiquitous in the auditory brainstem and present across multiple neural pathways involving every major division of the cochlear nucleus. While it is possible that this widespread brainstem hyperresponsiveness/ hyperactivity arises independently in each pathway via different mechanisms, we propose an alternative view: that over-activation of the auditory brainstem arises from forebrain-mediated neuromodulation broadly distributed throughout the brainstem.

FEATURED SPEAKER

BRAIN STIMULATION FOR THE TREATMENT OF TINNITUS: WHERE DO WE STAND AND WHAT THE FUTURE BRINGS?

B Langguth

University of Regensburg, Germany

First attempts to use brain stimulation methods for the treatment of Tinnitus were based on the assumption that abnormal activity of the auditory Cortex represents the neuronal correlate of tinnitus. It has been demonstrated that neuronal activity in the auditory cortex can be modulated by repetitive transcranial magnetic Stimulation (rTMS), transcranial electric Stimulation (tES) or epidural stimulation and that these activity changes can lead to tinnitus reduction in some patients. However the effect sizes are small and recent large trials have failed to demonstrate significant improvement with this approach. The limited effect of auditory stimulation can be explained by more recent concepts of tinnitus pathophysiology which assume abnormal activity and connectivity in multiple brain networks. These concepts are supported by tinnitus modulation via stimulation of non-auditory brain areas and by enhanced efficacy of stimulation protocols that target multiple brain regions. Another direction of research aims at the combination of brain stimulation with auditory stimulation for more targeted and efficient induction of neuroplastic changes. These approaches have shown to be

feasible in proof of concept studies and can be translated into clinical application in the near future. In summary, even if brain stimulation techniques are not yet at a stage to be applied as clinical routine treatment, they have largely contributed to a better understanding of tinnitus pathophysiology during the last 15 years.

PODIUM SESSION
TUESDAY, JUNE 9, 2015

FEATURED SPEAKER

**FOREBRAIN CHOLINERGIC CONTROL OF ATTENTION: MULTIPLE MODES,
MULTIPLE COGNITIVE MECHANISMS**

M. Sarter

*Department of Psychology and Neuroscience Program, University of Michigan,
Ann Arbor, MI*

Traditional descriptions of the basal forebrain cholinergic projection system to the cortex have focused on neuromodulatory influences, that is, mechanisms that modulate cortical information processing but are not necessary for mediating discrete behavioral responses and cognitive operations. However, amperometric recordings of real-time cholinergic presynaptic signaling in attentional taskperforming rats generated evidence in support of more deterministic contributions of cholinergic projections to cortical information processing. Through presynaptic receptors expressed on cholinergic terminals, thalamocortical projections can evoke brief cholinergic release events. These acetylcholine (ACh) release events occur on a fast, sub-second to seconds-long time scale ('transients'). In rats performing a task requiring the detection of cues as well as the report of non-cue events, cholinergic transients mediate the detection of cues specifically in trials that involve a shift from a state of monitoring for cues to cue-directed responding. Accordingly, ill-timed cholinergic transients, generated using optogenetic methods, force false detections in trials without cues (1).

Thus, the cholinergic-cortical projection system utilizes at least two modes of neurotransmission. Neuromodulatory cholinergic activity, varying on the scale of tens of seconds to minutes, influences cortical circuitry top-down and is highest when task-demands are high and alternative action is increasingly attractive. Low levels of cholinergic neuromodulation, as seen in rats prone for addiction-like behavior and hypothesized in humans expressing a subcapacity choline transporter, foster relatively poor and fluctuating levels of attention and/or vulnerability to distracters. Levels of cholinergic neuromodulation influence the likelihood and amplitudes of cholinergic transients. These transients mediate specifically the detection of cues when involving a shift in attentional mode. In other words, these transients assure the insertion of cue-related information into cortical circuitry (bottom-up).

Recent theories about tinnitus have focused on central, cholinergic-attentional mechanisms contributing to the maladaptive representation, or attentional bias to, aberrant neuronal activity underlying tinnitus perception (2). Our new insights into cholinergic function and underlying circuitry have supported a treatment approach, consisting of stimulation of alpha4beta2* nicotinic acetylcholine receptors, to enhance cholinergic neuromodulation and cue processing. In tinnitus patients, this treatment may suppress the processing of aberrant auditory inputs while amplifying the detection of behaviorally relevant auditory information. As these agonists were shown to produce beneficial attentional effects in adult ADHD in advanced clinical (Phase II) studies, they are potentially available to test the hypothesis that they also benefit tinnitus patients.

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FEATURED SPEAKER

ROLE OF THE AUDITORY CORTEX IN TINNITUS: HYPERSYNCHRONY, ATTENTION, AND RESIDUAL INHIBITION

*L. E. Roberts¹, D.J. Bosnyak¹, I.C. Bruce^{1, 2} and B.T. Paul¹
1Department of Psychology, Neuroscience, and Behaviour
2 Department of Electrical and Computer Engineering
McMaster University, Hamilton, Ontario, Canada*

It has been proposed that tinnitus is generated by hypersynchronous neural activity that develops among neurons in tonotopic of regions of primary auditory cortex (A1) affected by hearing loss, which is also the frequency region where tinnitus percepts localize (Eggermont and Roberts 2004; Roberts et al., 2008, 2010, 2013; Eggermont and Tass, 2015). We tested this model by comparing sound evoked EEG responses known to localize to neural sources in either primary (A1) or nonprimary (A2) auditory cortex between individuals with tinnitus and controls of similar age and hearing function, first under resting state conditions and then after a forward masking procedure (band limited noise, CF 5 kHz) that induced RI in the tinnitus subjects. Neural responses were evoked either by a 500 Hz sound known to be well below the tinnitus frequency region (TFR) of the tinnitus subjects or by a 5 kHz sound known to be well within the TFR. Differences between tinnitus and control groups in neural responses localizing to A1 depended on whether probe frequency was in the TFR or below it, whereas group differences in responses localizing to A2 did not (these responses were larger in tinnitus than control subjects at both probe frequencies). Changes in responding in A1 tracked RI in the tinnitus groups, but changes in responding in A2 did not. These findings are consistent with the view that while disinhibition of auditory cortical regions by auditory attention enhances sound-evoked cortical activity in A1 and A2 similarly in tinnitus subjects, hypersynchrony distributed preferentially to the TFR of A1 is an additional factor affecting sound-evoked activity in tinnitus. Suppression of neural activity in A1 by forward masking may disrupt hypersynchrony and

explain off-frequency masking effects observed in tinnitus and control subjects that are consistent with results from animal studies.
(Supported by NSERC of Canada)

FEATURED SPEAKER

ACTIVITY-DEPENDENT PROTEASOME REDISTRIBUTION IN AXONS GATES HOMEOSTATIC CHANGES IN PRESYNAPTIC FUNCTION.

FE Henry,^{1,2} JC Althaus,¹ SK Jakawich^{1,2}, CJ Carruthers¹, V Cazares^{2,3}, EL Stuenkel^{2,3}, Michael A. Sutton^{1,2,3}

1Molecular and Behavioral Neuroscience Institute, 2Neuroscience Graduate Program, and 3Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan 48109

Background: As the basic unit through which neurons communicate, the molecular mechanisms that govern synapse function remains critically importance to neuroscience. It is now clear that synaptic strength can be persistently altered by changing the protein composition of synaptic sites by regulated synthesis and degradation. Protein degradation by the 26S proteasome is important in modulating synaptic transmission, and it has been recently shown that the proteasome is trafficked to synaptic sites in dendrites in response to activity. The proteasome is also important for regulating presynaptic neurotransmitter release, but it is only sparsely expressed in axons, suggesting that activity-dependent trafficking within axons may be important to target the 26S proteasome to synaptic terminals. This trafficking might be particularly important for transsynaptic coordination of pre- and postsynaptic function, as recent work has shown that postsynaptic neurons homeostatically control neurotransmitter release of neurons that synapse onto them via diffusible messengers. This transsynaptic homeostasis is achieved through local dendritic protein synthesis driven by the Mtor complex 1 (mTORC1) signaling pathway, which drives synaptic translation and subsequent release of brain-derived neurotrophic factor (BDNF). BDNF, in turn, signals directly to the presynaptic terminal via its receptor tyrosine kinase TrkB. Intriguingly, this particular form of plasticity exhibits “metaplasticity,” as it is selectively implemented at synaptic terminals that are active during BDNF exposure. Here, we investigate the mechanisms responsible for this state-dependent gating.

Methods: Cultured hippocampal neurons were transfected with epitope-tagged 19S proteasome subunits – these recombinant proteasome proteins effectively assemble into native 26S proteasomes. We used confocal microscopy to monitor both the steady-state distribution and dynamic trafficking of proteasomes in axons in response to altered neural activity. GFP- and PAGFP-tagged 19S subunits were used for live cell imaging experiments. Fluorescence from axonal proteasomes was photoactivated at both synaptic terminals and extrasynaptic sites using a 405 nm laser, and the distribution of fluorescence monitored over time. These imaging experiments were followed by functional imaging studies examining

synaptic vesicle exocytosis at presynaptic terminals using vGlut1-pHluorin and through electrophysiological analysis of synapse function.

Results/conclusions: We found that the distribution of the proteasome in axons of cultured hippocampal neurons is dynamically modulated by activity. Conditions that increase firing enhances localization to synaptic terminals, whereas activity suppression drives redistribution away from synaptic terminals to extrasynaptic sites. These dynamics are mediated, at least in part, by direct phosphorylation of the proteasomal subunit Rpt6, which causes proteasome sequestration at active synaptic terminals. Defects in activity-dependent proteasome localization to synapses prevent the induction of homeostatic compensation in presynaptic terminals, whereas conferring synaptic proteasome localization rescues presynaptic compensation at otherwise inactive terminals. Together, our results demonstrate that dynamic proteasome trafficking in axons contributes to setting activity dependent rules for synaptic homeostasis.

PODIUM SESSION 3 TUESDAY, JUNE 9, 2015

INTRACRANIAL MAPPING OF A CORTICAL TINNITUS SYSTEM USING RESIDUAL INHIBITION

Gander, P.¹, Sedley, W.², Kumar, S.^{2,3}, Oya, H.¹, Kovach, C.K.¹, Nourski, K.V.¹, Kawasaki, H.¹, Howard III, M.A.¹, Griffiths, T.D.^{1,2,3}

1 Department of Neurosurgery, The University of Iowa, Iowa City, Iowa 52242, USA, 2 Institute of Neuroscience, Newcastle University, Newcastle Upon Tyne, Tyne and Wear, NE2 4HH, UK, 3 Wellcome Trust Centre for Neuroimaging, University College London, London, WC1N 3BG, UK

Aims: Tinnitus can occur when damage to the peripheral auditory system leads to spontaneous brain activity that is interpreted as sound. Many abnormalities of brain activity are associated with tinnitus, but it is unclear how these relate to the phantom sound itself, as opposed to predisposing factors or secondary consequences. Demonstrating 'core' tinnitus correlates (processes that are both necessary and sufficient for tinnitus perception) requires high-precision recordings of neural activity combined with a behavioural paradigm where the perception of tinnitus is manipulated and accurately reported by the subject. This has been previously impossible in animal and human research. Nonetheless, testable hypotheses have recently been proposed about the possible architecture of a 'tinnitus core' network, defined as the minimum neural network that must be active in order for tinnitus to be perceived.

Methods: We tested the hypothesis of a tinnitus core network in a 50 year-old male neurosurgical subject, with typical bilateral tonal tinnitus and high-frequency hearing loss, who had an extensive array of electrocorticography and depth electrodes placed in the left hemisphere for the localization of epilepsy. Intracranial recordings were collected during short-term modifications in perceived tinnitus loudness following acoustic stimulation (residual inhibition, RI). RI was assessed by periodic ratings of tinnitus loudness, in between which were 10 s blocks (from which data were used for analysis) in which no stimuli were presented and there was no task to perform.

Results: The experiment was performed on two separate days, with 15/30 trials on day 1 and 14/30 on day 2 constituting 'RI trials'. Results were derived from regression of neural activity, recorded electrocorticographically, against the degree of subjective tinnitus suppression. As anticipated, we observed tinnitus-linked low frequency (delta, 1-4 Hz) oscillations, thought to be triggered by low frequency bursting in the thalamus. Contrary to expectation, these delta changes extended far beyond circumscribed auditory cortical regions to encompass almost all of auditory cortex, plus large parts of temporal, parietal, sensorimotor, and limbic cortex. In discrete auditory, parahippocampal and inferior parietal 'hub' regions, these delta oscillations interacted with middle (alpha) and high (beta and gamma) frequency activity, resulting in a coherent system of tightly-coupled oscillations associated with high-level functions including memory and perception.

The surgical resection included the posterior end of parahippocampal cortex (PHC) which did show tinnitus-related neural activity changes. The resection resulted in significantly reduced seizure frequency, and complete and sustained cessation of tinnitus in the right (contralateral) ear, with no change to tinnitus in the left ear.

Conclusion: Our findings provide direct support for both the anatomical and physiological aspects of a hypothesized core tinnitus network, and go further in revealing the detailed workings of such a 'tinnitus system' through which the low-frequency tinnitus input signal propagates spatially, across the cortex, and spectrally, across frequency bands, so as to lead to a perceived auditory entity.

Disruption of activity in PHC has been associated with success of auditory cortex stimulation to treat tinnitus. Thus our finding of tinnitus elimination through disruption of PHC lends further evidence to its crucial importance in tinnitus.

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MULTISENSORY ATTENTION TRAINING AND FLUOXETINE FOR TREATMENT OF TINNITUS

Searchfield G. D.^{1,2}, Spiegel D. P.^{1,2,5}, Linford T.¹, Thompson B.^{2,3}, Petoe M. A.^{1,4}, Kobayashi K.^{1,2}, Stinear, C. M.², Poppe, T.^{2,3}, Sundram, F.² Russell, B.²*

1 Section of Audiology, School of Population Health, The University of Auckland, 261 Morrin Road, Glenn Innes, Auckland, New Zealand

2 Centre for Brain Research, The University of Auckland, 85 Park Road, Grafton, Auckland, New Zealand

3 Department of Optometry and Vision Science, The University of Auckland, 85 Park Road, Grafton, Auckland, New Zealand

4 The Bionics Institute of Australia, 384-388 Albert Street, Melbourne, Australia

5 McGill Vision Research, Department of Ophthalmology, McGill University, Montreal, Canada

Introduction: Tinnitus is the conscious perception of sound with no physical sound source. Some models of tinnitus pathophysiology suggest that networks associated with attention, memory, distress and multisensory experience are involved in tinnitus perception. The aim of this study was to evaluate whether a multisensory attention training paradigm that used audio, visual and somatosensory stimulation would reduce tinnitus, and whether the effect could be enhanced by a low dose of Fluoxetine.

Methods: Eighteen participants with predominantly unilateral chronic tinnitus were randomized between two groups receiving 20 daily sessions of either integration (attempting to reduce salience to tinnitus by binding with multisensory stimuli) or attention diversion (multisensory stimuli opposite side to tinnitus) training. This was followed by a double blind placebo controlled trial in 20 participants who received either a placebo or 20mg of Fluoxetine daily for 20 days along with the integration training. Tinnitus measures and resting state-functional magnetic resonance imaging (rsfMRI) were performed pre- and post-treatment.

Results: The training resulted in small but statistically significant reductions in Tinnitus Functional Index and Tinnitus Severity Numeric Scale scores and improved attention abilities. No statistically significant improvements in tinnitus were found between the training groups or between placebo and fluoxetine. RS-fMRI results suggest antagonistic effects of the training and Fluoxetine.

Discussion: This study demonstrated that a short period of multisensory attention training reduced unilateral tinnitus, but directing attention toward or away from the tinnitus side did not differentiate this effect. A low dose of Fluoxetine had no effect on behavioral measures above training alone, but did change rs-fMRI.

RESTING STATE FUNCTIONAL CONNECTIVITY IN TINNITUS PATIENTS VARIES WITH TINNITUS DURATION AND SEVERITY

Schmidt SA, Carpenter-Thompson JR, Husain FT.

Department of Speech and Hearing Science, The Beckman Institute, and The Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana-Champaign, IL

Background/aims: Resting state functional connectivity is defined as spontaneous fluctuations in the fMRI BOLD response that can be reliably organized into networks. Several recent studies have demonstrated that tinnitus patients exhibit resting state functional connectivity that differs from both normal hearing and hearing loss controls (see [1]). These differences include increased connectivity between limbic areas and networks not typically associated with emotional processing, as well as increased connectivity between attention and auditory processing regions. We conducted two studies that aim to further explore the resting state networks of tinnitus patients by examining subgroups of the tinnitus population, specifically those of varying tinnitus duration and severity. We hypothesized that patients with recent tinnitus would exhibit more alterations to connectivity with limbic regions, while those with long-term tinnitus would show more alterations relating to attentional processing, with the latter representing habituation to the tinnitus sound. We also hypothesized that greater connectivity between non-emotion networks and emotion-processing regions would be present in patients with high tinnitus severity when compared to those with low severity.

Methods: Two separate studies and analyses were conducted: one comparing long-term and short-term tinnitus patients, and the other examining low and high tinnitus severity groups (as measured by scores on the Tinnitus Handicap Inventory). No participants in any of the groups overlapped. Both analyses used a seed-based approach in the Conn toolbox to examine three resting state networks: the auditory, dorsal attention, and default mode networks.

Results: 1. Few differences in connectivity were seen between the recent and long-term tinnitus groups. An increased correlation between seeds in the auditory resting state network and the right middle cingulate and an increased correlation between the precuneus/posterior cingulate and seeds for the default mode network was noted in recent tinnitus patients compared to the long-term group. 2. In the severity analysis, an increased correlation between an auditory seed and the left middle temporal gyrus in high severity compared to low was observed, as well as an increased correlation between a default mode seed and the left cuneus/precuneus in low severity compared to high.

Conclusions: Resting state functional connectivity does vary with both duration and severity of the percept. The increased connectivity between default mode seeds and the posterior cingulate in patients with recent tinnitus supports our hypothesis of a heightened emotional response at rest, suggesting that individuals with recent onset have not yet habituated to their percept. In contrast, our hypothesis regarding increased correlations to limbic regions with increased tinnitus severity was not supported. However, decreased correlations between the posterior cingulate and the left cuneus/precuneus were found in the high severity group,

indicating a disruption of the default mode network, which agrees with findings from our earlier study [2].

This research was funded by the American Tinnitus Association and the Tinnitus Research Consortium.

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EFFECTS OF BK CHANNEL MODULATORS IN A MOUSE MODEL OF TINNITUS

Lowe, A.S.¹, Cresoe, S.A.³, Walton, J.P.^{1,2}

1Department of Biomedical Engineering, University of South Florida

2Department of Communication Sciences and Disorders, University of South Florida

3Department of Chemistry, University of South Florida

Recent studies have provided preliminary evidence that potassium channels may play a crucial role in the development and treatment of tinnitus, including the voltage-gated, Ca⁺ activated, BK channel. BK channels are found throughout the peripheral and central auditory system, and modulators of this channel have been shown to affect neuronal excitability. This study examined the effects of a BK channel pore blocker (paxilline) and opener (BMS-191011) on young adult CBA/CaJ mice after the induction of tinnitus using sodium salicylate (SS).

All treatments were given systemically via intraperitoneal injections, with baseline measurements followed by assessment of SS alone, and SS+PAX or SS+BMS on subsequent days. One group was tested for tinnitus with a behavioral measure of long duration gap detection, which utilizes pre-pulse inhibition (PPI) to a 50 ms silent gap embedded in narrowband noises centered at 6, 12, 16, 20, and 24 kHz. Peripheral thresholds of a second group were assessed using auditory brainstem responses (ABRs), and tinnitus was assayed using recovery of the different peak amplitudes following silent gaps in narrowband noise, again centered at 6, 12, 16, 20, and 24 kHz.

Previous studies found that SS-induced tinnitus was characterized by reductions in gap-PPI and increases in the ABR waveform peak 2 (P2)/ P1 and P4/P1 amplitude ratios in response to stimuli in the tinnitus percept region (12–20 kHz). Additionally, SS treatment was shown to decrease neural recovery to gaps in 16 kHz noise when calculated by taking the P1 amplitude of the response to the second noise burst as a percentage of the response to the first noise burst of the gap stimuli ABR response. Results from the current study again found biomarkers of tinnitus following SS-only; however, treatment with SS + BK modulators revealed conflicting electrophysiological and behavioral responses. Gap-PPI was significantly reduced for 12 and 16

kHz gap carriers following SS-only, however, SS+BMS improved gap detection (increased gap-PPI) for all frequency stimuli, suggesting a reduction in the tinnitus percept. However, there were no significant effects following SS+PAX when compared to SS-only. In contrast, BK modulators did not appear to improve electrophysiological measures of tinnitus or affect peripheral hearing thresholds. Our results indicate that while modulation of SS-induced tinnitus may occur in response to alterations in the BK channel, these changes are not reflected in the auditory brainstem response. However, the behavioral improvements following BMS treatment suggest that higher order auditory structures could underlie these effects. Direct recordings of changes in the auditory cortex will be examined to confirm these findings.

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HYPERACTIVE AUDITORY-LIMBIC-CEREBELLAR-RETICULAR NETWORK IN TINNITUS AND HYPERACUSIS

Y-C. Chen^a, X. Lib, L. Liub, J. Wang^{b,c}, M. Yanga, Y. Jiaoa, F-C. Zanga, K. Radziwond, GD.

*Chend, W. Sund, V. P. K. Muthaiahd, *G.-J. Tenga *R. Salvid,*

^aDepartment of Radiology, Southeast University, Nanjing, China;

^bDepartment of Physiology, Southeast University, Nanjing, China

^cSchool of Human Communication Disorders, Dalhousie University, Halifax, Canada

^dCenter for Hearing and Deafness, University at Buffalo, Buffalo, NY, USA

Objective: Cochlear hearing loss, induced by overexposure to ototoxic drugs or noise exposure, is a potent initiator of tinnitus and hyperacusis, auditory perceptual disorders that are often accompanied by affective, cognitive or attentional issues. Because of the complex multifactorial aspects of these disturbances, a complete map of the neural structures involved in these debilitating disorders is lacking. Therefore, our primary objective was to obtain a comprehensive map of the neural structures involved in the tinnitus-hyperacusis network and to identify regions of hyperactivity and strong functional coupling between the auditory pathway and other brain regions involved in emotion, arousal and attention.

Methods: To test this hypothesis rats were treated with a high-dose of sodium salicylate, an ototoxic drug that induces a temporary cochlear hearing loss. Behavioral measurements were conducted in two groups of rats to document tinnitus and hyperacusis. Electrophysiological measurements were conducted with a second group of rats to characterize the functional deficits in the cochlea and hyperactivity in the central nervous system. Functional magnetic resonance imaging (fMRI) studies were conducted with a third group of rats to identify regions of hyperactivity throughout the brain and identify changes in functional connectivity.

Results: Salicylate induced ~20 dB of hearing loss, produced behavioral evidence of tinnitus on a 2AFC behavioral paradigm, enhanced the amplitude of the acoustic startle reflex and

generated clear evidence of hyperacusis on a reaction time paradigm. Salicylate reduced sound-evoked neural responses from the cochlea, but paradoxically enhanced sound-evoked activity in the inferior colliculus, medial geniculate body, auditory cortex, amygdala, hippocampus and cerebellum. fMRI revealed significant increases in the amplitude of low-frequency fluctuations (ALFF) of the blood oxygen level-dependent response in the same regions where electrophysiological activity was enhanced. Functional connectivity analysis with seeds placed in the auditory cortex, thalamus and inferior colliculus revealed strong coupling within an auditory network comprised of auditory cortex, medial geniculate body, inferior colliculus plus strong functional connectivity between 4 major branches linking the cerebellum, amygdala, reticular formation and hippocampus to the auditory cortex.

Conclusion: Salicylate has long been known to induce tinnitus, but our behavioral reaction time paradigm indicates that it also induces hyperacusis, a novel and important finding. In addition to inducing a cochlear hearing loss, salicylate depressed the neural output of the cochlea, but paradoxically enhanced neural activity at selected sites in the central auditory pathway, cerebellum, reticular formation and amygdala. Activity within this tinnitus-hyperacusis complex is characterized by increased functional coupling within a network linking the central auditory pathway and regions outside the classical auditory pathways involved in arousal, emotional, memory, attention and motor planning. Tinnitus and hyperacusis clearly involve brain regions beyond the classical auditory pathway which may explain multidimensional features of these disturbing auditory percepts.

FEATURED SPEAKER

PLASTICITY OF AUDITORY_SOMATOSENSORY INTEGRATION IN TINNITUS

S.E. Shore

Kresge Hearing Research Institute, University of Michigan, Ann Arbor, MI

Robust functional connections from peripheral and brainstem somatosensory neurons to the cochlear nucleus (CN) provide a substrate for auditory-somatosensory integration. Our studies have shown that combining auditory with somatosensory stimulation can result in long term suppression or enhancement (“bimodal plasticity”) in principal neurons of the dorsal CN (DCN). Recently, we demonstrated that this bimodal plasticity is stimulus-timing dependent, with Hebbian and anti-Hebbian timing rules that reflect *in vitro* spike-timing dependent plasticity (Koehler and Shore, PLOS ONE, 2013). Subsequently, we assessed the stimulus-timing dependence of bimodal plasticity in a noise-damage tinnitus model. Guinea pigs were exposed to narrowband noise that produced a temporary threshold shifts and tinnitus. Following noise-exposure and tinnitus induction, stimulus-timing dependent plasticity was measured after pairing somatosensory and auditory stimulation with varying intervals and orders. In comparison with sham and noise-exposed animals that did not develop tinnitus, timing rules from DCN units in animals with tinnitus were more likely to be anti-Hebbian and broader for those bimodal intervals in which the neural activity showed enhancement, but narrower

for bimodal intervals causing suppression. The broadening of the timing rules in the enhancement phase in animals with tinnitus, and in the suppressive phase in exposed animals without tinnitus was in contrast to narrow, Hebbian-like timing rules in sham animals (Koehler and Shore, *J. Neuroscience*, 2013). Furthermore, these timing rules are altered by neuromodulators that target NMDA (Stefanescu and Shore, *ARO*, 2014) and cholinergic receptors (Stefanescu and Shore, *ARO*, 2015).

**PODIUM SESSION 4
TUESDAY, JUNE 9, 2015**

**TRANSDERMAL-INDUCED STIMULUS-TIMING DEPENDENT PLASTICITY IN
DORSAL COCHLEAR NUCLEUS IS ALTERED WITH NOISE DAMAGE AND TINNITUS.**

*D.T. Martel, C. Wu, S.E. Shore
Kresge Hearing Research Institute
1150 W. Medical Center Drive
Ann Arbor, MI, 48109*

Aims/Objectives: Nearly eighty percent of tinnitus patients can modulate their tinnitus with somatic maneuvers of the face and/or neck. This process is likely mediated by somatosensory connections to the cochlear nucleus (CN). The dorsal CN (DCN) integrates auditory inputs with somatosensory inputs from trigeminal and dorsal column systems. Fusiform cells of the DCN exhibit stimulus-timing dependent plasticity (STDP) in response to bimodal auditory-somatosensory stimulation: Hebbian-like plasticity occurs when neurons increase their activity in response to somatosensory- preceding auditory stimulation, but anti-Hebbian plasticity occurs when auditory- precedes somatosensory stimulation [1]. In tinnitus animals, Hebbian-like rules invert to anti-Hebbian rules. Inverted STDP, along with elevated spontaneous rates, thus provide neural correlates of tinnitus [2]. In the present study, bimodal stimulus-timing protocols used auditory and transdermal somatosensory stimulation in normal and noise-damaged animals with and without tinnitus to evaluate long-term alterations in DCN firing activity as a potential treatment for tinnitus.

Methods: Guinea pigs were either noise damaged with a 7 kHz-centered, half-octave noise band at 97 dB SPL for 2 hours to induce tinnitus, or served as normal controls. Gap detection was used to assess tinnitus. Transdermal electrodes were placed on the skin overlying the trigeminal ganglion or the C2 cervical vertebrae. Reference electrodes were placed on the nasal bridge or vertebrae. Two multichannel recording shanks were stereotaxically placed into the DCN fusiform cell layer. Somatosensory stimulation was achieved with current levels that did not evoke muscle contractions. Bimodal stimulus intervals of ± 20 ms, ± 10 ms, ± 5 ms were used to construct STDP timing rules. Comparisons were made with responses to unimodal electrical and auditory stimulation.

Results: Tinnitus animals showed elevated spontaneous activity at noise exposure and tinnitus frequencies, consistent with previous studies. Facial stimulation combined with sound produced Hebbian-like learning rules in normal animals, which were inverted in noise damaged and tinnitus animals, as shown previously with deep brain stimulation [2]. Neck stimulation produced anti-Hebbian rules in normal animals, which were inverted in noise damaged and tinnitus animals.

Conclusion: This study demonstrates that long-term alterations of DCN firing rates through STDP can be achieved with non-invasive transdermal stimulation. This regulation of neural activity can be harnessed to treat tinnitus, especially in somatic tinnitus patients.

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TRANSDERMAL-INDUCED STIMULUS-TIMING DEPENDENT PLASTICITY TO TREAT TINNITUS

*Marks, K; Martel, D; Leyzac, K; Shore, SE
Kresge Hearing Research Institute
University of Michigan Medical School*

Background: A majority of tinnitus subjects have the ability to modulate their tinnitus percept by moving or applying pressure to their head or neck area. This phenomenon likely arises in the dorsal cochlear nucleus (DCN), which integrates auditory and somatosensory information. Following deafness, DCN neural responses show increased excitability to somatosensory stimulation. Further, DCN fusiform cells exhibit stimulus-timing dependent plasticity (STDP), wherein the temporal ordering of paired auditory-somatosensory stimuli alters the firing rate of those neurons. Changes in firing rate can be either inhibitory or excitatory, depending on the sign and magnitude of the temporal difference between the bimodal stimuli¹. Furthermore, this change is long term, lasting up to 90 minutes. Animals showing behavioral signs of tinnitus have inverted timing rules compared to normal animals¹. Recently, we have shown that these timing rules can be generated using non-invasive transdermal stimulation, and that tinnitus animals show inverted timing rules compared to normal animals when generated with noninvasive stimulation². This study examined the effectiveness of the non-invasive bimodal stimulation as a tinnitus therapy for human subjects.

Methods: Adult subjects with chronic somatic tinnitus and normal or mild hearing threshold shifts were recruited. Subjects were assessed using extended frequency pure-tone audiometry, a somatosensory modulation checklist, the Tinnitus Functional Index (TFI), and custom tinnitus assessment software. The tinnitus testing software assessed subjects' tinnitus spectra using

likeness ratings and loudness matching. The treatment protocol paired electrical somatosensory and auditory stimulation, with a time interval previously shown to induce depression in animals. Acoustic stimuli matched the individual subject's tinnitus spectrum. Stimulus intensity was set to be 40 dB SPL greater than the peak difference between the matched tinnitus spectrum and the subject audiogram. Transdermal electrode placement was determined by somatic movements that elicited the greatest change in a subject's tinnitus. Electrical stimulation level was set above the subject's perception threshold but below levels that would induce muscle spasm. Levels for both stimuli were limited to maintain subject comfort. Subjects were treated daily for 20 minutes in a quiet room.

Results: TFI and tinnitus spectrum matching were used to evaluate the effectiveness of the bimodal treatment. Outcome measures were assessed at the start, mid-point and end of the treatment period. Patients demonstrated decreases in the perceived loudness of their tinnitus after several days of treatment, along with a redistribution of the tinnitus spectrum away from a hearing loss edge.

Conclusions: These results suggest that somatosensory pathways into the auditory system can be manipulated into altering tinnitus perception, providing an effective therapy for patients with chronic somatic tinnitus.

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SYNAPTIC REORGANIZATION IN INTRINSIC MICROCIRCUITS OF THE INFERIOR COLLICULUS IN NOISE-INDUCED TINNITUS

Sturm JJ, Roos H, Kandler K.

Department of Otolaryngology

University of Pittsburgh School of Medicine

3501 Fifth Avenue Room, Pittsburgh, PA 15261

Aims/Objectives: A hallmark of noise-induced tinnitus in humans and animal models is hyper-excitability of the Inferior Colliculus (IC), the major subcortical auditory integration center. This hyper-excitability involves increases in spontaneous and sound-evoked activity in the IC, as well as a decrease in the expression of markers for inhibitory synaptic transmission¹. However, the precise circuit mechanisms underlying this hyper-excitability are still debated. Because intra-collicular (intrinsic) circuits form the majority of synapses on IC neurons, we investigated

whether the increased excitability of the IC may be caused by the reorganization of intrinsic IC circuits.

Methods: We mapped the spatial organization and strength of intrinsic synaptic inputs with laser-scanning photostimulation (LSPS) of caged glutamate in IC brain slices from control mice and noise-exposed mice with and without behavioral evidence of tinnitus, as assessed by the gap detection method using the acoustic startle response². Whole cell recordings in brain slices were targeted to excitatory or inhibitory neurons expressing the fluorescent protein dtTomato under the vesicular glutamate transporter 2 (vglut2+) or the vesicular GABA transporter (vgat+) promoters, respectively.

Results: One week after unilateral noise-exposure, about 50% of noise-exposed mice (19/37 animals) showed behavioral evidence of tinnitus. We found that despite showing similar degrees of hearing impairment (10-20 dB), mice with and without behavioral evidence of tinnitus exhibited distinct patterns of synaptic reorganization, which increased the excitation:inhibition balance of IC circuitry in tinnitus mice, but not in non-tinnitus mice.

Conclusion: In the IC, noise trauma leads to a complex yet cell-type specific reorganization of excitatory and inhibitory local circuits, the nature and magnitude of which correlate with the presence or absence of behavioral evidence of tinnitus.

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THE EFFECTS OF CANNABINOID DRUGS ON ACOUSTIC TRAUMA-INDUCED TINNITUS IN RATS

Zheng Y., Reid P., Smith P.F

Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago Medical School, and the Brain Health Research Centre, University of Otago, Dunedin, New Zealand

Background: Chronic tinnitus is experienced by about 10% of the population and produces many detrimental effects on the quality of life. There are very limited drug treatment options, mainly due to a lack of understanding of the underlying mechanisms. It has been suggested that tinnitus is generated by neuronal hyperactivity in multiple areas of the brain. Given the anti-epileptic properties of cannabinoid drugs, they could be a new class of drug for tinnitus treatment. However, the use of cannabinoids as a form of treatment for tinnitus is

controversial. In the present study, we tested whether a combination of delta-9-tetrahydrocannabinol (delta-9-THC) and cannabidiol (CBD), delivered in a 1:1 ratio, could affect tinnitus perception in a rat model of acoustic trauma-induced tinnitus.

Materials and Methods: Male Wistar rats were divided into 4 groups: 1) sham (i.e. no acoustic trauma) with vehicle treatment; 2) sham with drug treatment (i.e. delta-9-THC + CBD); 3) acoustic trauma-exposed exhibiting tinnitus, with drug treatment; and 4) acoustic trauma-exposed exhibiting no tinnitus, with drug treatment. The acoustic trauma consisted of a 16 kHz, 115 dB pure tone delivered unilaterally for 1 h under anaesthesia and the animals were tested behaviourally for psychophysiological evidence of tinnitus using a conditioned lick suppression paradigm at 1 month post-exposure. Following the confirmation of tinnitus, the animals received either the vehicle or the cannabinoid drugs (1.5 mg/kg delta-9-THC + 1.5 mg/kg CBD, s.c) every day, 30 min before the tinnitus behavioural testing. Tinnitus perception was evaluated during the drug treatment period and re-evaluated again following a 2-week drug washout period.

Results: Acoustic trauma caused a significant immediate increase in the auditory brainstem response (ABR) thresholds in the exposed animals, which partially recovered over 6 months. Not every rat developed tinnitus following acoustic trams. Among those that did exhibit tinnitus, some of the animals had tinnitus at multiple frequencies while others had it only at a single frequency. The cannabinoids significantly increased the number of tinnitus animals in the exposed-no tinnitus group, but not in the sham group.

Conclusion: The results suggest that cannabinoids may promote the development of tinnitus, especially when there is pre-existing hearing damage.

EFFECT OF NUCLEUS ACCUMBENS STIMULATION ON MEDIAL GENICULATE NUCLEUS NEURONS

*Barry KM, Robertson D, Paolini AG, Mulders WHAM
The Auditory Laboratory
School of Anatomy, Physiology and Human Biology,
University of Western Australia,
35 Stirling Hwy,
Crawley, Western Australia*

Aims/Objectives: The neural circuitry between limbic and auditory brain regions has been proposed to distinguish between salient and abnormal neural activity at the level of the medial geniculate nucleus (MGN) of the thalamus (Rauschecker, Leaver, & Mühlau, 2010). In tinnitus, a failure of this circuitry may result in abnormal neural activity being brought to conscious perception. Interestingly, in humans with tinnitus, structural changes and abnormal activity have been found in limbic structures such as the nucleus accumbens (NAc) (Mühlau et al.,

2006). However, at present, no studies have been conducted on the influence of NAc on MGN neural activity. We investigated the functional connectivity between NAc and MGN using electrical stimulation of NAc while recording single neuron activity in MGN.

Methods: Anesthetized Wistar rats (n=14) were placed in a dual manipulator stereotaxic apparatus. A bipolar stimulation electrode was positioned in NAc while a recording electrode was placed in MGN. When a single neuron was isolated its spontaneous firing rate and response to sound were recorded. Then the effects of single shocks (0.5 ms pulse duration; range of 0-1mA) to NAc on action potential firing rates in silence were recorded. At the end of the experiment, animals were fixed with 4% paraformaldehyde using cardiac perfusion and brains collected to investigate anatomical location of stimulating and recording electrodes. Results: Histological analysis verified correct positioning of stimulating and recording electrodes. Of the 41 MGN neurons collected, 16 (36%) did not show any changes in firing pattern with stimulation of NAc. 25 of the 41 MGN neurons (64%) did show changes in firing pattern after electrical stimulation. The latency of effects was >20 ms after electrical stimulation and the types of effects seen were varied. 8 neurons (32%) that responded to electrical stimulation exhibited excitation. The remaining 17 (58%) neurons showed some pattern of inhibition of firing rate. 9 of these 17 neurons (58%) showed only signs of inhibition whereas the other 8 neurons also showed a rebound or excitatory effect after the inhibition.

Conclusion: This data supports a modulatory role of NAc on MGN neurons. The latency of effects seen suggests this role occurs via a poly-synaptic pathway. Inhibitory effects observed agree with the proposed action of NAc on MGN via the thalamic reticular nucleus (TRN) (Rauschecker et al., 2010). In tinnitus, this circuitry may be dysfunctional and NAc may no longer activate TRN and hence allow abnormal MGN activity to be translated into tinnitus.

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FEATURED SPEAKER

TINNITUS PATHOLOGY AND AUDITORY THALAMUS: EXPECT THE UNEXPECTED

D.M. Caspary, B. Kalappa, L.L. Ling, J.G. Turner, T.J. Brozoski, E. Sametskiy
Departments of Pharmacology and Surgery, Southern Illinois University School of
Medicine, USA

Aims/Objectives: Two competing hypotheses exist regarding a putative role for GABAergic inhibition in the pathogenesis of tinnitus at the level of auditory thalamus (medial geniculate body or MGB). Both hypotheses suggest tinnitus-related changes in thalamocortical output. 1)

A down-regulation of inhibitory neurotransmission has been consistently presented as underpinning the hyperactivity seen in animal models of tinnitus. Tinnitus-related reductions of markers for normal adult glycinergic and GABAergic inhibition have been associated with increased spontaneous and abnormal neuronal hyperactivity in dorsal cochlear nucleus, inferior colliculus and auditory cortex. 2) A competing hypothesis suggests that thalamocortical dysrhythmia (see ref. #1 for review) predicts that tinnitus pathology would show increased tonic inhibition for a subset of thalamocortical neurons resulting in abnormal bursting of thalamocortical projection neurons. In MGB, increased tonic inhibition is postulated to activate t-type Ca^{++} channels switching certain thalamocortical neurons to burst mode or altering burst metrics. Recent studies in sound-exposed rats with behavioral evidence of tinnitus and studies in tinnitus patients (1) lend support to the thalamocortical dysthymia hypothesis of tinnitus pathology.

Methods: *In vitro* and *in vivo* studies used a Long-Evans rat sound-exposure model of tinnitus (as in 2). Single unit recordings from awake rat MGB used advancable tetrode microwire assemblies and acoustic stimulation as described in (2). *In vitro* slice recordings followed standard patch-clamp protocols and were designed to examine gaboxadol evoked tonic currents in voltage clamp recordings while recording burst properties in current clamp mode, all two months following sound exposure (3).

Results: Single-unit recordings from the MGB of animals showed enhanced spontaneous firing, increased spontaneous and acoustically driven burst frequency which were positively correlated with the animals' behavioral tinnitus score. *In vitro* studies recorded extrasynaptic GABAAR currents from thalamic neurons contralateral to the sound exposure in adult-control and sound-exposed rats. Two months following the sound-exposure, gaboxadol-evoked tonic GABAAR currents showed significant tinnitus-related increases contralateral to the sound exposure. GABAAR subunit message levels for subunits thought to mediate tonic currents in MGB neurons were increased contralateral to the sound exposure. In response to suprathreshold injected current steps, MGB neurons showed significant, tinnitus-related increases in the number of spikes per burst in MGB neurons. No tinnitus-related changes in postsynaptic inhibitory GABAAR currents were observed.

Conclusions: Collective, we found little evidence in support of a tinnitus-related down-regulation of GABAergic inhibitory neurotransmission in the MGB. This was in stark contrast to what is seen in response to age-related deafferentation in MGB neurons. Consistent with recent studies showing tinnitus patients having increased power in delta and gamma band thalamocortical oscillations, we found tinnitus-related increases in tonic extrasynaptic GABAAR current which likely activate t-type Ca^{++} channels resulting in an increase in thalamocortical burst mode metrics. Both *in vivo* and *in vitro* findings support the thalamocortical dysrhythmia hypothesis reflecting increased thalamic inhibition underpinning tinnitus pathology in MGB.

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FEATURED SPEAKER

Workshop: Somatosensory tinnitus – practical tips for diagnosis and therapy

T. Sanchez (MD, PhD, São Paulo, Brazil)

Eberhard Biesinger (MD, Traustein, Germany)

There is a worldwide tendency of dividing tinnitus patients into different subgroups in order to better understand similar findings and easier define treatment strategies. Interesting characteristics of patients with somatosensory tinnitus have become more evident to be recognized and treated accordingly. This subgroup represents the individuals who can immediately modulate the loudness or pitch of their tinnitus through head/neck/jaw movements or pressure over the jaw or muscles, mainly - but not exclusively - the ones around the ear.

The aim of the workshop is to give enough clues to the audience about the main diagnostic tools that facilitate the identification of such specific patients with somatosensory influence. Once these patients are properly diagnosed, professionals can apply more specific - and often successful - therapies which are focused on the somatosensory influence.

The authors interact very well and will discuss well-defined and practical therapeutic approaches to ease your patient's management.

WEDNESDAY, JUNE 10, 2015

FEATURED SPEAKER

GAP MEASUREMENT OF TINNITUS: PROGRESS AND PITFALLS

Turner, J.

Southern Illinois University School of Medicine, Springfield, IL USA

Illinois College, Jacksonville, IL USA

OtoScience Labs, Jacksonville, IL USA

The startle reflex and its many adaptations have become valuable tools for a range of applications from mouse to human. The reflex and its habituation are routinely used in pharmaceutical development to assess adverse sensorimotor effects in preclinical toxicology testing. Startle can be elevated through anxiety or fear conditioning, making it useful for screening drugs or investigating the neural mechanisms of those conditions. Additionally, sensory cues presented before the startle stimulus (optimally 50-150 ms), have the ability to reduce, or inhibit the reflex. This feature, generally referred to as prepulse inhibition (PPI), has been used to assess sensory gating/filtering in hundreds of studies exploring schizophrenia and related conditions. PPI can also be used to determine auditory thresholds by systematically varying the frequency and intensity of the prepulse stimuli, allowing hearing thresholds to be

determined efficiently without anesthesia. A variation of the PPI test is to use a silent cue as an inhibitory prepulse in an otherwise continuous background carrier. If the subject is capable of hearing/processing the silent gap, the reflex will be inhibited as in PPI. This test has been used to determine gap detection thresholds but also in the study of tinnitus. This test, when applied to tinnitus, has been referred to as the Gap Test, GIS (gap inhibition of startle), or GPIAS test (gap prepulse inhibition of acoustic startle.) The hypothesis is that tinnitus is a disorder that specifically disrupts one's ability to hear silence, therefore processing of silent gap cues should be abnormal in animal models or humans with tinnitus. This presentation will review the data using the gap technique for measuring tinnitus across a wide range of species from mice to humans, specifically focusing on the challenges in using this technique and some of the questions that remain. While many studies have been published documenting gap deficits in animal and human tinnitus, whether these gap deficits are due to tinnitus, the hearing loss used to induce the tinnitus, or some related sensory gating or temporal or spectral processing dysfunction will be discussed.

Grant support provided by the Tinnitus Research Consortium to Southern Illinois University School of Medicine and by a Neurosensory Research Award from the US Department of Defense Psychological Health and Traumatic Brain Injury Program to OtoScience Labs.

FEATURED SPEAKER

An animal model of tinnitus that includes hyperacusis: how to differentiate them in the gap detection test

Kaltenbach, J., Salloum, R.

Department of Neurosciences, Cleveland Clinic, Lerner Research Institute

Tinnitus and hyperacusis represent different manifestations of an increase in gain of the auditory system, one affecting auditory signaling in silence, the other affecting the response to sound. It has been hypothesized that these two disorders may be manifestations of the same mechanism(s), which may include a reduction of synaptic inhibition, an increase in synaptic excitation, and/or non-synaptic changes in the biophysical properties of neurons that cause increases in their levels of excitability. Several behavioral animal models have been developed that provide opportunities to explore and elucidate those mechanisms. However, because these two disorders often occur together, their effects on behavioral measures needed to infer their presence in animals can be complicated, and isolating these effects and teasing apart their mechanisms can be quite challenging. This issue has major importance in studies employing behavioral measures, such as the gap detection method, on which inferences of tinnitus and hyperacusis induction commonly hinge. In this method, tinnitus is typically inferred when there is a weakening of the animal's ability to detect a brief gap of silence in a continuous background noise preceding the startle stimulus. This weakening is apparent as a decrease in the gap's suppressive effects on the acoustic startle response. However, recent studies have shown that the amplitude of the startle response can also be strongly influenced by hyperacusis-like

enhancements of the acoustic startle response itself, the degree of prepulse inhibition, or the suppressive effects of background noise on the startle response. This presentation will discuss how the concurrence of tinnitus and hyperacusis can be recognized, how their concurrence can affect measures of gap suppression of the acoustic startle response, and how such effects can be disentangled to permit meaningful measures of tinnitus without the confounding effects of hyperacusis and vice versa.

FEATURED SPEAKER

NOVEL THERAPIES FOR THE AUDITORY PERIPHERY IN DEAF EARS

Y Raphael

Kresge Hearing Research Institute, Department of Otolaryngology - Head and Neck Surgery, The University of Michigan, Ann Arbor, MI 48109-5648, USA

Objectives: Novel therapies are being developed for repair and regeneration of the cochlear epithelium and the auditory nerve in deaf ears. The objective of one set of experiments was to assess the influence of neurotrophin gene therapy on auditory neurons in deaf ears. The goal of the other experiments was to test methods for integrating exogenous cells in the mature deaf cochlea, in preparation for stem cell implantation.

Methods: Neurotrophin experiments were performed on guinea pigs deafened with an ototoxic lesion and on mice with a deafness mutation modeling human hereditary hearing loss. Adult guinea pigs were deafened by neomycin or kanamycin and furosemide. Adenoassociated viral vectors (AAV) with *BDNF* or *NTF3* gene insert were injected into the perilymph one week later. In cochleae that were obtained three months later, the extent and pattern of nerve sprouting was assessed, along with spiral ganglion nerve survival. Similar experiments were performed using a mouse model for a connexin 26 (*Cx26*) mutation, in which *cre-Sox10* drives excision of the *Cx26* gene from supporting cells of the auditory epithelium. In this model the peripheral fibers of the auditory nerve die back followed by death of the neurons. In the third set of experiments, we tested whether deaf cochleae can be “conditioned” to “accept” implanted exogenous cells and promote their survival and integration. To condition the cochlea, we used guinea pigs deafened with neomycin and performed procedures aimed at transiently lowering potassium levels in endolymph and opening the apical junctions in the auditory epithelium.

Results: Gene therapy with either BDNF or NT-3 leads to peripheral auditory nerve fiber regrowth, and treatment with BDNF leads to enhanced SGN survival. Counterintuitively, the presence of supporting cells may inhibit fiber sprouting into the basilar membrane area. Cessation of neurotrophin support weeks after the loss of hair cells does not appear to have detrimental effects of neuronal survival. In *Gjb2-CKO* mice injected with *Ad.BDNF* at 1 month of age spiral ganglion neurons in the basal cochlear turn are rescued. Exogenous cells injected into scala media survive in the conditioned cochleae for at least 7 days, but in un-conditioned (control) cochleae they degenerate promptly.

Conclusions and future applicability: We show that the cochlea can be manipulated to enhance nerve survival and sprouting and to accept and maintain exogenous cells. This can be accomplished in ears both environmentally and genetically caused cochlear pathologies. Changing or enhancing firing of auditory nerve by sprouting towards a cochlear implant, or by implanting stem cells that can become new hair cells, may change properties of connectivity in the cochlear nucleus thereby influencing tinnitus.

Support: The R. Jamison and Betty Williams Professorship, and NIH/NIDCD grants DC-010412, DC-007634, T32 DC-005356, and P30 DC-05188.

PODIUM SESSION 5 WEDNESDAY, JUNE 10, 2015

IDENTIFICATION OF BIOMARKERS IN A MODEL OF NOISE INDUCED TINNITUS: A LONGITUDINAL STUDY

*Holt A^{1,2}, Ghoddoussi F¹, Muca A¹, Apawu A¹, Hali M1, Wilson S¹, Berkowitz B¹
Wayne State University School of Medicine, 1 and John D Dingell VAMC2 Detroit, MI*

Background/Aims: Tinnitus, “ringing in the ears”, is the number one service related disability for veterans. Currently, no objective biomarkers for tinnitus exist and diagnosis is heavily dependent upon patient self-reporting. We have previously demonstrated that both noise- and drug-induced tinnitus result in deficits in GAP inhibition of the acoustic startle reflex (GiASR) 48 hours following tinnitus generation. In addition, these same tinnitus models result in increased spontaneous neuronal activity (SNA) in the inferior colliculus (IC), a brain region that is key for the integration of auditory signals. Manganese-enhanced MRI (MEMRI) uses the paramagnetic manganese (Mn²⁺) ion, a contrast agent and calcium analog, to determine calcium ion regulation and thus neuronal activity. In this longitudinal study of a noise induced tinnitus model, we test hearing (auditory brainstem responses - ABR), tinnitus (GiASR), and SNA (MEMRI) to determine how changes develop over time.

Methods: After baseline images were collected, neuronal activity was assessed in 12 regions of interest (ROIs) using MEMRI (n = 10/group), 24 hours, 4, and 12 weeks following acoustic trauma (16 kHz, 106 dB SPL, 1 hour) in male Sprague Dawley rats. Each animal was administered 66 mg/kg of MnCl₂ 24 hours prior to imaging (Bruker 7T scanner). Following a single dose of MnCl₂, (n = 4) Mn²⁺ clearance from ROIs was measured after 24 hours, 2, 4, 6 and 12 weeks. *In vivo* and *ex vivo* images (hourly for up to 12 hours) were obtained in the same animal (n = 4). Both T1-weighted and T1-mapping images were compared for each ROI. For the

duration of the study, GAP detection testing was conducted twice per week, across six frequencies (4, 8, 12, 16, 20 and 24 kHz).

Results: Our data suggest that subdivisions of the IC have differential rates of Mn²⁺ clearance, with the dorsal cortex of the IC clearing most quickly. Manganese levels appear to diminish within the first two hours after euthanasia. In addition, all animals were able to perform during GiASR testing, before and after noise exposure. Deficits in GAP detection were evident at specific frequencies. Even after repeated administration, differential manganese uptake was observed depending upon ROIs. Three months following noise exposure the IC exhibits significant increases in Mn²⁺ uptake. We plan to correlate GiASR with Mn²⁺ uptake at each time point.

Conclusions: Gap detection and MEMRI testing may serve as exciting new tools with translational applicability for both the diagnosis of tinnitus and identification of effective therapeutic agents.

Gap-prepulse inhibition of the startle reflex (GPIAS) for tinnitus assessment: current status and future directions

Alexander Galazyuk¹ & Sylvie Hébert²

1- Department of Anatomy & Neurobiology, Northeast Ohio Medical University, Rootstown, OH, USA.

2- School of speech pathology and audiology, Faculty of medicine, Université de Montréal, and International

*laboratory for research on Brain, Music, and Sound (BRAMS),
C.P.6128, succursale Centre-Ville, Montréal, Qc, CANADA, H3C 3J7*

The progress in the field of tinnitus largely depends on the development of a reliable tinnitus animal model. Recently a new method based on the acoustic startle reflex modification was introduced for tinnitus screening in laboratory animals. This method was enthusiastically adopted and now widely used by many scientists in the field due to its seeming simplicity and a number of advantages over the other methods of tinnitus assessment. Furthermore, this method opened an opportunity for tinnitus assessment in humans as well. Unfortunately multiple modifications of data collection and interpretation implemented in different labs make comparisons across studies very difficult. In addition, recent animal and human studies have challenged the original “filling-in” interpretation of the paradigm. Here we review the current literature to emphasize on the commonalities and differences in data collection and interpretation across laboratories that are using this method for tinnitus assessment. We also propose future research directions that could be taken in order to establish whether or not this method is warranted as an indicator of the presence of tinnitus.

Bimodal Stimulus Timing Dependent Plasticity in Primary Auditory Cortex is Altered After Noise-Induced Tinnitus

Gregory J. Basura¹, Seth D. Koehler², and Susan E. Shore^{1,3}

- 1) Department of Otolaryngology/Head and Neck Surgery; Kresge Hearing Research Inst. The University of Michigan; 1100 W Medical Center Drive; Ann Arbor, MI 48109*
- 2) Department of Biomedical Engineering, The University of Michigan; 1107 Carl A. Gerstacker Building; 2200 Bonisteel Blvd. Ann Arbor, MI USA 48109*
- 3) Molecular and Integrative Physiology, The University of Michigan, 1100 W Medical Center Drive; Ann Arbor, MI 48109*

Central auditory circuits are influenced by the somatosensory system, a relationship that may underlie tinnitus generation. In the guinea pig dorsal cochlear nucleus (DCN), pairing spinal trigeminal nucleus (Sp5) stimulation with tones at specific intervals and orders facilitated or suppressed subsequent tone-evoked neural responses, reflecting spike-timing-dependent plasticity (STDP). Furthermore, after noise-induced tinnitus, bimodal responses in DCN were shifted from Hebbian to anti-Hebbian timing rules with broadened temporal windows, suggesting a role for bimodal plasticity in tinnitus. Here, we aimed to determine if STDP principles like those in DCN also exist in primary auditory cortex (A1), and whether they change following noise-induced tinnitus. Tone-evoked and spontaneous neural responses were recorded 15 minutes after bimodal stimulation with random stimulus order and pairing intervals (0- 20ms). Firing rates were influenced by the interval and order of the bimodal stimuli. Noise-exposure shifted Hebbian to anti-Hebbian timing rules in noise-damaged animals. Those with tinnitus had increased spontaneous firing rates and significant increases in anti-Hebbian and enhancing timing rules, with broadened temporal windows. These findings suggest that bimodal plasticity in A1, in part, may be a conserved process following noise damage and may have implications for tinnitus generation as well as therapeutic intervention across the central auditory circuit.

AN OPTIMIZED CONDITIONED LICKING SUPPRESSION PARADIGM FOR ASSESSING BEHAVIORAL EVIDENCE OF TINNITUS

*Pace E(a), Bobian M(a), Panekkad A(b), Zhang X(a), Zhang H(c), and Zhang J(a)(d)**

- (a) Department of Otolaryngology-Head and Neck Surgery, Wayne State University School of Medicine, 4201 Saint Antoine, Detroit, Michigan 48201*
- (b) Department of Electrical Engineering, Wayne State College of Engineering, 5050 Anthony Wayne Drive, Detroit, Michigan 48202*
- (c) Department of Biological Sciences, University of Windsor, 401 Sunset Avenue, Windsor, Ontario, Canada N9B 3P4*
- (d) Department of Communication Sciences & Disorders, Wayne State University College of Liberal Arts & Sciences, 60 Farnsworth St., Detroit, Michigan 48202*

** Corresponding author*

Aims/Objectives: We sought to enhance behavioral testing for tinnitus by developing an optimized conditioned licking suppression paradigm. Our paradigm was devised to reliably track tinnitus manifestation and frequencies in individual rats without prolonged training periods.

Methods: Rats were water-deprived and allowed to receive water during daily 30-min testing sessions. They learned to access water by licking a spout during sound trials (6-8, 10-12, 14-16, 22-24, or 30-32 kHz, or BBN), but were punished with a mild electrical shock (0.25-0.75 mA) if they licked during silent trials. Suppression of silent trial licking to criterion levels was achieved within two to three weeks. Upon completion of baseline training, rats were noise exposed (8-16 kHz, 105-110 dB SPL, 2 h) and routinely tested for tinnitus development. Rats without tinnitus were later injected with sodium salicylate (i.p., 350 mg/kg) and tested for tinnitus by 3 hours after injections.

Results: All rats exhibited a significant increase in silent trial licking immediately after noise exposure, suggesting tinnitus. Only certain rats, however, exhibited lasting tinnitus behavior. As expected, licking activity during sound trials remained unchanged following noise exposure. ABR hearing threshold shifts were transient and demonstrated no significant differences between the tinnitus positive and negative groups. This suggests that our behavioral data reflected tinnitus perception as opposed to hearing loss or activity level changes. Finally, salicylate injections induced transient tinnitus behavior.

Conclusion: Our conditioned licking suppression paradigm provides a robust method for screening tinnitus in rats. The tinnitus behavior exhibited by our rats is comparable to other tests and matches clinical data in that only certain subjects maintained tinnitus following acoustic trauma. This paradigm may be used to reliably screen tinnitus in animals, which plays an important role in mechanistic studies and drug/device development.

SODIUM SALICYLATE ACTIVATES THE GABAB-GIRK PATHWAY TO HYPERPOLARIZE NEURONS OF RAT MEDIAL GENICULATE BODY

Wang, X.-X., Jin, Y., Chen, L.

*Auditory Research Laboratory, School of Life Sciences, University of Science and Technology of
China*

Objective: Our previous study shows that sodium salicylate (NaSal), a tinnitus inducer, can hyperpolarize the membrane potential of neurons in rat medial geniculate body (MGB) (Su *et al*, 2012, PLoS ONE 7, e46969). The purpose of the present study was to investigate the underlying cellular mechanism.

Methods: Whole-cell patch clamp recordings were made from horizontal brain slices containing the MGB of Wistar rats at P15-23. The change in the leak current was measured to represent

that in the resting membrane potential when the mechanism of NaSal-induced hyperpolarization was investigated. The rebound depolarization was recorded for assessing the effects of changes in the resting membrane potential on functional responses of MGB neurons.

Results: NaSal could induce an outward leak current, indicating the drug can hyperpolarize MGB

neurons. The current could be abolished by CGP55845, a GABAB receptor blocker, or by Ba²⁺ and Tertiapin-Q, blockers for G-protein-gated inwardly rectifying potassium (GIRK) channels, indicating that NaSal hyperpolarizes the resting membrane potential by activating the GABAB–GIRK pathway. The NaSal-induced hyperpolarization was shown to depress the rebound depolarization in MGB neurons.

Conclusions: Our study demonstrates that NaSal targets GABAB receptors to hyperpolarize MGB neurons and alter their functional behaviors. The NaSal-induced hyperpolarization is expected to change tonic firing to bursting firing in MGB neurons and serves as explanation for increased bursting firing and increased output of the MGB in NaSal-induced tinnitus. Our findings favor the thalamocortical dysrhythmia hypothesis of tinnitus.

FEATURED SPEAKER

AM-101 AND VAGAL NERVE STIMULATION FOR THE MANAGEMENT OF TINNITUS

Seidman, M

Henry Ford Health System, Detroit Michigan

Tinnitus affects 50 million Americans and 600 million people worldwide. Approximately 2-4% are severely affected. Tinnitus is considered a symptom; not a disease per se, as such a “cure” for a symptom is challenging and finding the root cause would facilitate these efforts. Short of a “cure” we tend to manage symptoms for our patients. There have been a plethora of treatment options ranging from dietary modification (i.e. salt, caffeine, alcohol, sugars, aspartame, NutraSweet, MSG avoidance), to specific supplements such as Ginkgo Biloba and lipoflavonoids, to sound therapies (masking, TRT, neuromonics), to centrally acting medications, cognitive behavioral therapy and electrical and magnetic stimulation of the brain, and the results are varied. Several additional therapies have been introduced and this talk will discuss both the clinical trial of a compound from Auris Medical, AM-101 (a glutamatergic compound) and the use of the Vagal Nerve Stimulator from Microtransponder. The, in progress, results of these two studies will be evaluated.

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2. Seidman MD, Moneysmith M. “Chapter 6: Nutraceuticals and Herbal Supplements”, In: Pharmacology and Ototoxicity for Audiologists. Eds: Campbell KCM, Belmont, M. Thomson Delmar Learning Publishers, Clifton Park, NY. 2005

PODIUM SESSION 6
WEDNESDAY, JUNE 10, 2015

TINNITUS OF MYOFASCIAL ORIGIN

Wijtmans E, Teachey W, Levine R
The Therapy Network, Virginia Beach, VA, USA

AIM/OBJECTIVES: Increase understanding of the importance of identifying and treatment of myofascial trigger points (MTrPs) in the treatment of tinnitus of musculoskeletal origin.

METHODS: Research, 1 literature review, 2 and 10 years clinical practice experience.

RESULTS/DISCUSSION: It is well established that muscles can give referred pain and symptoms to areas outside the muscle itself. In addition, on physical examination the following can be demonstrated: MTrPs, muscle shortening, muscle stiffness, taut bands, and occasionally associated regional autonomic changes. Referred symptoms into the head and neck can include facial pain, sinus pain, ear pain, headaches, dizziness, throat discomfort, hoarseness, lacrimation, perceived hearing loss, ear fullness, itching in the ears, and tinnitus.²

The phenomena and existence of MTrPs is well recognized. They are believed to be responsible for these referred symptoms. In the case of tinnitus, the primary responsible muscles are the sternocleidomastoid and masseter muscles, and to a lesser extent the lateral pterygoid muscle. However, all the muscles of mastication, the upper trapezius, the levator scapulae, and all the cervical musculature are directly and indirectly involved.

Traditional diagnostics, like radiographs, CT, MRI, and bloodwork do not identify or exclude the existence of MTrPs. Recent studies demonstrate that they can be identified by 2D and 3D sonography. However, in the clinical setting examination of the presence of MTrPs in the taut band relies on skilled hands and experience. Treatment of the referred symptom, such as tinnitus, involves deactivation of these MTrPs. This can be accomplished through (sustained) digital pressure, but will be more effectively achieved by injection or dry needling of the MTrP. In addition, the treatment will be much more effective if a so-called “local twitch response” (LTR) is obtained. Shah et al at NIH, demonstrated the vast changes that occur after the LTR in the biochemical milieu of MTrPs, in normalizing levels of the pH, and of neurotransmitters like bradykinins, substance P, TNF- α , norepinephrine, CGRP, IL-1 β , and others.

Overuse and abuse of muscles leads to the development of MTrPs. Common scenarios are a forward head posture, an uneven loading of the muscles during exercise or work related activities, trauma, and persistent muscular contractions from a physical cause (repetitive motions), or an emotional cause (stress response). There may also be exacerbating or perpetuating biochemical factors, like micronutrient deficiencies, which should be excluded.

Unfortunately, despite emerging research and decades of treatments, examination and treatment of MTrPs to combat tinnitus is not yet well studied or recognized.

As part of this oral presentation, I will demonstrate specific examination techniques and show a brief video of the treatment of MTrPs using dry needling.

CONCLUSION: Thorough physical examination for potential MTrPs and their subsequent treatment should be an essential component of the evaluation and management of patients with tinnitus.

1 Teachey WS, Wijnmans EH, Cardarelli F, Levine RA. Tinnitus of myofascial origin. *Int Tinnitus J.* 2012;17(1):70-73

2 Teachey WS. Otolaryngic Myofascial Pain Syndromes *Curr Pain Headache Rep.* 2004 Dec;8(6):457-62.

TREATING TINNITUS BY TREATING HEAD AND NECK MYOFASCIAL DYSFUNCTION

*Levine R, Lerner Y, Wijnmans E, Teachey W
Tel Aviv Medical Center; Old Dominion University - Norfolk, VA*

Background/aims: For more than 15 years it has been recognized that head and neck myofascial dysfunction [HNMD] can cause tinnitus (aka somatic tinnitus). More and more evidence is suggesting that HNMD may be as major a cause of tinnitus as hearing loss. Animal models support this idea, since it has been recently reported that, in animals with “tinnitus” from hearing loss, elevated spontaneous rates occurs only for neurons of the dorsal cochlear nucleus that can be excited by somatosensory stimulation. Consistent with this formulation are the anecdotal reports that tinnitus can be abolished with reduction of HNMD, such as recently shown for cervical facet blocks (1).

Methods: The most effective treatment for HNMD is weekly needling of trigger points. We report our experience with this technique from two centers with two very different tinnitus populations. One center [gENT] is a general ENT practice with more than 10 years of experience using this technique for a variety of ENT disorders, including tinnitus; in many tinnitus is not the chief complaint. The other [ccTinn] is from a clinic where tinnitus is everyone’s chief complaint. Results: From gENT in which about 135 have been treated in the past 4 years about 25% have their tinnitus completely abolished, another 25% have a major but incomplete quieting of their tinnitus, and about 50% are unimproved. The best results are from people whose tinnitus is not their major or severe complaint. The poorest results are from those with tinnitus as their chief

complaint. The more severe the tinnitus, the poorer the result. From ccTINN, which has been treating tinnitus for the last two years, of 43 patients 5% have had complete tinnitus relief, about a third had at least 50% relief, while about half have had no benefit. The poorer results from ccTINN are consistent with gENT's experience that the poorest results are from those whose tinnitus is their chief complaint.

Conclusions: We conclude that (a) the clear benefit of needling of trigger points to about half of tinnitus patients confirms the major role of head and neck myofascial dysfunction in the etiology of tinnitus and (b) the modest but incomplete response of those most troubled by their tinnitus suggests that other factors besides head and neck myofascial dysfunction are in play in these patients. A more comprehensive approach to these patients, such as the addition of other modalities (facet blocks, cognitive behavioral therapy, etc.) to the needling of their trigger points, needs to be assessed.

1. Teachey WS, Wijtman EH, Cardarelli F, Levine RA. Tinnitus of myofascial origin. *Int Tinnitus J*, 2012;17:70-73.

MULTI-SITE CLINICAL DATA FROM A NEW GENERATION OF CUSTOMIZED ACOUSTIC STIMULATION COMBINED WITH COUNSELING

Davis P, Smith S, Moruf S.

Affiliations: Neuromonics, Australia, BayAudio Australia, University of Miami, Miller School of Medicine, USA, Fayetteville VA, USA, Parker Center for Audiology, USA, Colorado Tinnitus and Hearing, USA

BACKGROUND/AIMS: Longitudinal data on current acoustic treatments of tinnitus, using well-established measures, is surprisingly scarce. Data on relative effectiveness, and cost-effectiveness, is even scarcer. Over the last decade, a clinical process (based on principles initially termed the Acoustic Desensitization Protocol), has evolved into a widely used full rehabilitation program with an FDA-cleared medical device that is often dispensed in private practices and military/veterans clinics in the USA and Australia. Previous randomized controlled clinical trials of the first generation have been published in some of the most rigorous medical journals¹. Numerous independent studies have reported equivalent results when the full clinical protocol was adhered to². A further iteration of the top-end device has recently been released, as well as progressively simpler mid-range and lower-end options.

METHODS: The present study reports longitudinal multi-site clinical data on the new mid-range and top-end devices. As the lower-end device does not involve a structured rehabilitation program, follow-up data was not available. Recruitment to each of the two treatment groups was representative of a 'real-life' clinical setting, which typically was by patient self-selection, moderated by adherence to candidacy criteria. In Australia, military patients were only dispensed the top-end system as it is government funded.

RESULTS: Analysis of the subject population indicated that patients using the mid-range device had lower mean pre-therapy tinnitus distress than the top-end device patients. Significant improvements in Tinnitus Reaction Questionnaire (TRQ) scores, as well as Minimum Masking Levels (MML) and Loudness Discomfort Levels (LDL) measures, were found in both device groups. There was no clear distinction between results from either private practice or government-funded patients. Mean changes in TRQs were correlated with the data-logging results, indicating a dose-related outcome that was more than a non-specific treatment effect. Cohen's d Effect Sizes were calculated, and results compared with meta-analysis data presented at the TRI 2013 conference². The latest generation of the treatment displayed broadly similar Effect Sizes. Mean Pre/ post therapy Significant Other Tinnitus Questionnaire composite data changes indicated that the subjects' significant other were also cognizant of a significant improvement in both device classes. A complex interaction with other factors, particularly the extent of hearing loss, was found.

CONCLUSION: Statistically significant, as well as clinically significant reductions in tinnitus distress, were found with both device classes over the six-month treatment period. Despite the cost being around half the price of correspondingly tiered hearing aids, results for the Neuromonics treatment indicated a highly efficient habituation response.

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1. Davis, PB, Paki, B, & Hanley, PJ. The Neuromonics Tinnitus Treatment: Third Clinical Trial. *Ear & Hearing*. 2007;. 28: 242-259.
2. Davis, PB, & Moruf, S. Comparison Of Recent Tinnitus Treatment's Effect Sizes. Research Poster Presented at the Tinnitus Research Initiative Annual Conference, Valencia, Spain, 2013; May 15-18.

VAGUS NERVE STIMULATION (VNS) PAIRED WITH TONES FOR TREATMENT OF TINNITUS

R. Tyler, J. Martin, C. Stocking, J. Martin, A. Deshpande, S. Vanneste, N. Stecker, A. Cacace*

**University of Iowa Hospitals & Clinics, 200 Hawkins Drive, 21167 PFP
Iowa City, Iowa 52242*

Aims / Objectives: This study describes 1) a new implantable device treatment modality for tinnitus. It includes 2) safety and efficacy outcomes of the treatment group compared to control from a blinded, randomized, two-arm study. The main objective of the study is to indicate a signal of effectiveness such that an appropriate outcome measure and sample size estimate can be determined for a pivotal study.

Methods: A 30-patient, randomized study funded by the NIH will complete enrollment in March, and will conclude by May 2015. Subjects between the ages of 22 and 65 years with

moderate to severe tinnitus (Tinnitus Handicap Questionnaire > 40%; Minimum Masking Levels > 7 dB) were enrolled. Previous treatments were unsuccessful. Subjects were implanted with a Vagus Nerve Stimulation (VNS) device, consisting of an implantable pulse generator and lead; the lead is wrapped around the cervical vagus nerve in a surgery performed by an otolaryngologist. Subjects were randomized to receive either VNS paired simultaneously with tones (treatment) or to receive unpaired VNS (control group) for six-weeks. Subjects were stimulated at home for 2.5 hours per day. After the randomized portion, all subjects received paired VNS treatment.

Results: Twenty-five subjects were implanted as of 3/13/2015. Daily device use and stimulation were well tolerated; compliance was very high (all patients met protocol criteria for compliance). One re-implant was required (extra surgery one week after the original surgery) due to a lead failure; the lead failure was analyzed and a corrective action was undertaken to correct the issue and no further instances have occurred. Most subjects felt stimulation as a neck or throat tingling or pressure during treatment. Four subjects had voice hoarseness likely due to surgery; one gradually improved and recovered completely within 12-weeks post-surgery. One improved but still had some paresis at a 12-week laryngoscope. One improved and is scheduled for a 12-week scope. One had mild hoarseness not yet confirmed via scope. One subject was accidentally stimulated for a short period of time (< 5 minutes) at high output current settings, and had pain during stimulation; the device was reset to lower settings and the patient did not experience further issues. Other adverse events were either minor surgical events (like incision pain, swelling, or soreness) or minor stimulation events (such as tingling, hoarseness, or coughing – only during stimulation). No patient discontinued the study due to an event. All of the above events are similar to those reported with the commercially available VNS system for epilepsy. Subjects typically had no significant issues using the device. No subject missed more than 3 consecutive days of device usage; all patients averaged over 5 days/wk of use. All adverse event information and efficacy analyses (with p values) will be reported.

Conclusions: VNS therapy paired with tones is being assessed as a possible new treatment therapy for tinnitus.

MINDFULNESS BASED TINNITUS STRESS REDUCTION (MBTSR) & ACCESSIBILITY THROUGH AN ONLINE COURSE: A NEXT STEP IN THE FIELD

Jennifer J. Gans, PsyD
University of California, San Francisco (UCSF)
VA of Northern California

This presentation explores tinnitus within the framework of brain functioning and current research into mindfulness. The talk is designed to familiarize participants with an 8-week

Mindfulness Based Tinnitus Stress Reduction (MBTSR) program that was developed and researched by the presenter at the University of California, San Francisco (UCSF). A study was conducted and published at UCSF where participants experienced a significant reduction in tinnitus handicap, depression, anxiety, and an increase in general quality of life (Gans et al 2013). The benefits of MBTSR were enduring, with improvements lasting through the end of the 12- month study window (Gans et al 2015).

MBTSR has launched MindfulTinnitusRelief.com – the first web-based program of its kind for learning how to live comfortably with tinnitus. MindfulTinnitusRelief.com has created a high quality, easily accessible online course with the potential to reach millions worldwide who are searching for relief from chronic bothersome tinnitus. The pros and cons of educational online learning for tinnitus management is addressed. Information gathered serves to aid in future planning and understanding of how this new medium can be most effective for its tinnitus users.

FEATURED SPEAKER

Is it time to add time?

- a critical discussion on measuring the temporal dynamics in tinnitus perception and its relevance to clinical research

Schlee, W; Pryss, R; Herrmann, J; Reichert, M; Langguth, B

Tinnitus research in the last decade, together with the medical sciences in general, has seen an enormous development with new and more detailed diagnostic techniques. Structural details of the tinnitus-brain can now be investigated with more detail, even complex aspects of large-scale functional brain networks can be reconstructed, the availability of clinical questionnaires measuring the various aspects of tinnitus have increased and we even started to discover blood parameters and genetic markers that are related to tinnitus. As a response to this, our theoretical models also evolved and became more and more able to explain the interrelations of important aspects like tinnitus loudness, distress, salience and attention. Nevertheless, these models all run into conflicts when it comes to explaining the temporal dynamics of tinnitus perception during the everyday life. Usually, a clinical questionnaire, a neuroimaging scan, a tinnitus matching or a blood test is acquired at a single time-point in the clinic. (In interventional studies at one time-point before and after the intervention.) With this measurement strategy, we assume that the tinnitus perception is static over time. But only a small proportion of tinnitus patients report a static perception of their tinnitus and rather describe a variety of transient changes in tinnitus loudness, frequency, distress or awareness. Can these transient changes all be explained by masking? Probably not. What other reasons can account for the transient fluctuations? How do they interact or may we even sum them up? Is there a regular

pattern? Answers to these questions will not only improve our theoretical models any further, they will also allow more precise measurements of clinical outcomes and enable the development of radically new ways for tinnitus treatment. Goal of this talk will be to present methodological aspects, possibilities and limits for assessing the temporal dynamics of tinnitus perception as well as to discuss theoretical considerations and the possible impact on clinical research.

FEATURED SPEAKER

A look into the future: matching animal experiments with human findings

Eggermont, J

Emeritus Professor

University of Calgary

Calgary, Alberta, Canada

Prediction is difficult, especially about the future. Yet, because research typically advances by new concepts and new techniques, it is fairly safe to project future research along these avenues. The big problem for investigating cause, source and mechanisms of tinnitus is the barely overlapping research approaches in humans and in animal models. Animal models provide mostly data on neural firings, human brains are probed for compound post-synaptic potentials—in the form of brain rhythms—and there is no simple relationship between the two. Animal research into tinnitus largely focuses on the auditory system, whereas most human recordings explore neural connectivity across the entire cortex, with relatively little emphasis on the auditory system.

I suggest that a potentially fruitful and unifying concept to study tinnitus in animals and humans is to consider it as an “auditory object”. There is a vast literature on scene analysis and stream segregation that explores aspects of auditory objects. These studies are done in humans as well as in animals, behaviorally as well as physiologically, and suggest that auditory objects are defined by their spectrotemporal synchrony and being spatially confined. Neural population representations reflect this in their firing synchrony, frequency specificity and binaural sensitivity. In tinnitus, the spatial aspects relate to the ears or “within the head”, and the spectro-temporal synchrony is reflected in spontaneous synchronous burst firing across aberrant neural populations (measurable in animals) and in enhanced power of specific brain rhythms and changed connectivity of brain areas in humans. The latter should be more intensively pursued in animals to strengthen the link between awake animal models and findings in humans.

POSTER SESSION 1
MONDAY June 8, 2015

1- THE EFFECT OF HEARING LOSS ON TINNITUS RELATED NEURONAL ACTIVITY

Muca A¹, Standafer E¹, Ahmad F¹, Apawu A¹, Ghoddoussi F¹, Hali M¹, Berkowitz B¹, Holt A^{1,2}
Wayne State University School of Medicine¹
John D Dingell VAMC², Detroit, MI

Background/Aims: Tinnitus, the perception of sound in the absence of an external stimulus, is the number one compensated military related disability. Studies have found that tinnitus may be linked to increased neuronal activity in brain regions responsible for hearing, following events causing acoustic trauma, such as exposure to loud noise. Our previous studies have demonstrated tinnitus and increased neuronal activity in a model of permanent threshold shift 48 hours after tinnitus onset. Therefore, we hypothesize that persistent tinnitus will also correlate with changes in neuronal activity. We have combined novel and established methodologies to determine the relationship between the persistence of hearing loss, tinnitus and neuronal activity.

Methods: Hearing thresholds were determined in male Sprague Dawley rats (n = 12) randomly divided into three groups: control, temporary threshold shift (TTS), and permanent threshold shift (PTS) using auditory brainstem responses (ABRs). Acoustic Startle Reflex (ASR) testing (pre-pulse and GAP detection), was used to determine hearing sensitivity and tinnitus status across six frequencies (4, 8, 12, 16, 20 and 24 kHz) weekly for eight weeks. Changes in neuronal activity were measured using manganese-enhanced magnetic resonance imaging (MEMRI) two months following noise exposure (10 kHz, 118 dB SPL 1/3 octave band, 4 hours - PTS; 16 kHz, 106 dB SPL, 1 hour - TTS) with MnCl₂ (66 mg/kg) administered 24 hours prior to imaging. One ear was plugged during noise exposure.

Results: After an initial significant elevation in hearing thresholds following noise exposure, hearing thresholds remained elevated in the PTS group, but were resolved in the TTS group when compared to normal hearing controls. Differential patterns of GAP detection were observed in the three groups with enhanced GAP detection one day after the noise exposure with GAP detection deficits during weeks 2-4 for the TTS group and during weeks 5-8 for the PTS group when compared to baseline performance. Two months following noise exposure, animals in the PTS group demonstrated significant decreases in Mn⁺² uptake within the auditory cortex (AC), dorsal cortex of the IC (DCIC), and dorsal cochlear nucleus (DCN) when compared to the control group. The hemisphere contralateral to the exposure often exhibited the greater

change in Mn^{+2} uptake when compared to controls. In the central nucleus of the IC (CIC) the TTS group had more Mn^{+2} uptake in the hemisphere contralateral to the plugged ear while the PTS group had less Mn^{+2} uptake in that same hemisphere. In addition, Mn^{+2} uptake in the CIC was diminished most in high frequency regions.

Conclusions: Neuronal activity was decreased in PTS animals as demonstrated by less Mn^{+2} uptake in the AC, DCIC and DCN. Deficits in GAP detection correlated with changes in Mn^{+2} uptake. Future studies will focus on following changes both in tinnitus status and neuronal activity over time in the same animal. By understanding the relationship between changes in GAP detection and MEMRI we can develop an objective measure of tinnitus.

2- GRAY MATTER DIFFERENCES IN TINNITUS SUFFERERS

M. Thomas, S. Schmidt, J. Carpenter-Thompson, F.T. Husain
Department of Speech and Hearing Science, Program in Neuroscience
University of Illinois at Urbana-Champaign
901 S. Sixth Street
Champaign, IL 61820

AIM: Tinnitus is the perception of sound without an external source or stimulus, which is often described as a high-pitched ringing or buzzing. The aim of this study was to investigate differences in gray matter volume in those with long-term tinnitus compared to those with recent onset, and control groups with matched hearing loss and normal hearing. Our hypothesis was that those with long-standing tinnitus will show greater volumetric changes compared to those with recent onset of tinnitus.

METHODS: There were four groups of participants in this study: those with long-term tinnitus (referred to as LTIN), those with recent tinnitus (RTIN), and for controls those with hearing loss and no tinnitus (HL) and those with normal hearing (NH). The RTIN group had had tinnitus for greater than six months but less than one year, and the LTIN group experienced tinnitus for greater than one year (16.83 ± 15.1). Most participants underwent an audiometric evaluation; those with tinnitus completed in addition the Tinnitus Handicap Inventory, (RTIN: 15.7 ± 10.2 ; LTIN 8.3 ± 6.8). Data were collected in the form of MPRAGE images using a 3T Siemens Magnetom Allegra head-only scanner (TR=2300ms, TE=2.83 ms, flip angle=9°, 160 slices, voxel size = $1.0 \times 1.0 \times 1.2$ mm³). Data were analyzed using voxel-based morphometry (VBM), which was performed after pre-processing in SPM8, a toolbox of Matlab 2012b. After the analysis, VBM data from each group were compared using two-sample *t*-tests to determine group differences. On both modulated and unmodulated data we conducted whole-brain and region

of interest group comparisons. The regions of interest were Brodmann areas 41, 42, and 22, ventral and dorsal cochlear nuclei, superior olivary complex, and the medial geniculate nucleus.

RESULTS: The ROI analysis is ongoing; however, preliminary results from the whole-brain analysis indicate that, in comparison to RTIN, LTIN showed declines in gray matter in the right precentral gyrus at $p > .005$ FWE. Note that the RTIN and LTIN groups, apart from the duration of their tinnitus, differed in terms of their hearing loss profiles.

CONCLUSION: Our preliminary results indicate that gray matter concentration decreases over time in individuals with tinnitus and perhaps with their hearing loss status coupled with tinnitus duration. In our earlier study (Husain, et. al, 2011), we found a decrease in the gray matter between the NH and HL groups, as well as between the HL and TIN groups, indicating the profound effect of hearing loss on gray matter changes. Our current study adds to that and indicates an effect of duration of tinnitus as well.

3- ULTRA-HIGH FIELD FMRI OF (SUB)CORTICAL AUDITORY STRUCTURES IN PATIENTS WITH TINNITUS.

George E¹, Arts R¹, De Martino F², Gülban Ö², Smit J¹, Van Zwieten G¹, Formisano E², Stokroos R¹.

1Department of ENT/Head and Neck Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands, 2Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands

Objectives: One of the plausible underlying mechanisms of tinnitus is tonotopic reorganization. Although some animal studies prove tonotopic reorganization as a result of auditory deafferentation, objective evidence in human is lacking. This is probably due to the resolution of the used Magnetic Resonance Imaging (MRI). The goal of the study is to investigate cortical and subcortical auditory structures using ultra-high field MRI.

Methods: This observational study includes seven patients with unilateral tinnitus and seven healthy controls, precision-matched for gender, age, handedness and audiometric hearing loss. The subjects were scanned with the ultra-high field MRI (7 Tesla) scanner. None of the scanned subjects had detected dead regions using the threshold-equalizing noise test. This study allows to map and characterize anatomically and functionally cortical and subcortical structures of the auditory pathway (primary auditory cortex and inferior colliculus) in patients with tinnitus and compare them to controls. Furthermore, the relation (functional connectivity) between the cortex and inferior colliculus was investigated.

The results and conclusions will be published for the first time at the 9th international TRI Tinnitus Conference, 2015 in Ann Arbor, Michigan.

4- FACTORS ASSOCIATED WITH TRANSCRANIAL MAGNETIC STIMULATION TINNITUS TREATMENT BENEFIT

Theodoroff SM^{1,2}, Griest SE¹, Folmer RL^{1,2}

1VA RR&D National Center for Rehabilitative Auditory Research, VA Portland Health Care System (VAPORHCS), Portland, Oregon; 2Dept. of Otolaryngology- Head & Neck Surgery, Oregon Health & Science University (OHSU), Portland, Oregon
National Center for Rehabilitative Auditory Research, 3710 SW US Veterans Hospital Road (NCRAR P-5), Portland OR 97239

Rationale: The majority of instruments used to measure tinnitus distress or severity were not developed to assess treatment outcomes (1). With this in mind, Meikle et al (2) developed the Tinnitus Functional Index (TFI) with the concept of responsiveness central to its design. The purpose of this study is to examine the subscales of the Tinnitus Functional Index (TFI) to identify specific factors associated with tinnitus treatment benefit following 10 sessions of repetitive transcranial magnetic stimulation (rTMS).

Aims/Objectives: The aim of this study is to examine associations between rTMS treatment outcome and the eight factor-based subscales on the Tinnitus Function Index (TFI): Intrusive, Sense of Control, Cognitive, Sleep, Auditory, Relaxation, Quality of Life, and Emotional. In addition, participants' responses on secondary outcome measures will be examined to identify other effects of rTMS treatment.

Methods: A randomized, subject and clinician blinded clinical trial of 1 Hz rTMS was conducted. Subjects received either active or placebo rTMS treatment on 10 consecutive work days. Outcomes were measured prior to receiving treatment (baseline) and immediately following the 10th rTMS session (post-rTMS). Follow-up evaluations were conducted up to 6 months after the last rTMS treatment session. The TFI was the main outcome measure. Secondary outcome measures included visual numeric ratings of tinnitus loudness; psychoacoustic tinnitus loudness-matching and minimum-masking-levels; Beck Depression Inventory and State Anxiety Inventory questionnaires. Data from the subjects in the active rTMS group will be presented (n = 35).

Results: We defined "responders" to rTMS treatment as subjects who improved >7 points on the total TFI score from baseline to post-rTMS treatment (n = 18). Repeated measures ANOVA revealed responders to rTMS treatment showed significant improvement ($p < 0.05$) for all eight subscales, with the Sleep and Cognitive subscales showing the most improvement. Compared to baseline TFI scores, the group of responders continued to improve up to 26 weeks following rTMS treatment, whereas non-responders did not exhibit improvement in TFI scores at any post-rTMS assessment. Graphs and plots of outcomes across all factors and time points (baseline, post-rTMS treatment, and 26 week follow-up) will be presented.

Conclusions: Tinnitus is the most prevalent service-connected disability for U.S. military Veterans (Veterans Benefits Administration, 2013) and negatively affects the quality of life for millions of people worldwide. Identifying factors associated with treatment responsiveness will

offer insight into predictive outcomes of using rTMS to reduce tinnitus severity.

References:

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5- INDIVIDUALIZED MULTI-SITE RTMS IN CHRONIC TINNITUS: A FEASIBILITY STUDY

Schecklmann M, Kreuzer P, Lehner A, Poepl TB, Langguth B
Department of Psychiatry and Psychotherapy, University of Regensburg, Germany

Background: Due to findings that prefrontal and temporoparietal areas are involved in the etiology of chronic tinnitus, daily repetitive transcranial magnetic stimulation (rTMS) of these areas is used as treatment. However, rTMS showed only moderate efficacy with high inter-individual variability. Here, we investigated the feasibility of individualized multi-site stimulation in chronic tinnitus.

Methods: During the first session of our standard two-week treatment with rTMS we applied different protocols to the left and right temporoparietal and left and right prefrontal cortex. For each stimulation site, patients with chronic tinnitus were stimulated with 200 pulses (except 1Hz: 50 pulses) and a frequency of 1Hz, 5Hz, 10Hz, 20Hz, and cTBS (continuous theta burst stimulation (cTBS)). Sham stimulation was done by repeating the most effective protocol by tilting the coil. Subjects wear earplugs and were asked immediately after each stimulation if their tinnitus was changed in its loudness. We aimed at testing this protocol in 25 patients. Patient who could report changes in tinnitus were treated individualized with the most effective stimulation of the prefrontal and the temporoparietal cortex, the remaining were treated with a standard multisite protocol (left prefrontal with 20Hz and temporal with 1Hz). Visits were done before, at the first and last day of treatment, two and ten weeks after treatment.

Results: Almost half of the patients (12 out of 25) could report sham-controlled reductions in tinnitus loudness after single interventions. One patient of the standard treatment group quit after the first session due to headache. Patients of the individualized group showed highest benefit after high-frequency stimulation and most of them after stimulation of the left prefrontal or temporoparietal cortex. Mean pre-to-post-treatment amelioration in the tinnitus questionnaire total score was 8.6 ± 8.9 in the individualized and 1.5 ± 8.5 in the standard treatment group.

Discussion: Our data show that almost 50% of tinnitus patients could report temporary changes after single rTMS sessions. Individual treatment response in single sessions can be transferred to repeated daily treatment with stable amelioration for several weeks after the treatment. In comparison to standard treatment, effects of individualized rTMS are dramatically increased. Future studies should investigate the specificity of high-frequency and left-sided rTMS.

6- Combined rTMS treatment targeting the Anterior Cingulate and the Temporal Cortex for the Treatment of Chronic Tinnitus

Peter M. Kreuzer^{1,4}, Astrid Lehner^{1,4}, Winfried Schlee^{1,4}, Veronika Vielsmeier^{3,4},
Martin Schecklmann^{1,4}, Timm B. Poepl^{1,4}, Michael Landgrebe^{1,2,4}, Rainer Rupprecht¹,
Berthold Langguth^{1,4}

1 Department of Psychiatry and Psychotherapy, University of Regensburg, Germany

2 Department of Psychiatry, Psychosomatics and Psychotherapy, kbo-Lech-Mangfall-Klinik
Agatharied, Germany

3 Department of Otorhinolaryngology, University of Regensburg, Regensburg, Germany

4 Interdisciplinary Tinnitus Center of the University of Regensburg, Regensburg, Germany

Background: Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a putative treatment for chronic tinnitus. Promising results have been obtained by consecutive stimulation of both lateral frontal and auditory brain regions within the same session. Recent findings indicate a potential benefit from stimulation of rather medial or deeper parts of the frontal cortex such as the anterior cingulate cortex (ACC).

Methods: We investigated a combined stimulation paradigm targeting the ACC with double cone coil rTMS, followed by stimulation of the temporo-parietal junction area with a figure-of-eight coil. The study was conducted as a randomized and double-blind pilot trial in 40 patients suffering from chronic tinnitus. We compared mediofrontal stimulation with double-cone-coil, (2000 stimuli, 10 Hz) followed by left temporo-parietal stimulation with figure-of-eight-coil (2000 stimuli, 1 Hz) to left dorsolateral prefrontal cortex stimulation with figure-of-eight-coil (2000 stimuli, 10 Hz) followed by temporo-parietal stimulation with figure-of-eight-coil (2000 stimuli, 1 Hz).

Results: The stimulation has been shown to be feasible with comparable dropout rates in both study arms; no severe adverse events were registered. Responder rates (primary outcome) did not differ in both study arms. There was a significant main effect of time for the change in the TQ score, but no significant time x group interaction. Also secondary outcomes (e.g. change of depressive symptoms) were non-significant.

Conclusion: This pilot study demonstrated the feasibility of combined mediofrontal/temporoparietal rTMS- stimulation with double cone coil in patients suffering

from chronic tinnitus but failed to show superior clinical effects compared to an actively rTMS treated control group.

Financial Disclosures: The study was supported by the Tinnitus Research Initiative and the American Tinnitus Association. The authors have no conflicts of interest, financial or otherwise, related directly or indirectly to the submitted work.

7- Psychopathological Symptoms and Quality of Life in Patients with Chronic Tinnitus

*Luciana Geocze, Samantha Mucci, Ricardo Rodrigues Figueiredo, Ektor Tsuneo Onishi,
Norma Oliveira Penido.
Germany*

Tinnitus is defined as the perception of sound when there is no external source present. The disorder called tinnitus is subjective and variable in relation to their intensity and frequency, and can impair the patient's life in a comprehensive manner, causing a personal, professional, social and family loss.

Aim: To evaluate the presence of psychopathological symptoms and quality of life (QoL) in patients with tinnitus and correlate with their discomfort.

Method: A cross-sectional study was conducted in a sample divided into three groups: Group A (N = 40) of patients with tinnitus and hearing loss, Group B (N = 26) of patients with tinnitus without hearing loss and Group C (N = 26) of individuals without tinnitus and without hearing loss (controls). BECK depression (BDI) and anxiety scales (BAI) were used and the Tinnitus Handicap Inventory (THI).

Results: The mean age of patients (Groups A + B) was 51 years (± 11.9); 65.2% (N = 43) were female, 63.6% (N = 42) were married or lived in a stable relationship, 37.8% (N = 25) attended elementary school, 34.8% (N = 23) high school and 28.6% (N = 18) higher education. Psychopathological symptoms were more present in the sample of patients than in controls ($p < 0.05$), and 37.9% had depression and 47% anxiety. There was no significant difference between groups A and B in relation to the degree of discomfort of tinnitus and the other variables. Positive associations between the degree of 2 discomfort and depression, anxiety and the concurrence of more than one psychopathological symptoms were observed. It was observed that the degree of tinnitus discomfort showed a strong correlation ($r > 0.40$) with symptoms of anxiety and depression, with the physical, social and mental health domains of quality of life.

Conclusions: Depression and anxiety are related to tinnitus annoyance. The QoL of these patients showed impaired in the fields "social aspect", "emotional aspect", "functional capacity". The presence of more than one disorder psychopathological was responsible for a

worsening in the degree of tinnitus. It was possible to verify that the concomitance of anxiety and depression; and depression and lack of social interactions, were able to predict an increased discomfort of tinnitus in these patients.

8- SALICYLATE- AND NOISE-INDUCED HYPERACUSIS AND LOUDNESS RECRUITMENT IN RATS

K. Radziwon, B. Auerbach, G-D. Chen, R. Salvi
University at Buffalo, The State University of New York
Department of Communicative Disorders and Sciences
Center for Hearing and Deafness
137 Cary Hall
3435 Main Street
Buffalo, NY 14214, USA

Background: Hyperacusis, which often accompanies tinnitus, is a loudness intolerance disorder in which everyday sounds are perceived as uncomfortably or even painfully loud. Hyperacusis can be debilitating, leading to the avoidance of social situations, negative emotional affect, concentration difficulties, and the dependence on hearing protective devices. Despite the high prevalence of hyperacusis in the general population and among musicians in particular, little research has been conducted on the biological underpinnings of this perceptual disorder. To date, hyperacusis research has largely been hindered by the absence of a reliable and valid animal behavioral model. Recently, we tested a behavioral paradigm that can reliably distinguish among hyperacusis, loudness recruitment, and normal loudness growth in rats using reaction time (RT) measures following both sodium salicylate (SS) administration and noise exposure. Ultimately, the goal of this research is to accurately identify animals experiencing hyperacusis so that further studies can determine the physiological and biological correlates of this perceptual disorder.

Methods: RT-intensity functions were obtained to identify rats with SS- and/or noise-induced loudness recruitment or hyperacusis. Rats were trained in a Go/No-go operant conditioning paradigm to detect broadband noise bursts (300 ms duration, 5 ms rise/fall time) ranging from 30 to 90 dB SPL. Reaction time measures, defined as the time between the onset of the noise burst to the time the rat responded to the stimulus, were taken for all hits (i.e., the correct detection of the noise bursts). To ensure that the animals were under stimulus control, 30% of all trials were catch trials in which no noise burst was presented. In addition to behavioral RT measures, electrophysiological recordings were also taken from another set of rats to measure neural activity in various structures along the auditory pathway. One group of rats was given SS, while the other group was exposed to noise. Local field potentials and rate level functions to broadband noise bursts and tone bursts were obtained both before and after treatment.

Results: Rats given an injection of SS known to induce tinnitus exhibited faster-than-normal RTs

to noise bursts >60 dB SPL. Given that these same rats had normal or even slower-than-normal RTs to noise bursts <50 dB SPL following SS, we are confident that these rats are experiencing sounds >60 dB as louder-than-normal, and therefore are experiencing hyperacusis. Physiologically, SS induced hyperactivity in the central auditory system. This same hyperactivity was found following noise exposure; however, the rats rarely exhibited behavioral evidence of hyperacusis following noise exposure. Rather, after noise exposure, the rats tended to have slower-than-normal RTs to low-level stimuli, with normal RTs to high-level sounds, i.e., loudness recruitment.

Conclusion: Using RT as a surrogate for loudness perception, we have demonstrated that we can reliably distinguish hyperacusis and loudness recruitment in rats. Future studies will attempt to determine why SS reliably induces hyperacusis whereas noise exposure rarely induces hyperacusis despite producing similar alterations in neural activity in the central auditory system.

9- TUMOR NECROSIS FACTOR- α , A PROINFLAMMATORY CYTOKINE, IS REQUIRED FOR TINNITUS AND HEARING LOSS-INDUCED BINAURAL PLASTICITY

Robert Gibboni¹, Sungchil Yang¹, and Shaowen Bao^{1,2}

¹Helen Wills Neuroscience Institute, University of California-Berkeley, and

²Department of Physiology, University of Arizona

Aims/Objectives: Tumor Necrosis Factor- α is a proinflammatory cytokine that is involved in homeostatic synaptic plasticity and sensory map development in the auditory cortex. We examined its role in hearing loss-induced binaural plasticity and tinnitus.

Methods: **TNF- α knockout and wildtype mice underwent unilateral noise-induced hearing loss** (NIHL, 8 kHz, 112 dB, 2 hours). Behavioral evidence of tinnitus was measured using the gap detection paradigm 10 days after NIHL. Binaural cortical plasticity was examined electrophysiologically.

Results: Wildtype, but not TNF- α knockout, mice showed robust binaural plasticity following unilateral NIHL. In addition, wildtype, but not TNF- α knockout, mice showed behavioral evidence of tinnitus (i.e., impaired gap detection) following unilateral NIHL, or following a high dose of salicylic acid. Micro-infusion of recombinant TNF- α in the right hemisphere auditory cortex resulted in tinnitus in normal hearing wildtype mice.

Conclusion: Our results implicate TNF- α in tinnitus etiology, and suggest that tinnitus may be a neural inflammatory disorder.

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10- Fractal tones for normal hearing listeners with tinnitus

*Kuk, F
Widex
Denmark*

Introduction: The use of sound stimulation with fractal tones and amplification, in combination with counseling has been reported effective in managing tinnitus sufferers with a hearing loss. However, there is a lack of evidence supporting the use of fractal tones for tinnitus sufferers who do not require amplification. Recently a new ear level tinnitus device – Zen2go was developed specifically for normal hearing subjects. It consists of 3 Zen sound stimulation programs containing fractal tones and noise. This clinical trial was conducted to evaluate the effectiveness of the Zen2go and Widex Zen Therapy in reducing tinnitus distress on normal hearing subjects.

Method: Forty subjects with significant tinnitus distress (THI >18) and no need for amplification were recruited. Thirty six completed the data collection. The subjects were then split into two groups and matched on their hearing thresholds and THI scores. One group was fitted with Zen2go and returned for follow up visits at 1, 2, 4, 6 and 12 months. Subjects were provided sound stimulation only during the first two months. If at that time, their THI scores were still above 18, other components of WZT i.e. relaxation techniques and cognitive behavioral intervention were included. The other group is a control group who returned for follow up visits at 2, 4 and 6 months. The control group was told they are on a waiting list for treatment. THI, TFI and visual analogue scales (VAS) were administered at 2, 4, 6 months and finally at 12 months of finished treatment.

Results and Conclusions: Analysis of data showed significant improvements in tinnitus distress in the treatment group but not the control group ($p < 0,001$). Clinically and significant improvements in tinnitus reduction were observed on the THI, TFI and VAS scores after two months ($p < 0,001$) of treatment (i.e., just fractal tones). No changes were observed in the control group of subjects. These results showed that combining Zen2go (fractal tones and noise) with counseling is an effective treatment option for people with normal hearing/slight hearing losses and tinnitus.

11- The effect of MDMA on tinnitus: Preliminary results.

*Hadfield D.¹, Searchfield G. D.^{1,2}, Poppe T.^{2,3}, Spiegel D.P.^{1,2,5}, Wise K.^{1,2}, Shekhawat G.S.^{1,2},
Kennedy M.⁴, Jensen M.², Sundram F.², Russell, B.²*

*1 Section of Audiology, School of Population Health, The University
of Auckland, 261 Morrin Road, Glenn Innes, Auckland, New Zealand*

*2 Centre for Brain Research, The University of Auckland, 85 Park
Road, Grafton, Auckland, New Zealand*

3 Department of Optometry and Vision Science, The University of

*Auckland, 85 Park Road, Grafton, Auckland, New Zealand
4 The University of Otago, Dunedin, New Zealand*

Background: Some tinnitus patients have reported that the drug Ecstasy provides tinnitus relief; 3, 4-Methylenedioxymethamphetamine (MDMA) is the primary psycho-active substance in Ecstasy. Based on these clinical observations this study aimed to investigate MDMA as a potential pharmacological solution to tinnitus.

Methods: In Phase I a double blind, randomized, placebo controlled cross-over trial was conducted to determine the minimum effective dose (30-70 mg) of MDMA for the treatment of tinnitus. Behavioral measurements were obtained before, during and after treatment to assess the potential therapeutic effect of MDMA. Phase II was designed to study the neural correlates of MDMA effect in tinnitus patients using RSfMRI.

Results: Preliminary results of this study will be presented.

12- EPIDEMIOLOGICAL STUDY OF TINNITUS PREVALENCE IN THE CITY OF SÃO PAULO

Jeanne Oiticica¹

Roseli Saraiva Moreira Bittar¹

(1) Department of Otolaryngology, University of São Paulo School of Medicine

Introduction: The public and private health care in the city of São Paulo has no data on tinnitus prevalence.

Objective: Determine tinnitus prevalence in Sao Paulo city.

Study Design: Clinical Trial.

Casuistic and Methods: Cross-sectional study by field questionnaire with 1960 interviews. Predictor variables included gender, age, tinnitus. Results: The prevalence of tinnitus was 22%. It affects women greater (26%) than men (17%). It was also observed progressive prevalence spread with increasing age. Approximately one third of cases (32%) claim to have constant tinnitus, while most states intermittent tinnitus (68%). The majority (64%) reported feeling annoying, while others (36%) denied any bother. Among women annoying tinnitus was significantly higher (73%) than males (50%). The percentages were: mildly annoying (11%), moderately annoying (55%), and severely annoying (34%). Tinnitus interferes with daily activities in 18% of those reporting to be annoying.

Conclusion: The tinnitus population in the city of São Paulo was more prevalent than previously estimated. Generally affects more often women, those without occupation, and increases significantly with advancing age. Most respondents referred annoying tinnitus, and this fact was more prevalent in females. The degree of discomfort measured by visual analogue scale showed moderate tinnitus, with average responses on 6.3.

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POSTER SESSION 2 MONDAY JUNE 8, 2015

13- THE IMMEDIATE EFFECTS OF ACOUSTIC TRAUMA ON THE INFERIOR COLLICULUS: A WIENER-KERNEL ANALYSIS

A.N. Heeringa^{1,2} and P. van Dijk^{1,2}

*1Department of Otorhinolaryngology / Head and Neck Surgery, University of Groningen,
University Medical Center Groningen, Groningen, the Netherlands*

*2Graduate School of Medical Sciences (Research School of Behavioural and Cognitive
Neurosciences), University of Groningen, Groningen, the Netherlands*

Background: Noise-induced tinnitus and hyperacusis are thought to correspond to a disrupted balance between excitation and inhibition in the central auditory system. Previous experiments in our lab showed that sound-evoked excitation and inhibition of the inferior colliculus (IC) can be studied in detail using a Wiener-kernel analysis, which allows for a decomposition of the excitatory and inhibitory contributions to neural responses. The current study aimed at investigating the effects of immediate acoustic trauma on excitation and inhibition with a Wiener-kernel analysis.

Methods: Neural activity was recorded from the IC of anesthetized albino guinea pigs before and immediately after a one-hour bilateral exposure to an 11-kHz tone of 124 dB SPL. For the Wiener-kernel analysis, neural activity was recorded during the presentation of a 1-h continuous Gaussian-noise stimulus of 70 dB SPL. Response characteristics obtained with Wiener-kernel analysis were compared with excitatory and inhibitory responses to pure tones. The electrode remained at the same location in the IC during the entire experiment, which allowed for a direct comparison between before and after acoustic trauma.

Results: IC units had a lower characteristic frequency (CF) after acoustic trauma as compared to before. Wiener-kernel analysis showed that excitation and inhibition in low-CF units (CF < 3 kHz) was not affected, inhibition in mid-CF units (CF between 3 kHz and 11 kHz) disappeared whereas excitation was not affected, and both excitation and inhibition in high-CF units (CF > 11 kHz) disappeared after acoustic trauma. This specific differentiation could not be identified with

the tone-evoked receptive-field analyses, in which inhibitory responses disappeared in all units and excitatory responses in only the high-CF units.

Conclusions: This study demonstrated that effects of acoustic trauma on the IC can be identified with a Wiener-kernel analysis. We showed an acoustic trauma-induced disrupted balance between excitation and inhibition, which was apparent in units that were tuned to frequencies below the trauma frequency (mid-CF units) in particular. Our findings might give additional insight in the central pathophysiological mechanisms of acute noise-induced tinnitus and hyperacusis.

14- Blast-Induced Tinnitus and Neural Activity Changes along the Auditory Axis in Rats

*Hao Luo(a), Xueguo Zhang(a), Edward Pace(a), Srinivas Kallakuri(b) and Jinsheng Zhang(a)(c)**

(a) Laboratory of Tinnitus and Neuroscience Research, Department of Otolaryngology-Head and Neck Surgery, Wayne State University School of Medicine, Detroit, Michigan 48201

(b) Department of Biomedical Engineering, Wayne State University College of Engineering, Detroit, Michigan 48202

(c) Department of Communication Sciences & Disorders, Wayne State University College of Liberal Arts & Sciences, Detroit, Michigan 48202

Introduction: High-pressure blast shock waves are known to cause tinnitus. Although the underlying mechanism may be due to damage to structures in the ear and/or direct brain impact that triggers a cascade of neuroplastic changes in both auditory and non-auditory centers, there is a lack of investigation of electrophysiological changes following blast-induced tinnitus.

Methods: In this study, we used a rat model (n=39) and tested behavioral evidence of tinnitus following a single 22 psi blast exposure to the left ear. We then investigated electrophysiological changes by simultaneously recording from the dorsal cochlear nucleus (DCN), inferior colliculus (IC) and auditory cortex (AC) at one day, one month and three months after the blast exposure.

Results: Our behavior data showed that blast-induced tinnitus occurred at all frequency bands immediately after blast, at median and high frequency bands one month post-blast, and eventually at a high-frequency band three months post-blast. Compared to control rats, early onset hyperactivity was found in the DCN of rats with tinnitus, which lasted for a month before shifting to hypoactivity three months after blast. In addition, the low frequency region in the DCN of tinnitus positive rats was more affected than other frequency regions at one day and one month after blast exposure, whereas at three months, the DCN was broadly affected except for the low frequency region. Hyperactivity exhibited at all frequency regions in the IC of

rats with tinnitus at one day after blast, and while the induced hyperactivity persisted throughout a three months recording period, it was more robust in middle-frequency loci at one month after blast exposure and in middle-to-high frequency loci at three months after blast. In the AC of rats with tinnitus, spontaneous activity began increasing at one month after blast exposure and manifested as robust hyperactivity at all frequency regions three months post-blast.

Conclusion: Overall, these results demonstrated that blast-induced tinnitus does not involve a uniform manifestation of increased SFR along the auditory axis. Instead, changes in SFR can happen in different directions and at different levels of the central auditory system. The data also suggest that onset tinnitus may result from hyperactivity in the lower auditory brainstem, whereas chronic tinnitus may be related to high-level auditory structures. This information may be important for developing treatment strategies for blast-induced tinnitus.

15- PSYCHOPHYSIOLOGICAL ASSOCIATIONS BETWEEN TINNITUS AND SLEEP: A CROSS-VALIDATION OF TINNITUS AND INSOMNIA QUESTIONNAIRES

*Schecklmann M, Pregler M, Kreuzer P, Poepl TB, Lehner A, Crönlein T, Wetter TC,
Frank E, Landgrebe M, Langguth B
Department of Psychiatry and Psychotherapy, University of Regensburg, Germany*

Background: Based on the idea of common etiological factors in chronic tinnitus and psychophysiological insomnia, the aim of the present study was to assess the prevalence of insomnia in chronic tinnitus and the association of tinnitus distress and sleep disturbance. Furthermore, we evaluated whether the Tinnitus Questionnaire is sufficient for comprehensive assessment of insomnia symptoms in chronic tinnitus.

Methods: We retrospectively analysed data of 182 patients with chronic tinnitus who completed the Tinnitus Questionnaire (TQ) and the Regensburg Insomnia Scale (RIS) for assessment of tinnitus distress and sleep disturbance, respectively. Descriptive comparisons with the validation sample of the RIS including only patients with psychophysiological insomnia, correlation analyses of the RIS with TQ scales, and principal component analyses (PCA) in the tinnitus sample were performed. TQ total score was corrected for the TQ sleep items.

Results: Prevalence of insomnia was high in tinnitus patients (76%) and tinnitus distress (corrected for sleep items) correlated with sleep disturbance ($r=0.558$). TQ sleep sub-score correlated with the RIS sum score ($r=0.690$). PCA with all TQ and RIS items showed one sleep factor consisting of all RIS and the TQ sleep items. PCA with only TQ sleep and RIS items showed sleep- and tinnitus-specific factors. The sleep factors (only RIS items) were sleep depth and fearful focusing. The TQ sleep items represented tinnitus-related sleep problems.

Discussion: Tinnitus complaints and sleep disturbances are highly related as indicated by cross-correlation of the questionnaires TQ and RIS and the high prevalence of insomnia in chronic tinnitus. Together with the results of the PCA the TQ seem to be sufficient as screening tool for tinnitus-related insomnia. Chronic tinnitus and primary insomnia might share similar psychological and neurophysiological mechanisms leading to impaired sleep quality. Future studies may shed light on the influence of disturbed sleep on daytime tinnitus distress.

16- RTMS INDUCED OSCILLATORY POWER AS NEUROPLASTIC MARKER IN CHRONIC TINNITUS

Schecklmann M, Gollmitzer J, Schmidt E, Langguth B

Department of Psychiatry and Psychotherapy, University of Regensburg, Germany

Background: Chronic tinnitus is associated with neuroplastic changes such as changes in spontaneous activity along the auditory pathway, tonotopic reorganization of the auditory cortex, increased activity and connectivity in specific cortical networks. Ten years ago, daily repetitive transcranial magnetic stimulation (rTMS) of auditory and prefrontal cortex was introduced as potential treatment showing only moderate efficacy. Here, we investigated the effect of sham-controlled single rTMS sessions on oscillatory power as elicited with electroencephalography (EEG) to probe the capacity of rTMS to interfere with tinnitus-specific cortical activity.

Methods: We measured 20 patients with bilateral chronic tinnitus and 20 healthy controls which were comparable for age, sex, handedness, hearing level with a 63-channel EEG system wearing earplugs. Educational level, intelligence, depressivity, hyperacusis were controlled by analysis of covariance. Left and right temporal and left and right prefrontal cortex was stimulated with 200 pulses at 1Hz and with an intensity of 60% stimulator output. Stimulation of central parietal cortex with lower intensity (6-fold reduced intensity, not targeting the cortex) served as sham condition. Before and after each session five minutes of resting state EEG were recorded. Stimulation sessions were randomized over two sessions with one week interval in between.

Results: Sensor-based analyses showed that left temporal stimulation induced sham-controlled, baseline-corrected (post minus pre measurement) tinnitus-related decreases in frontal theta and delta power. Right frontal stimulation showed decreases in the oscillatory power of the right temporal beta3 and gamma band. Discussion: Short sessions of low-frequency rTMS were capable to show neuroplastic effects specific for stimulation site and frequency band at specific recording sites. Future studies should try to bridge the gap between immediate changes in oscillatory activity and therapeutic efficacy.

17 - Sound localization accuracy in lateralized tinnitus

Petteri Hyvärinen¹, Catarina Hiipakka², Olli Santala², Ville Pulkki², Antti A. Aarnisalo¹

1 Helsinki University Central Hospital, Department of Otorhinolaryngology – Head and Neck

Surgery

2 Aalto University School of Electrical Engineering, Department of Signal Processing and Acoustics

Activity changes in the dorsal cochlear nucleus (DCN) of the brainstem have recently been associated with tinnitus symptoms. On the other hand, earlier animal studies have suggested a role for the DCN in sound localization in elevation. Information about sound localization ability of subjects with tinnitus could help in identifying the affected parts of the nervous system, but there have not been enough studies on the subject to draw any conclusions.

We investigated sound localization in subjects with self-reported lateralized tinnitus (N = 8). We compared the results to two control groups: one with normal hearing (N = 9) and the other with hearing loss matched to the tinnitus group (N = 8). The target sounds were 500-ms pink noise bursts presented at 65 dB SPL, A-weighted. Vertical localization tests were repeated three times with one ear blocked at a time and without blocking. Further, all tests were done with and without background noise (continuous diffuse white noise at 50 dB SPL, A-weighted). For the control groups, an additional condition with simulated tinnitus (4-kHz tone at 30 dB SPL, located at 90° to the right) was also included.

We found that tinnitus subjects localized worse than controls especially in the horizontal plane. Blocking of the ears degraded localization in elevation more in tinnitus and hearing loss matched groups than in the normal hearing group. Also, introducing the simulated tinnitus sound decreased performance differences between tinnitus and hearing loss matched groups, whereas it did not have similar effects for the normal-hearing subjects.

18-Differential Modulation of Electrocortical Responses Evoked from Primary and Nonprimary Auditory Cortex by Forward Masking in Tinnitus

Roberts L.E.^{1,2}, Bosnyak D.J.^{1,2}, Bruce, I.C.^{1,2,3}, Paul, B.T.¹

1 Department of Psychology, Neuroscience, and Behaviour; 2 McMaster Institute for Music and the Mind; 3 Department of Electrical and Computer Engineering

McMaster University, Hamilton, Ontario, Canada L8S 4K1

It has been proposed that tinnitus is generated by aberrant neural activity that develops among neurons in tonotopic regions of primary auditory cortex (A1) affected by hearing loss, which is also the frequency region where tinnitus percepts localize (Eggermont and Roberts 2004; Roberts et al., 2008, 2010, 2013). These models suggest (1) that differences between tinnitus and control groups of similar age and audiometric function should depend on whether A1 is probed in tinnitus frequency region (TFR) or below it, and (2) that brain responses evoked from

A1 should track changes in the tinnitus percept when residual inhibition (RI) is induced by forward masking. We tested these predictions by measuring (128-channel EEG) the sound-evoked 40-Hz auditory steady-state response (ASSR) known to localize tonotopically to neural sources in A1. For comparison the N1 transient response localizing to distributed neural sources in nonprimary cortex (A2) was also studied. When tested under baseline conditions where tinnitus subjects would have heard their tinnitus, ASSR responses were larger in a tinnitus group than in controls when evoked by 500 Hz probes while the reverse was true for tinnitus and control groups tested with 5 kHz probes, confirming frequency-dependent group differences in this measure. On subsequent trials where RI was induced by masking (narrow band noise centered at 5 kHz), ASSR amplitude increased in the tinnitus group probed at 5 kHz but not in the tinnitus group probed at 500 Hz. When collapsed into a single sample tinnitus subjects reporting comparatively greater RI depth and duration showed comparatively larger ASSR increases after masking regardless of probe frequency. Effects of masking on ASSR amplitude in the control groups were completely reversed from those in the tinnitus groups, with no change seen to 5 kHz probes but ASSR increases to 500 Hz probes even though the masking sound contained no energy at 500 Hz (an “off-frequency” masking effect). In contrast to these findings for the ASSR, N1 amplitude was larger in tinnitus than control groups at both probe frequencies under baseline conditions, decreased after masking in all conditions, and did not relate to RI. These results suggest that aberrant neural activity occurring in the TFR of A1 underlies tinnitus and its modulation during RI. They indicate further that while neural changes occur in A2 in tinnitus, these changes do not reflect the tinnitus percept. A model for tinnitus and forward masking is described that integrates these findings within a common framework. (Supported by NSERC of Canada)

19-ADVANCED NEUROIMAGING AS A POTENTIAL BIOMARKER IN TINNITUS

Piccirillo J, Peelle JE, Roland L, Kallogjeri D

*Department of Otolaryngology-Head and Neck Surgery, Washington University in St. Louis
School of
Medicine, St. Louis, Missouri, USA*

Aims/Objectives: Resting-state functional connectivity MRI (rs-fcMRI) neuroimaging provides objective measurement of functional neural network connectivity. Previous research demonstrated that disturbances in functional connectivity in various brain networks, such as the attention, default mode, executive control, somatosensory, audition, and visual, are associated with bothersome tinnitus symptoms. Increasingly, advanced neuroimaging, like rs-fcMRI, are included in clinical tinnitus research studies. The objective of this presentation is to assess the role of neuroimaging as a biomarker of the status of connectivity within key cortical networks in patients with bothersome tinnitus.

Methods: We will discuss the results from three different clinical studies of patients with bothersome tinnitus to illustrate the benefits and challenges of neuroimaging.

Results: The first example applied rs-fcMRI pre- and post-Mindfulness Based Stress Reduction (MBSR) group therapy in 13 tinnitus subjects.(Roland et al. 2015) MBSR emphasizes focused, nonjudgmental awareness of present moment experiences without efforts to alter or avoid them and teaches an attentional skill. Behavioral response to MBSR, as measured by patient self-report measures, showed statistically significant and clinically meaningful improvement. Consistent with this positive behavioral result, analysis of the rs-fcMRI data showed overall increased connectivity in the attention networks after MBSR. Similar changes were not identified in the default mode network. In the second example, we used rs-fcMRI to assess the neural effects of active (n= 16) or sham (n=14) rTMS.(Roland et al. 2015) There was no behavioral response to rTMS. Consistent with this negative behavioral response, analysis of the rs-fcMRI data failed to show any changes in neural connectivity. In the third clinical trial example, we used rs-fcMRI to assess changes in connectivity among 20 subjects with bothersome tinnitus after use of a computer-based brain training program. The overall study results did not demonstrate a significant behavioral improvement. Consistent with this negative result, rs-fcMRI analyses also failed to show changes in connectivity after intervention. Of note, in this study rs-fcMRI analysis failed to show any differences in functional connectivity at baseline between the bothered tinnitus patients (n=40) and the healthy non-tinnitus controls (n=20).

Conclusion: These three examples from actual clinical trials illustrate the potential utility, variability, and challenges of rs-fcMRI to serve as a biomarker of change in connectivity after an intervention. In most cases, the results of rs-fcMRI analyses coincided with behavioral reports, with changes in neural connectivity being seen only in cases of improvements in behavioral symptoms. Additional research to standardize imaging protocols and analytic approaches should lead to improved reliability and utility of functional connectivity neuroimaging. Ideally, the results of rs-fcMRI could help explain heterogeneity in subgroups, identify candidates for treatment, and define unique therapeutic subgroups.

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hypermetabolic in tinnitus as measured by functional near-infrared spectroscopy.

Issa M, 1Bisconti S, 1,2Kileny P, 1,2Basura G.

1Center for Human Growth and Development; and the 2Department of Otolaryngology, Head and Neck Surgery; University of Michigan, Ann, Arbor, MI 48109.

Background: Tinnitus is the phantom perception of sound in the absence of a physical sound stimulus. The underlying etiology of tinnitus perception is not currently clear, yet basic science mechanisms suggest neuronal hyperactivity within central auditory pathways, including primary auditory cortex (A1).

Objective: The aim of this study was to measure metabolic activity within A1 under conditions of auditory stimulation and silence in patients with subjective bilateral tinnitus as compared to non-tinnitus controls using functional Near-Infrared Spectroscopy (fNIRS).

Methods: Participants with bilateral subjective tinnitus with near normal hearing and non-tinnitus controls were tested using a passive listening task. Hemodynamic activity was monitored over the fronto-temporal-parietal cortex under random periods of stimulation with 750 Hz or 8000 Hz tones, broadband noise (BBN) or silence.

Results: Based on anatomic location and increased activity with stimulation, channels were able to isolate the region of interest (ROI; A1) from the adjacent non-region of interest (n-ROI). Controls had no inter-hemispheric difference with any task, and demonstrated activation with all stimulation relative to baseline. Interestingly, the tinnitus group demonstrated elevated baseline activation in both ROI and n-ROI. The elevated response in the tinnitus ROI was suppressed only with BBN; an effect not seen in control brains or with specific tones.

Conclusions: These preliminary data demonstrate that both A1 and adjacent, non-auditory cortices are hyper-metabolic in the tinnitus brain suggesting that these regions may be contributing to tinnitus perception. These data for the first time demonstrate significant changes in the tinnitus brain using fNIRs technology suggesting that this non-invasive tool may be an important first step in the diagnosis and management of this pervasive problem.

21- Tinnitus Severity and Gray Matter: a VBM analysis.

*Richard O. Bidó Medina, Jake Carpenter-Thompson, Sara Schmidt, Fatima T. Husain.
University of Illinois at Urbana Champaign. Beckman Institute for Advanced Sciences and
Technology. Speech and Hearing Sciences, 901 South Sixth Street Champaign, IL 61820*

Background/Aims: According to the American Tinnitus Association, tinnitus has a significant prevalence in America (10-15% of the general population). Tinnitus severity is determined by the distress it may cause, rather than its loudness or its pitch. It can negatively affect quality of life by impairing sleeping habits, increasing stress and leading to frustration, anxiety and

depression. The goal of this investigation was to identify changes in gray matter in the cerebral cortex and the subcortical structures in subjects with tinnitus with different levels of severity.

Methods: We used a Voxel-Based Morphometry (VBM) analysis of structural MRI images to assess whole-brain changes in gray matter. This was supplemented by a region of interest analysis (ROI) in order to examine changes in areas previously associated with tinnitus. The data were collected in 37 adults (aged: 29-69) suffering from chronic tinnitus. A rigorous audiometry assessment was performed; to rate the tinnitus severity we used the Tinnitus Handicap Inventory (THI). The 37 subjects were divided into two groups according to their THI scores: LOW (n=18, with a THI score in the range of 4 to 18) and HIGH (n=19, with a THI score in the range of 18 to 50). The MRI images (MPRAGE) were obtained from each subject and then preprocessed utilizing the Statistical Parametric Mapping software (SPM8) and the VBM analysis was carried out using two different toolboxes (DARTEL and VBM8) to obtain changes in modulated data (index of gray matter volume). The statistical analysis consisted of a two-sample t tests (statistical threshold was set at familywise error FWE corrected $p < 0.05$).

Results: We obtained different results for each toolbox. When conducted in DARTEL, the whole-brain analysis showed greater volumes of gray matter in the LOW group versus the HIGH in cerebellum, superior temporal gyrus, supramarginal gyrus, medial frontal gyrus, anterior cingulate, parahippocampal lobe, inferior temporal gyrus and the insula, and for HIGH compared to LOW, greater volumes in cerebellum (anterior lobe), inferior frontal gyrus, caudate body, and occipital subgyrus were noted. Analysis using VBM8 toolbox revealed greater volumes in the HIGH group for the posterior cingulate compared to the LOW group. The ROI analysis was only significant when conducted through DARTEL. We looked for changes in: auditory cortices (Brodmann areas 22 and 42), superior olivary complex, medial geniculate nuclei, ventral dorsal cochlear nucleus and inferior colliculus (all bilateral). The LOW group showed greater volumes in Brodmann area 42 and the MGN compared to the HIGH group.

Conclusions: High severity of tinnitus is associated with decreases in volume across certain structures in the central auditory pathway and the limbic system in comparison to low tinnitus severity. Previous studies conducted in our lab, between tinnitus versus a normal hearing control group, did not reveal significant changes in gray matter, however those studies lacked a subgroup with a high severity component. It is therefore possible that only high severity tinnitus causes alterations in gray matter volume. The volumetric changes in our results are in areas linked to emotional processing, depression and anxiety, suggesting the strong affective component of this disorder.

**22- TITLE – INTENSITY, DURATION, AND LOCATION OF HIGH DEFINITION
TRANSCRANIAL DIRECT CURRENT STIMULATION FOR TINNITUS RELIEF**

*G Shekhawat, F Sundram, M Bikson, D Truong, D De Ridder, C Stinear, D
Welch, G Searchfield*

*Section of Audiology, Tamaki Innovation Campus, School of Population
Health, University of Auckland, New Zealand*

Aims/Objectives - Tinnitus is the phantom perception of sound. The aim of this study was to compare current intensity (centre anode 1 mA and 2 mA), duration (10 minutes and 20 minutes) and location (Left Temporoparietal Area [LTA] and Dorsolateral Prefrontal Cortex [DLPFC]) using 4x1 high definition transcranial direct current stimulation (HD-tDCS) for tinnitus reduction.

Methods – Twenty seven participants with chronic tinnitus (>2 years) and mean age of 53.5 years underwent two sessions of HD-tDCS of the LTA and DLPFC in a randomized order with a 1 week gap between site of stimulation. During each session a combination of 4 different settings were used in increasing dose (1 mA, 10 min; 1 mA, 20 min; 2 mA, 10 min; and 2 mA, 20 min). The impact of different settings on tinnitus loudness and annoyance was documented.

Results – Twenty one participants (77.78%) reported a minimum of 1 point reduction on tinnitus loudness or annoyance scales. There were significant changes in loudness and annoyance for duration of stimulation [$F(1, 26) = 10.08, p < 0.005$] and current intensity [$F(1, 26) = 14.24, p = 0.001$]. There was no interaction between the location, intensity, and duration of stimulation.

Conclusion - A current intensity of 2 mA for 20 minute duration was the most effective setting used for tinnitus relief. The stimulation of the LTA and DLPFC were equally effective for suppressing tinnitus loudness and annoyance.

**POSTER SESSION 3
TUESDAY JUNE 9, 2015**

**23- MODULATION OF DOPAMINE-SENSITIVE NEURONS IN THE INFERIOR
COLLICULUS: ROLE IN NOISE INDUCED HEARING LOSS AND TINNITUS**

Apawu A¹, Fyk-Kolodziej B¹, Hali M¹, Dolan D², Halsey K², Walker P¹, Holt A^{1,3}

Wayne State University School of Medicine¹Detroit, MI

University of Michigan² Ann Arbor, MI

John D Dingell VAMC³ Detroit, MI

Background/Aims: Dopamine (DA), a multi-modal neurotransmitter, has been implicated in auditory processes. The inferior colliculus (IC) is a brain region responsible for the integration of

auditory signals. The presence of tyrosine hydroxylase (TH), the rate-limiting enzyme in the production of DA, has been reported within axon terminals in the IC, suggesting that DA is released in the IC. Receptors for DA are distributed throughout auditory pathways including the IC. Gene expression and immunocytochemistry for TH in the IC decrease significantly following hearing loss. The present work begins to unravel the role of DA neurotransmission in hearing by using pharmacological manipulation of DA D1 and D2-like receptors within the IC.

Method: Hearing thresholds were tested in male Sprague Dawley rats ($n = 15$) before and after bilateral stereotaxic cannulae implantation into the IC. Three weeks following surgery, rats were either injected bilaterally with: **a.** 2 μl of saline, **b.** 2 μl of the D1 receptor antagonist, R(+)-SCH- 23390 hydrochloride (10 μM), **c.** 2 μl of the D2 receptor antagonist S(-)-Eticlopride hydrochloride (10 μM) or **d.** 2 μl of a mixture (10 μM) containing both antagonists. Twenty minutes later, animals were exposed to a 16 kHz, 106 dB SPL tone for 1hr. Hearing thresholds were measured at 4, 12 and 20 kHz at several time points after the exposure (1 - 12 hrs and 3 weeks). To determine sensitivity to sound and tinnitus susceptibility, acoustic startle reflex (ASR) was tested both before and after sound exposure. The tract tracer Fluorogold was administered three weeks after the noise exposure to verify cannulae placement and spread of DA antagonist within the IC.

Results: Following sound exposure in saline treated animals, hearing thresholds (auditory brainstem responses) were elevated at each frequency tested ($p < 0.0001$). In animals pre-treated with a D1 DA receptor antagonist or a D1/D2 mixture, threshold shift was significantly blunted ($p < 0.05$). Dopamine receptor antagonist administration also affected ASR, with significantly enhanced startle inhibition during pre-pulse testing. Our preliminary findings suggest that antagonists can decrease adaptation of distortion product otoacoustic emissions (DPOAEs) at acoustic levels well above hearing threshold.

Conclusion: The results suggest DA sensitive IC neurons in the IC mediate susceptibility to noise induced hearing related pathology perhaps via modulation of the medial olivocochlear (MOC) reflex. The MOC reflex believed to protect outer hair cells from noise over-stimulation. Future experiments will evaluate the role DA in MOC reflex mediated protection from hearing loss and tinnitus.

24- Physical Activity and Tinnitus: How Physical Activity may Decrease Tinnitus Severity.]

*Carpenter- Thompson, Jake
University of Illinois, USA*

AIM: To provide functional and behavioral evidence for a beneficial relationship between physical activity and tinnitus severity.

METHODS: Volunteers with tinnitus were recruited from the Urbana-Champaign area and

divided into higher and lower tinnitus severity groups. Upon further analysis we found that those in the higher distress group also had lower levels of physical activity and vice versa. Therefore, subjects were grouped into higher tinnitus distress and lower physical activity level (HDLP) and lower tinnitus distress and higher physical activity level (LDHP) groups. Ninety affective stimuli from the International Affective Digital Sounds database were presented to the subjects while in a Magnetom Trio 3T fMRI scanner. The data was processed using SPM8 software to generate within and between group contrasts. Reaction time and number of responses were analyzed using SPSS software to establish group differences.

RESULTS: Increased amygdala response was observed in the HDLP group compared to the LDHP group when listening to affective stimuli. Increased frontal response was observed for the reverse comparison.

CONCLUSION: Our results suggest that higher levels of tinnitus severity and lower levels of physical activity may be associated with increased limbic response. Additionally, lower tinnitus severity levels and higher levels of physical activity may be associated with increased frontal response. Therefore, increased levels of physical activity may benefit those with tinnitus by increasing response in frontal regions to better control their emotional reaction to tinnitus and in effect reduce tinnitus severity.

25- Effect of Modulation of the Gating System Using Transcranial Direct Current Stimulation on Tinnitus Perception.

A. Maudoux¹, P.E. Turkeltaub², J.P. Rauschecker¹

1. *Laboratory of Integrative Neuroscience and Cognition, Dep. of Neuroscience, Georgetown University Medical Center, Washington, DC*

2. *Cognitive Recovery Laboratory, Dep. of Neurology, Georgetown University Medical Center, Washington, DC*

Background: Tinnitus is defined as a perception of sound in the absence of any external auditory stimuli. Despite the prevalence of this disorder, tinnitus pathophysiology remains poorly understood. A large body of evidence suggests that this symptom is related to plasticity-related changes in the auditory system at one or more sites along the peripheral and/or central auditory pathways. However, the ensuing plastic changes in the central auditory structures by themselves seem neither sufficient nor required to give rise to chronic tinnitus, implying that extra-auditory regions might modulate the auditory sensation. We have proposed previously that tinnitus perception arises only if two conditions are met: (1) a tinnitus signal is being generated within the auditory system, and (2) this uninformative signal fails to be suppressed by a cortico-striatal limbic network encompassing ventromedial prefrontal cortex and nucleus accumbens (NAc) (“gating theory”) [1].

Methods: Our model makes a precise prediction about the brain regions involved and as

such provides a framework that is easily testable. In our current study, we chose to test this model using a combination of transcranial direct current stimulation (tDCS) and functional magnetic resonance imaging (fMRI). In a randomized, double-blind, sham-controlled cross-over design, chronic tinnitus subjects are submitted to a 15 minutes of 2-mA tDCS anodal stimulation of the ventromedial prefrontal cortex (vmPFC) and cathodal stimulation of the right dorsolateral prefrontal cortex (dlPFC). Participants are scanned before and after each of the tDCS sessions. The locations of anode and cathode are based on a recent study showing that this noninvasive direct stimulation of prefrontal cortex can induce neural activity in the distally connected midbrain, with a direct behavioural effect on an attractiveness rating task [2]. Using this stimulation protocol we aim at targeting major regions of the gating system such as the prefrontal region and the NAc. Our primary outcome measure is a change in tinnitus intensity and/or distress assessed with a Visual Analog Scale (VAS). We are also looking at how the tDCS stimulation modifies the pleasantness rating of a series of affective auditory stimuli [3]. During the fMRI session, subjects are listening to tinnitus-like and nontinnitus sounds and are making pleasantness ratings of sound stimuli.

Results: We will present our preliminary results regarding the behavioral effects of the tDCS stimulation on the perception of tinnitus and on the pleasantness rating of affective auditory stimuli. The imaging analysis will examine tDCS-induced changes in neural function associated with the behavioral changes.

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26 - PAIRED ASSOCIATIVE STIMULATION OF THE AUDITORY CORTEX

*Schecklmann M, Engel S, Markewitz R, Kreuzer P, Poepl TB, Langguth B
Department of Psychiatry and Psychotherapy, University of Regensburg, Germany*

Background: Paired associative stimulation (PAS) is a specific repetitive transcranial magnetic stimulation (rTMS) protocol where every magnetic pulse is combined with an external stimulus. Based on a close timing between the TMS induced action potential and the cortical arrival of the external stimulus in the stimulated area neural plasticity is induced by mechanisms of spike-timing dependent plasticity. After a first proof-of-principle study of PAS of the auditory cortex by our group, we here extend these findings by investigating the effects of stimulus duration and of sham stimulation on primary and secondary auditory cortical activity by using amplitude-modulated tones.

Methods: The left temporal cortex of 18 healthy controls with normal hearing was stimulated in two experimental parts. One PAS session consisted of 200 stimulations with an interstimulus interval of 45ms between tone onset (400ms length, 4kHz frequency) and the TMS pulse which was proven to be effective in the pilot study. Part 1 contrasted effects of a short (23ms) and a long (400ms) PAS-tone on secondary auditory cortex activity (short vs. long condition); part 2 contrasted effects of verum and sham stimulation (6-fold reduced intensity of the magnetic field, not targeting the cortex) on primary and secondary auditory cortex activity (verum vs. sham condition). Primary auditory cortex activity was measured with auditory steady state responses (ASSR) as elicited by 40Hz amplitude-modulated (AM) sinus tones. Secondary auditory cortex activity was elicited with ASSRs using a 20Hz AM tone and late auditory evoked potentials (AEPs) for the 40Hz and 20Hz AM tone. Evoked activity was done for the PAS tone (4kHz carrier frequency) and a control tone (1kHz carrier frequency) - each tone presented 70 times (60dB SL, 800ms length). As STDP is based on close timing of pre- and post-synaptic activity we concentrated on evoked activity by using analyses time-locked to the tone onset.

Results: For part 1, the short PAS condition showed an increase in AEP amplitude accompanied by a decrease for the long PAS condition specific for the PAS carrier frequency. Verum and sham stimulation showed comparable decreases in AEP amplitude independent from the PAS protocol. Part 2 showed no effects for the contrast short vs. long condition. 20Hz ASSR amplitude showed sham-controlled decreases for the PAS-specific carrier frequency. ASSR amplitudes of the control tone or of the 40Hz AM tone showed no significant effects.

Discussion: PAS of the auditory cortex seem to be restricted to the secondary auditory cortex as effects could only be found for the AEPs and the 20Hz ASSRs which have neural generators rather in secondary than in primary auditory cortex. AEPs findings raise the importance of habituation effects and of duration of the PAS tone and challenge the validity of the transfer of PAS using sine tones to evoked potentials using AM tones.

27 - STRUCTURAL AND FUNCTIONAL MRI MAPPING OF HUMAN AUDITORY CORTEX AT 7T AND ITS POSSIBLE APPLICATION TO MEASURING CORTICAL RE-ORGANIZATION IN HEARING-IMPAIRMENT AND TINNITUS.

J. Besle¹, O. Mougin², R. Sanchez-Panchuelo², P. Gowland², R. Bowtell², S. Francis² & K. Krumbholz¹

1MRC Institute of Hearing Research, Nottingham, UK

2Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham, UK

Aims/Objectives: In animal models, deprivation of auditory input following peripheral hearing loss results in cortical tonotopic re-organization that has been proposed to be responsible for the generation of tinnitus. Although robust cortical tonotopic patterns can be measured in humans using fMRI, how they relate to the putative functional subdivisions of auditory cortex is

not understood. This limits our ability to measure tonotopy in functionally distinct areas and study its re-organization in hearing-impaired and tinnitus patients.

Methods: Here, we measured intra-cortical changes in frequency selectivity and myelination in 12 normal-hearing subjects using MRI at ultra-high magnetic field (7T) in order to locate primary auditory cortex and compare its location to tonotopic gradients measured in the same subjects. Using functional MRI (sparse 2D GRE EPI, 1.5 mm resolution, phase-corrected for B0-related distortions), we estimated best frequency and frequency selectivity using trains of narrowband noises at 7 single centre frequencies. For structural mapping of myelination, we estimated the R1 longitudinal relaxation rate (3D MP2RAGE, 0.6 mm resolution) and the magnetization transfer ratio (3D MTRAGE, 0.7 mm resolution). All structural and functional measures were projected onto a flattened model of the supra-temporal cortex, segmented from the high-resolution processed MP2RAGE volume. Structural measures were corrected for cortical thickness and curvature. Group-averaged maps were created using spherical registration.

Results: In all subjects/hemispheres, core (primary) auditory cortex could be identified as an area of increased frequency selectivity and myelination. Although there were slight systematic differences in the relative location of selectivity and myelination-defined cores, both aligned with the main direction of Heschl's gyrus (HG). In all subjects/hemispheres, we also identified 2 central tonotopic gradients (high-to-low-to-high) centred on Heschl's gyrus (HG), each oriented at 70° relative to the long axis of HG (and 140° with each other), as well as a posterior high-low gradient on the planum temporale. Unexpectedly however, there was considerable inter-subject variability in the relative location of core auditory cortex and tonotopic gradients, with higher myelination and selectivity corresponding to either or both central tonotopic gradients, depending on the subject/hemisphere.

Conclusion: We discuss how these measurements could be transposed to studying re-organization of tonotopic maps in hearing-impaired and tinnitus patients and how the apparent lack of consistency in the functional organization of auditory cortex is likely to complicate the measurement and interpretation of this cortical re-organization, if observed.

28 - MODERATE VAGUS NERVE STIMULTION DIRECTS MORE CORTICAL PLASTICITY THAN MORE IN VNS

M. S. BORLAND, E. P. BUELL, C. T. ENGINEER, N. A. MORENO, M. M. PANTALIA,
P. SHARMA, M. C. LANE, J.M. BUELL, M. P. KILGARD, The University of Texas at
Dallas, Richardson, TX

Repeated pairing of a movement or a sensory event with vagus nerve stimulation (VNS) can reorganize cortical maps. Repeatedly pairing a tone with a brief period of VNS increases the proportion of primary auditory cortex (A1) responding to the paired tone (Engineer et al.,

2011). Based on earlier VNS studies, we predicted an inverted U relationship between VNS current and map reorganization. Microelectrode maps were constructed from thirty-nine rats that had received VNS repeatedly paired with a tone. In rats that received moderate levels of VNS (0.4-0.8 mA), nearly twice as many cortical neurons were tuned to frequencies near the paired tone frequency. Rats that receive greater VNS intensity (1.2-1.6 mA) had significantly fewer neurons tuned to the same range. This result is consistent with the memory enhancing effects of VNS and suggests that both phenomena may share common mechanisms. It is likely that any future use of VNS-directed plasticity to treat neurological or psychiatric conditions would only be effective across a limited range of VNS parameters.

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29 - Cortical Overrepresentation of the Edge-Frequency Where the Audiogram is Steepest in Individuals with Chronic Tinnitus and Normal Hearing

**Ciesla, Katarzyna;*

Lewandowska, M.; Wolak, T.; Niedzialek, I.; Rusiniak, M.; Pluta, A.; Skarzynski, H.

Institute of Physiology and Pathology of Hearing, Poland

World Hearing Center, Institute of Physiology and Pathology of Hearing, Warsaw\Kajetany, Poland

Introduction: Animal studies have shown that tinnitus can induce reorganization of tonotopic maps of the primary auditory cortex (PAC) (Eggermont & Roberts, 2004). Findings in human remain, however, inconsistent (Mühlnickel et al 1998, Langers et al 2012). Mühlnickel et al (1998) observed a shift of the tinnitus frequency in the auditory cortex whereas Langers et al (2002) did not find a tonotopic cortical map reorganization in tinnitus subjects with normal or near-normal hearing up to 8 kHz. It is also a matter of debate whether tinnitus is most closely associated with the frequency range that corresponds to the hearing loss (Roberts et al., 2008) or with the edge-frequency where the audiogram is steepest (Sereda et al, 2014). An fMRI trial was designed to evaluate tonotopic organization of PAC in individuals with chronic (>6 months) tinnitus.

Method: Thirty five patients with chronic bilateral tinnitus were divided into two groups with: 1) normal hearing (≤ 25 dB) up to 8kHz (n=20, 8 F, 12 M, mean age=39.5 year \pm 9.3, NH or 2) hearing loss (n=15, 6 F, 9 M, mean age=43.8 year \pm 13, HL). Seventeen individuals (8 F, 9 M, mean age=35.5 year \pm 11, C) with normal hearing was a control group. Individuals with hyperacusis, anxiety, or depression were excluded. Tinnitus pitch in the normal hearing group was in range from 2.5-5kHz and for the hearing-loss subjects: from 400Hz to 12kHz. fMRI data were acquired in a 3T scanner (Siemens Trio, 12ch head matrix, Serene Sound System of

Resonance Technology Corp.). Functional imaging sessions included three 9min20s EPI runs. There were 56 brain volumes acquired in one run in a sparse sequence (TR=10s, TA=2s, TE=30ms, FA=90, matrix 96x96x37, resolution 2x2x2mm, iPAT=2, no gap, ascending slice order, axial orientation flipped to exclude eyes). Auditory stimulation involved 8s FM tone bursts with central frequencies: 0.4, 0.8, 1.6, 3.2, 6.4kHz. All sounds were presented binaurally at 80dB(A) (Humphries et al, 2010). Statistical analyses were performed using SPM12 and in-house MATLAB algorithms. Subsequent steps involved: slice timing correction, realignment (with additional scrubbing when needed), coregistration with T1-iso images, segmentation of T1-iso images, normalization of T1-iso and EPI images, smoothing with a 4mm FWHM Gaussian kernel. Next, subject data were analyzed using GLM, by implementing time courses of all presented sounds compared to silence. One-sample t-test maps were produced for each tone burst (0.4, 0.8, 1.6, 3.2, 6.4kHz). Group t-test statistics were calculated for three study groups separately. Frequency-specific statistical maps were used to create parametric maps representing: winner-tests and maximum intensity projections at both individual and group-level. For each voxel and each tone burst an index was calculated corresponding to the weighted t-value in a voxel and its neighbors. Winner-tests compared index values of all sounds in a voxel and indicated the winning sound (central frequency), accommodating winning sounds in close neighbourhood. Only t-values corresponding to a significance level $p < 0.001$ (uncorrected) for individual maps and $p < 0.05$ (FWE) for group maps were used for comparisons. Mean and maximum percent of BOLD signal change in the PAC regions corresponding to each frequency as well as the size of these areas (no. of voxels) were compared between tinnitus and control groups (*two sample t tests*).

Results: Individual and group parametric maps revealed tonotopic organization of the PAC. Tone bursts involving low frequencies were represented along the Heschl gyrus. High-frequency sounds were represented radially and perpendicularly to the Heschl gyrus, in medial direction. A direct comparison of parametric maps reflecting tone bursts with central frequencies 0.4-6.4kHz failed to demonstrate any statistically significant differences between tinnitus patients and controls. NH had significantly ($p < 0.05$) higher (but still ≤ 25 dB) hearing thresholds in both left and right ear than C group for 3 up to 8 kHz. 3 kHz was the edge-frequency where the audiograms for both ears were the steepest in this group. A size of the right PAC area corresponding to 3.2kHz in NH was significantly ($t(1,35)=2.1$, $p < 0.05$) larger (407.5 ± 229.4) than in C group (267.4 ± 183.9). Analogously, a size of the left PAC region representing 3.2kHz in NH was significantly ($t(1,35)=2.87$, $p < 0.01$) greater (349.8 ± 190) than in C (201.8 ± 103.8). This effect was not observed between the HL and C subjects. There were also no significant differences between groups in mean and maximum BOLD signal change in the region corresponding to 3.2kHz.

Conclusions: Changes in tonotopic map organization might be observed in tinnitus and normal hearing individuals in the area corresponding to the edge-frequency in the audiogram (and to tinnitus pitch). The effect was not found for patients with tinnitus and hearing loss (≤ 50 dB) whose tinnitus pitch was also more varied. Further studies are needed to clarify the relationship between the edge-frequency in audiogram and its cortical representation in individuals with tinnitus.

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30 - RTMS FOR THE TREATMENT OF CHRONIC TINNITUS: OPTIMIZATION BY STIMULATION OF THE CORTICAL TINNITUS NETWORK

A. Lehner^{1*}, M. Schecklmann¹, T. B. Poepl¹, P. M. Kreuzer¹, V. Vielsmeier², B. Langguth¹
1Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany

2Department of Otorhinolaryngology, University of Regensburg, Regensburg, Germany

Background: Low-frequency repetitive transcranial magnetic stimulation (rTMS) of the auditory cortex has been shown to significantly reduce tinnitus severity in some patients. There is growing evidence that a neural network of both auditory and non-auditory cortical areas is involved in the pathophysiology of chronic subjective tinnitus. Targeting several core regions of this network by rTMS might constitute a promising strategy to enhance treatment effects.

Objective: This study intends to test the effects of a multisite rTMS protocol on tinnitus severity in comparison to a standard treatment protocol.

Methods: 50 patients with chronic tinnitus were randomized to either multisite stimulation (left dorsolateral prefrontal, 1000 stimuli, 20 Hz; left temporoparietal, 1000 stimuli, 1 Hz; right temporoparietal, 1000 stimuli, 1 Hz) or standard stimulation (left temporoparietal, 3000 stimuli, 1 Hz). Tinnitus severity was assessed using the Tinnitus Questionnaire at four time points: baseline, after the last treatment session (day 12) and after follow-up periods of three and six months. A change of tinnitus severity over time was tested using repeated measures ANOVA with the between-subjects factor treatment group.

Results: There was a significant effect of time meaning that there was a significant reduction of tinnitus severity over time irrespective of the treatment group. The interaction effect between time and group was not significant. At a descriptive level, both groups improved similarly from baseline to day 12. While a further reduction of tinnitus severity was perceived in the multisite group after 3 and 6 months, patients treated with standard stimulation worsened in the follow-up period. This development was not significant though but can only be seen on a descriptive level.

Conclusions: These data supports results from previous study which suggest that rTMS treatment is able to reduce tinnitus severity. However, multisite rTMS does not seem to be superior to single site treatment of the temporoparietal cortex.

31 – A Device System for Pairing Vagus nerve Stimulation (VNS) with tones for treatment of tinnitus

*B. Tarver *, C. Burrell, N. Engineer, R. Jain.
MicroTransponder Inc., 2802 Flintrock Trace, Suite 226
Austin, TX 78738*

Aims / Objectives: This poster is intended to describe the device system developed by MicroTransponder for use in treating disabling tinnitus. The intent is to give the reader sufficient information to understand the system and how it performs. A complete system will be available for demonstration at the poster sessions.

Methods: A 30-patient, randomized study funded by the NIH will complete enrollment in March, and will conclude by May 2015. This study utilizes the system described herein. The paired VNS system is an active implantable device that is comprised of five main components: (1) an Implantable Pulse Generator (IPG), (2) an implantable lead, (3) Tinnitus Application & Programming Software (TAPS) and (4) a wireless transmitter and (5) headphones for the patient to wear to listen to the tones. When used as intended the system provides a drug free way to treat chronic tinnitus by pairing tone therapy with Vagus Nerve Stimulation. The implantable portion of the system (IPG and lead) are implanted in an outpatient surgery that takes about 90 minutes to perform. After a neck and chest incision are made, the lead electrodes are attached to the left Vagus Nerve in the neck. The lead is tunneled from the neck to the chest incision (pectoral region), where it is connected to the IPG, and the IPG is surgically placed subcutaneously in the pectoral region. After the system is tested in the OR to verify proper operation, the incisions are sutured closed and the patient returns home after recovery. The software (TAPS) is delivered to the clinical site preloaded onto a laptop. The software, via the wireless transmitter, allows the audiologist to program the output settings of the IPG, including amplitude, frequency, and pulse width. The system simultaneously stimulates the vagus nerve while providing an audio tone that the patient hears through the headphones.

Both the tone and stimulation last ½ a second, and are provided approximately every 30 seconds for a 2.5 hour period (approximately 300 tones/stimulations are provided). After surgery and recovery, the patient returns for the audiologist to program the system settings and verify proper operation. The patient is then trained in proper use of the device to initiate daily stimulation at their own home. Patients are provided an easy to use computer system that only requires a few simple steps to operate.

Results: Daily device use and stimulation were well tolerated; compliance was very high (all patients met protocol criteria for compliance). Subjects typically had no significant issues using the device. Subjects typically repositioned the wireless transmitter if there were communication issues. No subject missed more than 3 consecutive days of device usage; all patients averaged over 5 days/wk of use.

Conclusions: The paired VNS for tinnitus system was practical, relatively easy-to-use, and provided therapy as intended for this 30-subject, pilot study. The system is expected to be utilized without significant changes in a pivotal study.

**32 - I KNOW WHAT YOU HEAR: OBJECTIFICATION AND DIFFERENTIAL
DIAGNOSIS OF VASCULAR PULSATILE TINNITUS BY TRANSCANAL SOUND
RECORDING AND SPECTRO-TEMPORAL ANALYSIS**

Jae-Jin Song¹, Gwang Seok An², Dirk De Ridder³, So Young Kim¹, Hyun Seok Choi¹, Joo Hyun Park⁴, Byung Yoon Choi¹, Ja-Won Koo¹, Kyogu Lee²

- 1. Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seongnam, Korea.*
- 2. Music and Audio Research Group, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea.*
- 3. Unit of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand.*
- 4. Department of Otorhinolaryngology-Head and Neck Surgery, Dongguk University Ilsan Hospital, Goyang, Korea.*

Objectives: Although the symptoms are frequently classified as “objective tinnitus”, in most cases vascular pulsatile tinnitus (VPT) is not equal to objective tinnitus because it is typically not easy to objectively document VPT. Thus, the present study developed a novel transcanal sound recording and spectro-temporal analysis method for the objective and differential diagnosis of VPT.

Methods: This method was tested using six VPT subjects and six normal controls based on recordings obtained from the ipsilateral external auditory canal (EAC) using an insert microphone with the subject’s head in four different positions: 1) neutral head position, 2) head

rotated to the tinnitus side, 3) head rotated to the non-tinnitus side, and 4) neutral position with manual compression of the ipsilateral carotid artery. The control group underwent the same measurements. The recorded signals were first analyzed in the time domain, and short-time Fourier transform (STFT) was performed to analyze the data in the time-frequency domain.

Results: On temporal analysis, the ear canal signals recorded from the VPT subjects exhibited large peak amplitudes and periodic structures, whereas the signals recorded from the control subjects had smaller peak amplitudes and weaker periodicity. On spectro-temporal analysis represented by 3-dimensional waterfall diagrams, all of the VPT subjects demonstrated pulsesynchronous, mutually exclusive, acoustic characteristics that were representative of their respective presumptive vascular pathologies, whereas the control subjects did not display such characteristics.

Conclusion: The present diagnostic approach may provide additional information regarding the origins of particular VPT cases as well as an efficient and objective diagnostic method. Furthermore, this approach may aid in the determination of appropriate imaging modalities, treatment planning, and evaluation of treatment outcomes. Future studies with a larger sample size, diverse etiologies, and more refined recording techniques are warranted.

POSTER SESSION 4 TUESDAY, JUNE 9, 2015

33 - Transdermal-Induced Auditory-Somatosensory Stimulus Timing Dependent Plasticity in Dorsal Cochlear Nucleus

Calvin Wu¹, David T. Martel^{1,2}, Susan E. Shore^{1,2,3}

*1 Kresge Hearing Research Institute, Department of Otolaryngology,
University of Michigan, Ann Arbor, MI*

2 Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI

*3 Department of Molecular and Integrative Physiology, University of Michigan, Ann
Arbor, MI*

The cochlear nucleus (CN) is the first site of multisensory integration in the ascending auditory pathway. The principal output neurons of the dorsal CN (DCN), fusiform cells, receive somatosensory information relayed by the granule cells from the trigeminal and dorsal column pathways. Fusiform cells integrate somatosensory and auditory nerve fiber inputs via long-term potentiation (LTP) or long-term depression (LTD) in a manner consistent with stimulus timing dependent plasticity (STDP). In the present study, we evoked both Hebbian (LTP when somatosensory stimuli precede auditory stimuli and LTD when auditory stimuli precede) or anti-

Hebbian STDP in the guinea pig fusiform cells via paired auditory and transdermal electrical stimulation on the facial and neck regions. LTD and LTP persisted for 1–3 hours after bimodal stimulation, and follow STDP timing rules. Varying auditory stimulus duration, but not somatosensory stimulus location, changed STDP polarity: when 50 ms pairing tones were used, STDP were predominantly Hebbian, while pairing tones of 10 ms evoked predominantly anti-Hebbian plasticity. This inversion of LTD and LTP was strongly correlated with spike duration. Furthermore, as a proof-of-principle, this study demonstrates that transdermal manipulations using precise auditory-somatosensory timing parameters can non-invasively induce LTP or LTD in fusiform cells. In particular, LTD induction may be harnessed to alleviate tinnitus-related hyperactivity in DCN.

34 - Stimulus-timing-dependent modifications of rate-level functions in animals with and without tinnitus.

Roxana A. Stefanescu¹, Seth D. Koehler², Susan E. Shore³

1Kresge Research Institute, Department of Otolaryngology, University of Michigan Medical School, Ann Arbor, Michigan.

2Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland.

3Kresge Research Institute, Department of Otolaryngology, Department of Molecular and Integrative Physiology, Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan.

Tinnitus has been associated with enhanced central gain manifested by increased spontaneous activity and sound-evoked firing rates of principal neurons at various stations of the auditory pathway. Yet, the mechanisms leading to these modifications are not well understood. In a recent *in vivo* study, we demonstrated that stimulus-timing-dependent bimodal plasticity mediates modifications of spontaneous and tone-evoked responses of fusiform cells in the dorsal cochlear nucleus (DCN) of the guinea pig. Fusiform cells from sham animals showed primarily Hebbian learning rules while noise-exposed animals showed primarily anti-Hebbian rules, with broadened profiles for the animals with behaviorally verified tinnitus (Koehler SD, Shore SE. *J Neurosci* 33: 19647-19656, 2013a). In the present study we show that well-timed bimodal stimulation induces alterations in the rate-level functions (RLFs) of fusiform cells. The RLF gains and maximum amplitudes show Hebbian modifications in sham and no-tinnitus animals but anti-Hebbian modifications in noise-exposed animals with evidence for tinnitus. These findings suggest that stimulus-timing bimodal plasticity produced by the DCN circuitry is a contributing mechanism to enhanced central gain associated with tinnitus.

35 - Identifying neural changes linked to tinnitus using the post-auricular muscle reflex
Wilson CA, Berger JI, Coomber B, Carver A, Turner WG, De Boer J, Sereda M, Palmer AR & Wallace MN

MRC Institute of Hearing Research, Nottingham, UK

A commonly-used behavioural test for tinnitus in animals – gap-induced pre-pulse inhibition of acoustic startle (GPIAS) - relies on a short gap in continuous background noise providing a cue to inhibit the response to a loud startling stimulus. Impaired GPIAS following tinnitus induction has been shown in a number of species, as well as in humans with tinnitus. The impairment was originally thought to be caused by tinnitus ‘filling in’ the gap but there have been suggestions that another mechanism is involved. Preliminary work in humans measuring GPIAS of eye blink responses showed gap detection deficits in tinnitus subjects, but the underlying mechanisms of this effect were unclear (1). The eye blink response has a relatively long latency (>40 ms) that is subject to attentional modulation and not specifically linked to the auditory system.

We have developed a variation of the GPIAS method in which we measure GPIAS using the reflex pinna movement in guinea pigs. The post-auricular muscle reflex (PAMR) is the human analogue of the pinna reflex and may represent a possibility for developing an objective tinnitus test for the clinic. The PAMR is a short-latency (10-12 ms) response that involves two or three synapses in the brainstem and is more tightly linked to auditory input and less susceptible to attentional modulation. However, gap-induced pre-pulse inhibition (PPI) of the PAMR has not previously been demonstrated.

In the present study, we measured gap-induced PPI of the PAMR in eleven normal-hearing subjects. PAMR responses were recorded electromyographically with surface electrodes placed over the insertion of the post-auricular muscle to the pinna. Gap detection was evaluated with 1 kHz background sounds, presented monaurally to the right ear at 60 or 70 dB SPL, and startling stimuli comprising very brief broadband noise bursts presented at 90 - 105 dB SPL. Eye direction has been shown to have a dramatic effect on the amplitude of the PAMR reflex (2). Therefore we investigated the effect of eye position – looking forward or to the right – on the amplitude of the PAMR reflex response. Preliminary data suggest that the PAMR is susceptible to gap-induced PPI, and the amplitude of the response is greater when the subject is looking to the stimulus presentation side. Future studies will examine further the parameters that affect gap-induced PPI of the PAMR, and subsequently establish whether deficits in gap detection using the PAMR are characteristic of subjects with tinnitus.

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36 - AUDITORY EVOKED MAGNETIC FIELD SIGNATURES OF DYNAMIC RANGE ADAPTATION OF LEVEL CODING: RELEVANCE TO TINNITUS AND HYPERACUSIS

A. Hassel¹, M. Andermann², B. Cramer¹, H. Riedel², A. Rupp², E. Diesch¹

1Central Institute of Mental Health, Department of Clinical and Cognitive Neuroscience, University of Heidelberg, J5, 68159 Mannheim, Germany

2Department of Neurology, Section of Biomagnetism, University Hospital Heidelberg, Heidelberg, University of Heidelberg, Germany

Introduction: Across natural settings, the level of acoustic signals varies over the very wide range of approximately 120-140 dB. The dynamic range of auditory system neurons is much smaller, typically between 20 and 40 dB. Animal studies show that the auditory system handles the conflict between sensitivity and accuracy arising from this mismatch by dynamically adjusting the response range of single neurons (Dean et al. 2005). Here we investigate if dynamic range adaptation of sound level coding may be demonstrated in auditory evoked magnetic field recordings.

Methods: The magnetic auditory middle latency response was recorded in healthy subjects. Tone pips with a frequency of 2000 Hz and a duration of 25 ms were presented binaurally. The SOA was 125 ms. Two stimulus levels were presented under both fixed and roving conditions. Stimulus level was either high or low in fixed blocks and alternated randomly in roving blocks. The averaged response was fitted to a source montage with temporal, frontal, central, parietal, and occipital sources. Source amplitude was integrated across an analysis window from 10 to 85 ms post stimulus. In a second study, the steady-state auditory evoked magnetic field was recorded in healthy subjects. An amplitude-modulated tone with a 40 Hz modulation frequency was presented continuously. Every 2000 to 2200 ms the stimulus changed in level. The difference between levels was 18 dB and the transition period duration was either 500 ms or 125 ms. The steady-state response (SSR) was recovered by bandpass filtering. A bilaterally symmetric spatiotemporal two-dipole source model was fitted to the response and its envelope amplitude was computed from the dipole moment time series using the Hilbert transform.

Results: In the middle latency study, response amplitude was larger for high than for low level stimuli. For temporal sources, response amplitude was larger in the roving than the fixed presentation condition and the response amplitude difference between high and low level was larger in the roving than the fixed condition. In the steady-state study, response amplitude tracked stimulus level. There was an amplitude overshoot effect following low-to-high level transitions and an amplitude undershoot effect following high-to-low level transitions. These effects were more pronounced for the 125 ms than for the 500 ms transition period.

Conclusions: The dynamic range adaptation hypothesis predicts high sensitivity for the fixed low level condition, low sensitivity for the fixed high level condition, and intermediate sensitivity for the high level/low level roving condition. The interaction effect obtained in the middle latency study corresponds to this hypothesis. Furthermore, the overshoot and undershoot effects observed in the steady-state study fit the hypothesis that the process of

dynamic range adaptation takes a few hundred milliseconds to complete. Given the reduction of inhibitory processes in tinnitus and the gain increase at several stages of the auditory system (Diesch et al. 2010), the question arises if dynamic range adaptation of sound level coding may also be compromised. We hypothesize that dynamic range adaptation paradigms might be usefully deployed to the study of tinnitus and hyperacusis.

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Diesch E, Andermann M, Flor H, Rupp A. *Neuroscience* 2010; 167: 540-553.

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37 - THE EFFECT OF PHYSICAL THERAPY TREATMENT IN PATIENTS SUFFERING FROM CERVICOGENIC SOMATIC TINNITUS

Michiels S., De Hertogh W., Truijen S., Van de Heyning P.

University of Antwerp (Universiteit Antwerpen)

Department of Rehabilitation Sciences and Physiotherapy

Universiteitsplein 1

2610 Wilrijk (Antwerp)

Belgium

Background/Aims: Tinnitus can be related to many different aetiologies such as hearing loss or a noise trauma, but it can also be related to the somatosensory system of the cervical spine. The objective of this study was to investigate the effect of a standardized physical therapy treatment protocol on cervicogenic somatic tinnitus (CST) and to identify a subgroup within the tinnitus population that benefits most from this physical therapy treatment.

Methods: Patients with severe subjective tinnitus (Tinnitus Functional Index(TFI) 25-90 points), in combination with neck complaints (Neck Bournemouth Questionnaire(NBQ) > 14 points) were included. Exclusion criteria: tinnitus with clear otological aetiologies, severe depression, traumatic cervical spine injury, tumors, cervical spine surgery or conditions in which physical therapy is contra-indicated. Patients were randomized in an immediate-start therapy group and a group with a delayed start of therapy by 6 weeks to create a control group. The immediate-start and delayed-start patients received a physical therapy treatment directed to the cervical spine of 12 sessions of 30 minutes during six weeks. TFI, NBQ and global perceived effect (GPE) were collected at baseline, after six weeks wait-and-see in the delayed-start group, immediately after the last treatment session and 6 weeks after the last treatment session. A set of cervical biomechanical and sensorimotor tests was performed at baseline and 6 weeks after the last treatment session.

Results: In total, 40 patients were included in the study. Immediately after treatment, the average TFI-score decreased significantly ($p=0.04$) but increased again six weeks after the last treatment session. The NBQ-score decreased significantly directly after treatment ($p<0.001$)

and maintained after 6 weeks follow-up ($p=0.001$). In week 6 of the study, a substantial improvement of the tinnitus was present in 58% of the immediate-start group compared to no improvement in the delayed-start group. Patients suffering from low-pitched tinnitus are significantly more likely to benefit from the applied treatment than patients suffering from high-pitched tinnitus (87% versus 48%) ($p=0.04$). When combining the low-pitched tinnitus with the 'increase of tinnitus during inadequate postures during rest, walking, working or sleeping', a group of patients could be identified that all experienced substantial improvement of their tinnitus immediately after treatment and after 6 weeks follow-up. Co-variation of tinnitus and neck complaints was present in 49% of the study population. The co-varying group had significantly lower TFI-scores after treatment ($p=0.001$) and after 6 weeks follow-up ($p=0.03$).

Conclusions: After treatment, the TFI and NBQ decreased significantly and a substantial improvement of the tinnitus was present in week 6 in 58% of the immediate-start group compared to no improvement in the delayed-start group. The presence of co-variation between tinnitus and neck complaints, a low-pitched tinnitus and 'increase of tinnitus during inadequate postures during rest, walking, working or sleeping' have proven to be good predictors for TFI decrease after physical therapy treatment directed to the cervical spine.

38 - Short-term reduction in tinnitus percept following compensatory auditory stimulation

Simon Henin¹, Dovid Fein¹, Eric Smouha², Lucas C. Parra¹

1. Department of Biomedical Engineering, City College of New York, 160 Convent Avenue, New York, New York 10027, USA

2. Department of Otolaryngology–Head and Neck Surgery, Mount Sinai Medical Center, New York, NY, USA

The perception of tinnitus correlates with elevated hearing thresholds and reduced cochlear compression. We hypothesized that reduced peripheral input leads to elevated neuronal gain, resulting in the aberrant percept. The aim of this study was to test whether compensating for these peripheral deficits could reduce the tinnitus percept. To further enhance the effects on neuronal gains we paired this intervention with transcranial direct current stimulation (tDCS), which is thought to boost neuronal plasticity. A randomized sham-controlled single-blind pilot study was conducted combining compensatory auditory stimulation (CAS) with tDCS in a 2x2 cross-over design. CAS was adapted to each subject's individual audiogram. Each intervention lasted 20 minutes and outcome measures included minimum masking level and visual analog scale assessed immediately before and after. In a cohort of 15 clinical tinnitus patients, CAS significantly reduced tinnitus severity as measured by the minimum masking level but not the visual analog scale. Contrary to prior reports, tDCS in isolation was not effective, nor did it improve the effects of CAS. Since CAS in this study used natural stimuli, it can be delivered on a continuous basis much like hearing aids. The present results suggest that careful tuning of gain and compression may alleviate tinnitus in a clinical population.

39 - **PHYSIOLOGICAL CHARACTERISTICS OF MULTIPLE AUDITORY FIELDS IN THE TINNITUS ANIMAL MODEL**

E. Buell, M. Borland, N. Moreno, P. Sharma, C. Lane, M. Pantalia, M. Buell, M. Kilgard
University of Texas at Dallas, School of Behavioral and Brain Sciences, 800 W. Campbell Rd.,
Richardson, TX 75080

Specific Aim: To test the hypothesis that hyperactivity in cortical regions outside of A1 is associated with the rat model of tinnitus.

Tinnitus is associated with abnormal activity throughout the central auditory system and in many non-auditory structures¹ (Salvi et al. 2000). The proposed experiments will test the hypothesis that tinnitus is an emergent property of pathological neural activity in multiple brain regions. Recordings were made in inferior colliculus and two non-primary auditory fields (AAF & PAF).

Materials and Methods

Subjects

Fifteen female adult Sprague-Dawley rats were used in this study. Seven were noise-exposed as part of the experimental group and eight remained naïve for the control group.

Auditory Brainstem Recordings

Auditory brainstem recordings (ABRs) were recorded using custom headcap electrodes, BRAINWARE v8.12 (Tucker-Davis Technologies), and a speaker (Motorola model #40–1221). Recording and reference screws were placed over cerebellum and cerebral cortex.

Tinnitus Testing

The behavioral correlate of tinnitus was determined using the Turner Gap Detection Method. A 50 ms silent gap inserted into the narrowband noise (8, 10, 16 kHz and broadband noise) 100 ms before a 100 dB noise burst. Animals pass the task when they are able to detect the silent gap. Animals are placed in “Tinnitus” group when they fail the task/are unable to detect the gap for 2+ consecutive weeks.

Anesthetized Recordings

Four parylene coated tungsten microelectrodes (1–2 M Ω , FHC, Bowdoin, ME) record neuron responses from layer 4/5 of the right primary auditory cortex in barbiturate anesthetized rats. We obtained 839 sites in experimental group (7 rats) and 939 sites in naïve group (8 rats). Inferior colliculi recordings were obtained by drilling 9 mm posterior and 1.5 mm lateral of Bregma. The stimuli used to generate neural responses consist of 1,296 tones at 81 frequencies (1 to 32 kHz) and 16 intensities (0 to 75 dB)

Current Results

Our current data suggests that there are significant increases in spontaneous activity for tinnitus in all fields except the anterior field in tinnitus animal models. Excitability (driven

spikes) does not currently show significance as in previous experiments, which indicates more data is needed before forming conclusions. Both the posterior field and inferior colliculus show significant shifts in tonotopicity.

Conclusions Results from A1 are consistent with research citing cortical changes in response to noise-exposure and tinnitus. 2 □ Significant reorganization in characteristic frequency. □ Significant increase in spontaneous firing rate. Auditory Brainstem Responses indicate profound losses at high frequencies (32 kHz), moderate losses at mid-frequencies (10-16 kHz), and no loss at low frequencies (4kHz). Hearing loss at tinnitus frequency is consistent with what is often seen clinically. The anterior shows significant changes in latency and bandwidth only. The posterior field shows changes in tonotopicity, which is consistent with previous work demonstrating this field's susceptibility to shifts. Inferior colliculus data indicates tonotopic changes, as well.

References

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40 - PREFERENCE OF TONE TYPES FOR AUDIOMETRIC TESTING BY PATIENTS WITH TINNITUS

*Short, C., Walker, M., Skinner, K. & Lentz, J.
Indiana University Bloomington
Department of Speech and Hearing Sciences
200 South Jordan Avenue
Bloomington, IN 47405*

Objective: For audiometric testing, ASHA recommends using pulsed or warbled tones when testing patients who report tinnitus. Although research supports the use of pulsed tones in tinnitus patients, there is relatively little work on warble tones. To explore the utility of warble tones in testing patients with tinnitus, this study takes first steps to determine 1) which of the tone types (continuous, pulsed, or warble) is most preferred by patients with and without tinnitus, and 2) which yields the lowest audiometric thresholds. We also evaluated 3) if thresholds are similar for the different tone types and 4) whether the preferred tone type leads to the lowest thresholds.

Methods: Using mixed factorial design, audiograms with a 2-dB step size were collected from 20 study participants (10 with tinnitus; 10 without tinnitus) using steady, warble, and pulsed tones in randomized order. Group membership was determined by the presence or absence of tinnitus, and all subjects were tested on each tone type, yielding the within subjects measure. After testing with each tone type, participants completed a questionnaire concerning each

tone's level of appeal, the difficulty faced when listening for the tone, and a rating of the how much the participant liked the tone. Participants also completed a final comprehensive questionnaire determining overall tone type preference.

Results and Conclusions: Preliminary analyses indicate that participants most preferred pulsed, followed by warbled, then steady tones. This trend was present for both groups of subjects, with the presence of tinnitus having little effect on the preferred tone type. Continuous tones tended to yield better thresholds by 5-8 dB, even though they were the least-preferred by participants. Our preliminary conclusions support ASHA's recommendation that pulsed tones are preferred by listeners with tinnitus, but steady tones may yield better audiometric results. Warble tones may be a viable option if the other two types are unsuccessful, but our data indicate little benefit to using them over either pulsed or steady tones for audiometric testing.

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41 - **Multimodal Synchronization Therapy: Exploring the effects of pinna stimulation**

Cory D. Gloeckner¹, Craig D. Markovitz¹, Benjamin T. Smith¹, Robert J. Hughes¹, Hubert H. Lim^{1,2,3}

1. Department of Biomedical Engineering, University of Minnesota, USA

2. Department of Otolaryngology - Head and Neck Surgery, University of Minnesota, USA

3. Institute for Translational Neuroscience, University of Minnesota, USA

Objectives: We propose a noninvasive approach, which we call Multimodal Synchronization Therapy (mSync), for treating tinnitus. mSync attempts to activate multimodal brain centers using sensory, motor, cognitive and limbic pathways with precise timing to modulate auditory neurons driving the tinnitus percept. In our previous work, we combined broadband noise and somatosensory electrical stimulation in animals that led to facilitation or suppression of auditory activity depending on inter-stimulus timing and body stimulation location. Since the previous study did not include pinna stimulation, we further investigated the effect of inter-stimulus timing between acoustic and pinna stimulation on spiking activity within the auditory cortex, a region linked to the tinnitus percept.

Methods: We positioned a 32-site electrode array in the right primary auditory cortex (A1) of 16 ketamine-anesthetized guinea pigs and compared spontaneous and acoustic-driven activity before and after different mSync and control paradigms. Needle electrodes were used to electrically stimulate the left pinna, right pinna, and right mastoid. Each location was paired with broadband noise stimulation presented to the left ear with varying inter-stimulus delays (single electrical pulse relative to acoustic onset: -25 to +25 ms in 10 ms steps). The right mastoid condition was included in order to compare the results with our previous experiments, and the acoustic only condition was included as a control case.

Results and Conclusions: The results were consistent with those from our previous experiments in which mSync induced greater modulatory effects compared to the acoustic only condition (and compared to the body only and no stimulation conditions obtained from the previous experiments). Interestingly, the left and right pinna conditions induced greater modulatory effects compared to the mastoid condition. Varying inter-stimulus delays also altered the ratio of suppression versus facilitation for pinna stimulation. These results suggest that varying mSync parameters, such as inter-stimulus delay and specific ear regions, can differentially alter auditory neurons and potentially modulate the tinnitus percept. Further studies are needed in an awake and tinnitus animal model to verify the therapeutic effects and corresponding neural effects of mSync.

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42 - TINNITUS - EVIDENCE FOR THE EXISTENCE OF A CENTRAL MASTER CLOCK? A PHYSICIST EXPLAINS HIS THOUGHTS.

Hampton P.J.

Worcester, UK

Objective: To consider possible answers to ‘Twelve Child-like Questions’ and postulate a viable physical mechanism for Tinnitus.

1. How does the Auditory System play its part in the early warning against predators?
2. Why are the Semi-Circular Canals (SCCs) of the Vestibular System (VS) located on each ear?
3. Why is the Cochlea snail shaped?
4. Why is the Basilar Membrane (BM) and Organ of Corti (OC) tapered along its length?
5. Why is the width of the BM so narrow?
6. If each Cochlea contains a bank of audio ‘Analogue to Temporal Code Convertors’ (ATCCs), do these need a sampling clock signal to function?
7. How does the brain measure inter-aural time differences (ITDs)?
8. Why are the Outer Hair Cells (OHCs) of the Cochlea arranged in four fairly neat rows?
10. Why are the Stereocilia of the OHCs embedded in the tectorial membrane (TM)?
11. Why are the Stereocilia of each OHC arranged in a W – formation?
12. Why does Tinnitus heard after a loud concert (often) go away after a while?

Methods:

1. A thorough reading of relevant literature.
2. Attending TRI conferences and ITS seminars, and asking such questions of many of World Class Researchers.
3. Considering how a team of engineers and physicists could produce a working autonomous entity with the functionality of the human auditory, vestibular and visual systems with respect to self-navigation, locomotion and aversion to danger.

Results: Some possible responses to the ‘twelve child-like questions’ are discussed in the oral presentation.

Conclusion: It seems there is plenty of circumstantial evidence to support a need for a central neural clock. For localisation of sounds such a clock, operating at a frequency above the highest BM characteristic frequency (CF), would be a huge asset. A similar sampling frequency would give the auditory system the fine-grain resolution it clearly possesses and would also enable the cochlear amplifier to utilise a parametric upconversion process to achieve gain at the CF despite the constraints of the relatively narrow lateral BM/OC fibres. If the sampling clock signal is supplied by the OHCs then the sampling frequency should be above twice the highest operating frequency of these cells. For many reasons an upper sampling frequency limit of around 24 kHz seems reasonable. Simple calculations concerning the dimensions of the basilar membrane would appear to make this seem probable. At the very least GPs and ENTs can tell tinnitus sufferers that there is now a theory on the table which says that tinnitus is simply the auditory system working in a 'safe mode' (sampling at a sub-harmonic of the normal sampling frequency) due to some OHC damage, and that the alternative would be a greater degree of deafness. Now it is over to you researchers to find out if this really is what is happening.

43 - Acute Autonomic, Endocrine, and Immune Stress-Related Responses in Tinnitus.

*Alsalman, O; Suckfüll, M; Dobie, R; Althaus, M; Ellers-Lenz, B; Russ, H; Csikós, J
University of Texas at Dallas*

The empirical and systematic implications of the physiological processes underlying an individual's experience with tinnitus are not yet fully understood. Individual differences in reaction to stressful situations can be detected in the visceral nervous system, adrenal cortical secretions, and activation of the immune system. This study examined whether baseline measures of stress related biomarkers are greater in male subjects with tinnitus; and whether the reactivity of these stress-related biomarkers are also greater in male subjects with tinnitus when compared to healthy controls.

We measured specific endocrine (measured by cortisol), immune (measured by neopterin) and visceral (measured by salivary alpha amylase) secretions in response to an induced-stress task. Saliva essays for cortisol, alpha-amylase, and neopterin were collected pre and post induced stress task at four different time intervals. Our results demonstrated differences in alpha-amylase (sAA) reactivity in the tinnitus group at baseline measures as well as 30 and 60min posttest when compared to the healthy controls.

In furtherance, the main effect of a group of participants achieved statistical significance, while the main effect of the time and interaction between the time and the group did not achieve statistical significance; suggesting that sAA responses to acute stress are not immediate but rather prolonged in the tinnitus group.

A spearman's correlation was run to determine the relationship between the perceived stress scale and sAA. There was a negative correlation between the PSS and sAA ($r = -.530$, $p = .016$).

Furthermore, other stress related biomarkers of the immune (measured by neopterin) and adrenal cortical secretion (measured by cortisol) yielded no statistical significance. Future research should therefore further consider the role and underlying mechanisms of stress related biomarkers in response to tinnitus-related distress. In conclusion, the results of this study demonstrated the feasibility of utilizing acute autonomic, endocrine, and immune stress related responses as objective biological markers of tinnitus-related distress.

44 - Coexistence of Tinnitus and Somatosensory Vertigo- Clinical Implications

**Pawlak-Osinska, K; Kazmierczak, H
Nicolaus Copernicus University, Poland*

The goal of the study was to observe the coexistence of tinnitus and vertigo of somatosensory origin. The authors were interested in searching for differences between tinnitus with and without the accompanying pathology of the somatosensory pathway.

Material: Two groups were selected among the patients suffering from tinnitus and diagnosed at the ORL Department since the beginning of 2015: Group I with tinnitus accompanied by pathological somatosensory evoked potentials (SEP) and Group II with tinnitus and normal recording of SEP. The patients from Group I additionally suffered from vertigo, which was confirmed as somatosensory on the basis of detailed otoneurological study – VNG, cVEMP, oVEMP, VEP, SEP, vHIT, posturography. The only abnormality was that of somatosensory projection, with no signs of both labyrinths or visual system pathology. Both groups consisted of 30 patients.

Method: The comparison of age, detailed characteristic of the tinnitus, pathology in videonystagmography (VNG) and presence (with location) of cervical arthrosis were performed. In Group I, the pathology of somatosensory evoked potentials was analyzed (in Group II no disturbances of SEP were present).

Results: The age of the patients in Groups I and II was similar: 50,0 and 51,4y. In Group I, everybody except for 9 persons demonstrated cervical arthrosis: the pathology of C5-C6 prevailed. In Group II, the majority of patients (18) had no cervical pathology; if it existed – the location was at C5-C6 and C6-C7 equally. In Group I, SEP demonstrated abnormal latency of P11 together with prolonged latency of N13 (16 persons), then pathology of solely N13 (7 cases); pathology of only P11 was observed in 1 person, there was no pathology of P27. The characteristic of tinnitus was as follows: significantly greater intensity in Group II (13dB above the audiometric hearing level versus 20,2dB), higher pitch in Group I (2776,7Hz versus 1933,0Hz), slightly greater irritation in Group I (6,8 versus 6,2 according to 10 steps scale), definitely worse masking in Group II. Interestingly, VNG revealed accompanying unilateral weakness of the labyrinth in the caloric test in Group II in 8 patients, while there was no strictly peripheral vestibular pathology in Group I (according to diagnosis of vertigo of somatosensory origin). In Group I, the directional preponderance in rotatory test, hypersensitivity in caloric test

and a great number of square waves during cervical test and positional test were observed.

Conclusions: The tinnitus group with accompanying somatosensory pathway pathology revealed to be different from tinnitus patients with no SEP pathology. Firstly, the cervical arthrosis was nearly obligatory in the somatosensory group and it probably was the main source of somatosensory pathology, generated at the cervical, not intracranial level. The vestibular signs such as directional preponderance – the indicator of unbalance of vestibular system (here: due to disturbed signals from its somatosensory component) –, hypersensitivity (the lack of proper vestibular integration and control) and plenty of square waves in VNG recording of cervical test may be helpful in the diagnosis of the somatosensory (cervical) tinnitus. The somatosensory group seems to need a different treatment for tinnitus: they are more sensitive to masking, and cervical rehabilitation together with neurostimulation of somatosensory pathway should be the essential part of the therapy.

POSTER SESSION 5 WEDNESDAY JUNE 10, 2015

45 - PREVALENCE OF TINNITUS AND/OR HYPERACUSIS IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW

S. Nemholt (1), J.H. Schmidt (2), N. Wedderkopp (3), D. M. Baguley (4)

(1) Institute of Clinical Research, University of Southern Denmark, The Social Division, Capital Region of Denmark, and Department of Audiology, Odense University Hospital, Odense, DK.

(2) Department of Audiology, Odense University Hospital, Department of ENT Head and Neck Surgery, Odense University Hospital and Institute of Clinical Research, University of Southern Denmark, Odense, DK.

(3) Sport Medicine Clinic, Orthopedic Department, Hospital of Lillebaelt Institute of Regional Health Service Research and Center for Research in Childhood Health University of Southern Denmark. Odense DK

(4) Department of Audiology Cambridge University Hospitals, Cambridge UK And Department of Hearing and Vision Sciences, Anglia Ruskin University, Cambridge UK

Aims/Objectives: To find possible explanations for the high degree of variation between different epidemiological studies in regard to the question: “Is the prevalence of tinnitus and/or hyperacusis in children/young people (aged 5 to 19 years) higher in individuals, who have either hearing loss, psychological conditions or have been noise exposed in relation to children where these factors are not known?” The aims are to assess the degree of variation among prevalence studies of tinnitus and hyperacusis in children, and to provide a synthesis of prevalence data. We will conduct a systematic review of published studies to address the following objectives:

- To systematically review studies of the epidemiology of tinnitus and hyperacusis in children and young people in order to establish the reported prevalence estimates.
- To determine factors implicated in the variability of estimates, including those deriving from definitions.
- To investigate which methodological factors may determine differences in prevalence estimates

Since the variable “severity” is generally less reported than “perception”, the prevalence of chronic bothersome tinnitus and/or hyperacusis will be explored when possible.

Methods: Methods for this systematic review have been developed according to recommendations from the PRISMA checklists and the PRISMA Flow Diagram will be used to describe the flow of information through the different phases of the systematic review. Electronic searches has be conducted in the databases PubMed, EMBASE and SCOPUS. Primary and additional outcomes will be the prevalence of tinnitus/hyperacusis and the severity, respectively. The study is PROSPERO registered (1) and a study protocol has been published. (2) The study protocol has the definition of checklist items, including a descriptive checklist, a quality checklist and a results checklist.

Results: At this point the data extraction has been done. After removal of duplicates the electronic searches provided 967 references. Out of these 105 articles have been selected for full text analysis, as they may be relevant to the systematic review.

Discussion: Many of the studies included are heterogeneous, and they are therefore difficult to compare directly.

(1): This review protocol is registered in the PROSPERO International Prospective Register of Systematic Reviews, registration number CRD42014013456.

(2): Nemholt S, Schmidt JH, Wedderkopp N, Baguley DM. Prevalence of tinnitus and/or hyperacusis in children and adolescents: study protocol for a systematic review. *BMJ Open* 2015;5:1 e006649 doi:10.1136/bmjopen-2014-006649

46 - HYPERACUSIS IN ATHLETES WITH SPORT-RELATED CONCUSSIONS BEYOND THE ACUTE RECOVERY PHASE

*Hébert, S.; Assi, H; Alarie, C; Moore, RD; Turgeon, C. & Elleberg, D.
Université de Montréal*

Background/aims: Sport-related traumatic brain injuries or concussions are a major public health problem, with an estimated 1.6 to 3.8 million injuries each year in the United States. One consequence of concussion is noise hypersensitivity, which has been found to be an early predictor of post-concussive syndrome. Although auditory processing in sport-related concussion has been investigated, no study has objectively tested sound intolerance or loudness growth. Accordingly, the aim of this study was to examine noise sensitivity in

concussed athletes beyond the acute phase of recovery using psychoacoustical loudness functions.

Methods: Thirty-five collegiate athletes (20 concussed, age = 21.8, range 16-30; 15 controls age = 22.5, range 20-28, not different in age or education) with normal hearing were recruited from university sport teams. Concussed participants were on average 8.2 weeks from their injury. All participants completed a battery of questionnaires that assessed noise sensitivity, symptoms of depression and of anxiety. Participants were then tested on an adaptive psychophysical loudness function task, which identifies six boundaries lying between seven loudness categories : Inaudible, Very soft, Soft, OK, Loud, Very loud and Too loud. Trains of three frequency-modulated 4-kHz tones are presented at different levels and participants judged each trial using the above loudness categories. The task stopped when five 1-dB steps reversals were completed for all boundaries.

Results: Results revealed highly significant differences between groups on loudness categories from OK/Loud to Intolerance thresholds (p s between .01 and .002), symptoms of depression ($p=.03$) and marginally on noise sensitivity questionnaire ($p = .058$) but not on anxiety ($p=.97$). Intolerance thresholds were highly negatively correlated with noise sensitivity and depressive symptomatology (all p s <.003) whereas noise sensitivity was positively correlated with anxiety ($p<.001$).

Conclusions: These findings suggest the presence of hyperacusis in concussed athletes, and that this hypersensitivity to sounds tends to persist beyond the acute phase of recovery.

47 - Dissociating Mechanisms of Tinnitus and Hyperacusis: A Survey and a Behavioral Study

Jenise Chappell

University of Illinois at Urbana-Champaign

The broad objective of this research design is to improve understanding of mechanisms of hyperacusis and tinnitus generation. Our aims are to (1) identify the cooccurrence of tinnitus and hyperacusis and (2) identify the common otoacoustic emission (OAE) correlates that underlie both tinnitus and hyperacusis. We hypothesize that, in agreement with current literature, a high percentage of subjects with tinnitus (approximately 40-79%) will also report hyperacusis complaints and the generation of tinnitus and increased sensitivity to sound share a common physiological pathway. A two part study will be conducted. In order to meet our first aim, inclusionary surveys will be issued using Survey Monkey website to assess both global and local population of individuals with tinnitus who also experience hyperacusis. Survey respondents, within driving distance to the testing site at University of Illinois, may choose to self-disclose their tinnitus, hearing and hyperacusis status. Thereafter, an audiological assessment, OAE testing, and behavioral experiment will be conducted for those meeting

inclusionary criteria. Experimental subjects will be divided into 4 groups, those with: 1) hyperacusis and normal hearing, 2) tinnitus and normal hearing, 3) hyperacusis, tinnitus, and normal hearing, and 4) a control group without tinnitus or hyperacusis. Test subjects with tinnitus will complete additional testing to assess their tinnitus perception. Investigation of DP levels will assist in identifying similarities or differences in the generation of tinnitus and hyperacusis. The long-term goal of the research study is to establish guidelines to assist in the appropriate fitting of hearing aids for patients with tinnitus and/or hyperacusis and to undertake brain imaging to dissociate neural correlates of tinnitus from those of hyperacusis in the normal hearing population.

48 - HYPERACUSIS QUESTIONNAIRE AS A TOOL FOR MEASURING HYPERSENSITIVITY TO SOUND IN A TINNITUS RESEARCH POPULATION

M Sereda^{1,2}, DJ Hoare^{1,2}, C Fearnley³, K Fackrell^{1,2}

1 NIHR Nottingham Hearing Biomedical Research Unit, Nottingham, UK

*2 Otolaryngology and hearing group, Division of Clinical Neuroscience, School of Medicine,
University of Nottingham, UK*

3 School of Medicine, University of Nottingham, UK

Background/aims: Hyperacusis (hypersensitivity to external sounds) and tinnitus are comorbid. It is estimated that around 40% of people with tinnitus also report hyperacusis and this may be significant for the acceptability and adherence to certain tinnitus management options such as sound therapy. Therefore a clear measure of hypersensitivity to sound is important for tinnitus management. The Hyperacusis Questionnaire (HQ) was developed to specifically measure hyperacusis, with three subscales measuring attentional, social and emotional aspects of hypersensitivity to sound [1]. It is often used for assessment in both clinical practice and research. However, this questionnaire has not been previously validated for the use in a tinnitus research population. The aim of this study was to evaluate the psychometric function of the HQ in a large UK population of research participants with tinnitus.

Methods: Questionnaire data including the HQ, Tinnitus Handicap Inventory (THI); Tinnitus Handicap Questionnaire (THQ); Beck's Depression Inventory (BDI); Beck's Depression Inventory fast screen (BDI-fast); and the Beck's Anxiety Inventory (BAI) were collected between 2008 and 2013 from 264 research participants with tinnitus. We evaluated the reliability (internal consistency and floor and ceiling effects), validity (discriminant validity), and factor structure (Confirmatory Factor Analysis) of the HQ questionnaire.

Results: In the Confirmatory Factor Analysis the χ^2 was significant ($p < 0.001$) and approximation fit indices did not fall within the acceptable criteria, indicating that the fit for the model was not optimal. Several items showed low loadings with their designated factor (below 0.6). In particular item 1 (using earplugs) had unacceptably low loadings (0.31) and did not relate to the other items within the scale. Internal consistency was high ($\alpha = 0.88$). Discriminant validity of

the HQ revealed moderate correlations with the THI ($r = 0.52$), THQ ($r = 0.32$) and BDI ($r = 0.43$) and weak correlations with BAI ($r = 0.3$) and BDI-fast ($r = 0.3$). Floor and ceiling effects were present in four items in particular.

Conclusions: The original 3 subscale model proposed by Khalifa et al. was not supported. Although the HQ measures constructs that are distinguishable from general health and tinnitus, the evidence suggests that the 3 subscale model does not accurately assess hypersensitivity to sound in a tinnitus population and the removal of item 1 from the questionnaire is indicated. Therefore, further work needs to be carried out on the structure of the questionnaire to establish its reliability for measuring hypersensitivity to sound in tinnitus research population.

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49 - SCREENING FOR HYPERACUSIS IN CHRONIC TINNITUS

Schecklmann M, Langguth B

Department of Psychiatry and Psychotherapy, University of Regensburg, Germany

Background: Hyperacusis in chronic tinnitus was shown to represent a specific subtype of tinnitus with greater need for treatment. Thus, screening tools for hyperacusis are necessary in the diagnostic assessment of chronic tinnitus. Here, we investigate the validity of the two hyperacusis items (“Do you have a problem tolerating sounds because they often seem much too loud? That is, do you often find too loud or hurtful sounds which other people around you find quite comfortable?”; “Do sounds cause you pain or physical discomfort?”) of the TSCHQ (Tinnitus Sample Case History Questionnaire)[1] of the TRI (Tinnitus Research Initiative) database with a German hyperacusis questionnaire (GÜF, Geräuschüberempfindlichkeitsfragebogen) [2].

Methods: We analysed data of 161 patients with chronic tinnitus who completed the GÜF, audiometry and other inventories with respect to tinnitus, depression, and quality of life. We investigated the association of the GÜF and the TSCHQ screening questions for the sum score and for the single items with correlation, contrast, principal component, and discriminant analysis.

Results: TSCHQ items and the GÜF total score were significantly associated. Association analyses indicated the interrelationship of the TSCHQ items with fear hyperacusis items of the GÜF (fear with respect to sounds and fear-related behavior such as avoidance of sounds). Other factors of the GÜF were hearing-related problems in environmental noise and problems in quality of daily life due to hyperacusis. Correlating these three factors with tinnitus-specific parameters, audiometric measures, and tinnitus-unspecific measures of quality of life and

depression affirmed this factor structure. Establishing subgroups with and without hyperacusis in chronic tinnitus based on the TSCHQ items, discriminant analysis showed a sensitivity of 64% and a specificity of 71%.

Discussion: Both TSCHQ items can serve as screening questions with respect to self-reported hyperacusis in chronic tinnitus with a specific focus on fear hyperacusis. Different dimensions of hyperacusis should be considered in scientific and clinical context.

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50 - The impact of tinnitus on adult Nigerians: health related Quality of Life assessment of sufferers using the Hospital Anxiety and Depression Scale (HADS) and the RAND-36 item health survey 1.0 questionnaires

Adeyi A. Adoga, Daniel D. Kokong, Tonga L. Nimkur, Emoche T. Okwori

Department of Otorhinolaryngology, Head and Neck Surgery, Jos University Teaching Hospital, PMB 2076, Jos, Plateau State, Nigeria

Background: Tinnitus is a distressing ailment with limited options for therapy and affecting the quality of life of sufferers. This study aims to investigate the impact of tinnitus on the health related quality of life, the psychological and emotional wellbeing of patients in our environment.

Patients and Methods: Consecutive patients with tinnitus presenting to the Otorhinolaryngology outpatient clinic of the Jos University Teaching Hospital and The Ear, Nose and Throat Clinic, Jos were assessed and administered the Hospital Anxiety and Depression Scale (HADS) and the RAND-36 item health survey 1.0 questionnaires.

Results: We studied 49 patients, age range 22- 79 years (mean=36.8; median=35.5; SD=+/-12.7) consisting of 22 (44.9%) males and 27 (55.1%) females, male to female ratio of 1:1.2. Patients in the age range 31 to 40 were in the majority (n= 20; 40.4%). Depressive symptoms were recorded in 14 (28.6%) female patients and 11 (22.4%) male patients. Anxiety symptoms were recorded in 18 (36.7%) female patients and 16 (32.6%) male patients. 34 (69.4%) of our patients scored low on all QoL domains except pain levels irrespective of age or gender with statistically significant positive correlations between all the QoL domains studied for all patients (p-value <0.001). There was no statistically significant correlation between the age of the patients and the QoL scores (pvalue >0.5). A statistically significant inverse correlation was found between emotional distress (anxiety and depression) scores and each of emotional wellbeing scores.

Conclusions: Our study demonstrates high prevalence of tinnitus amongst the younger population in our region especially females with significant reduction in their HRQoL. This should help in raising the awareness of the impact of tinnitus on the QoL, psychological and emotional wellbeing of patients in our region with a view to improving outcome for tinnitus sufferers. We recommend a further study on a larger sample population to determine the socioeconomic impact of tinnitus on the Nigerian population.

51 - MINDFULNESS BASED TINNITUS STRESS REDUCTION PILOT STUDY: A SYMPTOM PERCEPTION SHIFT PROGRAM

Jennifer J. Gans, PsyD, Patricia O'Sullivan, PhD, Vallena Bircheff, BA

This pilot study aims to investigate whether a novel mind-body intervention, Mindfulness Based Tinnitus Stress Reduction (MBTSR), may be a beneficial treatment for chronic tinnitus. Eight tinnitus patients who had previously received Tinnitus Counseling (standard of care) at the University of California, San Francisco (UCSF) Audiology Clinic participated in the MBTSR program. The program included eight weeks of group instruction on mindfulness practice, a one-day retreat, supplementary readings, and home-based practice using meditation CDs. Using a pre-post intervention design, mean differences (paired t-tests) were calculated. Benefits were measured by a reduction in clinical symptoms, if present, and a tinnitus symptom perception shift. Tinnitus symptom activity and discomfort as well as psychological outcomes were assessed by self-report questionnaires. Both quantitative and qualitative data were gathered. Results indicate that Effect Sizes, if supported by a larger study, may be clinically significant and demonstrate a substantial decrease for items measuring perceived annoyance and perception of handicap of tinnitus. Change scores on study measures all moved in the hypothesized direction, with the exception of negligible change found for the Acting with Awareness ($d = -.05$) factor of mindfulness. This pilot study provides preliminary evidence that an eight-week MBTSR program may be an effective intervention for treating chronic tinnitus and its co-morbid symptoms, and may help reduce depression and phobic anxiety while improving social functioning and overall mental health. These promising findings warrant further investigation with a randomized controlled trial.

52 - Study of the association between the tinnitus annoyance and the genetic background

T. Watabe¹⁾, T. Matsunaga²⁾, S. Wakabayashi¹⁾, T. Kojima¹⁾, N. Oishi¹⁾, S. Kanzaki¹⁾, K. Ogawa¹⁾

1) Department of Otolaryngology, School of Medicine, Keio University, Tokyo, Japan

2) The laboratory of Auditory Disorders, National Institute of Sensory Organs, National Tokyo Medical Center. Tokyo, Japan

It is well known that tinnitus has been associated with several psychological factors such as depression, anxiety disorder and so on. It is recently reported that the gene polymorphism may contribute to depression, anxiety disorder and the response to antidepressant drugs. In this study we examined the association of those polymorphisms with the severity of tinnitus.

The sample in this study included the 83 patients who visited to Department of Otolaryngology in Keio University Hospital for the chronic tinnitus with history for more than 3 months and more than 30 score for Tinnitus Handicap Inventory (THI) in 2013 to 2014. The subjects underwent the questionnaire such as Self-rating Depression Scale (SDS) for depression, State-trait anxiety inventory (STAI) for anxiety and THI in addition to the auditory evaluation such as audiometry and, pitch and loudness matching test. The candidate gene polymorphism associated with depression, anxiety and fear was selected on the basis of the database of the disease with genetic component. 15 polymorphisms in total for *methylenetetrahydrofolate reductase gene (MTHFR)*, *catechol-O-methyl transferase gene (COMT)*, *monoamine oxidase B gene (MAOB)*, *angiotensin receptor 1 gene (AGTR1)*, *brain-derived neurotrophic factor gene (BDNF)*, *FK506-binding protein 5 gene (FKBP5)*, *tryptophan hydroxylase 1 gene (TPH1)*, *solute carrier family 6 (neurotransmitter transporter) member 15 (SLC6A15)*, *solute carrier family 6 (neurotransmitter transporter) member 4 (SLC6A4)*, *5-hydroxytryptamine receptor 2a gene (HTR2A)*, *breakpoint cluster region gene (BCR)*, and *adenylate cyclase-activating polypeptide 1 gene (ADCYAP1R1)* were listed. Trend test and Fisher exact test were used to identify the association between the severity of tinnitus and the above-mentioned polymorphisms. $p < 0.05$ was considered to be significant.

The 83 subjects who were included in this study were mean age 61.20 ± 13.62 ; 43 men and 40 women. The baseline THI and SDS were 53.48 ± 22.73 and, 43.67 ± 8.90 , and showed normal distribution. There was a significant correlation between THI and SDS, as reported previously. The subjects divided into 49 with mild to moderate score and 34 with severe to catastrophic score according to THI. No polymorphisms revealed the significant association with the THI severity. But the polymorphism in MAOB gene (rs1799836 (T/C)) showed the near association with the severity of THI in female cases. T allele (Major) in this variant might show severer annoyance with tinnitus than C allele (Minor). It is expected that the genetic factor will be the one of the factor to contribute to the tinnitus severity. In the future, we will continue to add the samples, thus getting the reliable factor as a biomarker to assess the tinnitus severity.

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53 - THE LONG-TERM OUTCOMES OF SIGNIFICANT OTHER INVOLVEMENT IN TINNITUS MANAGEMENT

Scaglione, T; Eshraghi, A; Davis, P

University of Miami- Ear Institute, Miami, Florida, USA

Background/Aims: Tinnitus, or noises in the head/ears, is known to have detrimental effects on a patient's quality of life. Little research is focused on the perception of the tinnitus impact on the patient by the viewpoint of the patient's significant other (SO). Furthermore, there is currently no known published data indicating what impact the SO may have in the patient's tinnitus management process or how the patient's tinnitus may impact their SO's quality of life. We proposed a Significant Other's Tinnitus Questionnaire (SOTQ) and Significant Other's Tinnitus Questionnaire- Long Term (SOTQ-LT) to assess the severity of the patient's tinnitus disturbance from their SO's perspective both at time of initial tinnitus and one year post-initial tinnitus evaluation. The objective of this study is to investigate the benefit of these novel questionnaires in the management of chronic tinnitus.

Methods: This is a prospective study evaluating the involvement of the SO in the tinnitus management process using the SOTQ, SOTQ-LT, and Tinnitus Reaction Questionnaire (TRQ). In phase one, the SO was asked to complete the SOTQ at all patient visits up to three months after his/her initial tinnitus visit and counseling of the SO. Concurrently, the patient was asked to complete the TRQ. Twenty-one patients and their SO participated in this study. In phase two, patients from phase one received the Tinnitus Reaction Questionnaire (TRQ) and SOTQ-LT questionnaires and their SO received the SOTQ and SOTQ-LT by mail. All data gathered were analyzed and appropriate statistical tests performed to compare the results of phase two with the results of phase one.

Results: Phase one results indicated the SO rated tinnitus as more disturbing than the sufferer did, although this difference was not statistically significant. The SOs and the patients each rated various domains more highly than the other; however, the composite score tended to average out those differences. The SO's rated avoidance of social situations as a significantly more frequent problem than the patients did. There was no significant difference between the two groups in terms of tinnitus interfering with sleep, relaxation or concentration, as both SO's and patients rating them as being disturbed quite frequently. There was no significant difference between the groups in terms of the perceived ability to work. The result of phase one is analyzed and compared with the results of phase two demonstrating that the involvement of the SO is beneficial to the management of the patient's tinnitus.

Conclusions: Results demonstrated that involving a patient's SO in the tinnitus management process has a positive impact on the patient's quality of life and serve as a beneficial counseling tool for both the patient and SO alike. Results from this study encourage the use of both the SOTQ and SOTQ-LT within the routine tinnitus test battery.

POSTER SESSION 6

WEDNESDAY, JUNE 10, 2015

54 - IS CURRENT CLINICAL ASSESSMENT ADEQUATE TO EVALUATE TINNITUS BOTHERSOME?

I.G. Toostani^{1,4}, A. Delbem¹, P., T.G. Sanchez^{2,3}

¹ USP - Interunidades Bioengenharia (EESC/FMRP/IQSC), Universidade De São Paulo, São Carlos, SP, Brazil;

² USP-Faculdade de Medicina da Universidade de São Paulo, SP, Brazil;

³ Instituto Ganz Sanchez, São Paulo, Brazil; ⁴ FGS - Fanavaran Gostaresh Salamat, Tehran, Iran.

Abstract: Tinnitus, a subjective and individual perception of a sound in the absence of external sound sources, affects 10-23% of population in different epidemiologic studies. An intriguing question is why 80% of them do not present significant bothersome. Currently, validated questionnaires are applied to evaluate the patient's self-impression of handicap and to monitor the effect of a chosen treatment. However, estimating the bothersome of tinnitus is still an unpredictable task, what can compromise the goal of optimizing the different treatment strategies to cover patient's distress factors.

Aims and objectives: To investigate the predictability factors involved in the patient's bothersome with tinnitus in relation to different diagnosis tools, using the reported value of visual analogue scale (VAS).

Material and Method: This study included the clinical records of 2185 tinnitus patients seen in a private specialized clinic. All applied for a similar diagnostic protocol which contains: 1) physical characteristics of tinnitus (time, of onset, type of sound, localization, factors influencing loudness changes) and bothersome through VAS and TBF-12 questionnaire; 2) related symptoms: hearing loss, sound intolerance, aural fullness, balance symptoms; 3) audiological battery (audiometry up to 16kHz, tympanometry, loudness discomfort levels, pitch and loudness matching blood tests; A linear regression model was applied for determining whether patient's diagnostic variables are correlated with tinnitus bothersome and specifying the direction of such correlation. Fifty seven independent diagnostic variables were selected as inputs in order to evaluate predictability of tinnitus bothersome according to the score of VAS.

Results: Implemented linear model with 30% of accuracy exhibited 21 of the 57 diagnostic variables, which were meaningfully associated with bothersome. It presented positive correlation mainly with TBF12 score, hearing loss and also Hypersensitivity, worsening factor as stress and LMT respectively, furthermore it exhibited inverse correlation correspondingly with worsening factors as silence/stress, duration, pain factors and comorbidities as depression/panic/insomnia.

Conclusion and discussion: According to linear regression model, current assessments of tinnitus cognitive and emotional distresses cannot evaluate the majority confounding factors in

patient's judgment of tinnitus annoyance. This uncertainty might explain the irreproducibility of many treatment strategies, as a consequence of lack of cognitive-emotional assessment instrumentation. Future studies on brain network connectivity and neurofunctional modeling of tinnitus, associated to enriched questionnaires, may have a major and predictable role in clinical assessment.

55 - Tinnitus in 7 and 12 –year-old children in Poland

*Danuta Raj-Koziak, Anna Piotrowska, Henryk Skarżyński, Piotr Skarżyński
Institute of Physiology and Pathology of Hearing
Poland*

Introduction: The prevalence of paediatric tinnitus has been reported as ranging between from 7.5% to 37.5% in normally hearing children (Nodar, Holgers, Coelho, Aksoy, Mahboubi) and increases from 23% to 56% in children with hearing loss (Nodar, Viani, Coelho, Mahboubi).

Objectives: To assess the prevalence of tinnitus sensation reported by the population of 7 and 12 years old children from primary schools in Warsaw. To assess tinnitus prevalence in group with normal hearing status and in children with hearing loss.

Material: Observational cross-sectional study of first (7-year-old) and sixth grade (12-year-old) of students (N=23 176) from 173 primary schools in year 2012/2013 - 15 199 of them were included into the study.

Methods: Children had performed hearing test and completed the questionnaire. Tinnitus in questionnaire was defined as sound that lasts more than 5 minutes within the last 6 months. Questionnaire was completed at school by experienced audiometricians before the hearing test was conducted. Hearing threshold levels were determined for the right and left ear at frequencies 0.5, 1, 2, 4 and 8 kHz with the use of class IV audiometer –sense examination platform. Normal hearing was defined as air thresholds values of 20 dB or less for all tested frequencies. Differences between groups for categorical variables such as age, gender, hearing status were assessed.

Results: Overall 6% of the 7- and 12-year-old students reported having tinnitus. 7 year old children reported tinnitus more frequent comparing to 12-year-old children. The prevalence of tinnitus was significantly related to hearing loss and was found to be 5.6% of children with normal hearing vs. 9.0% children with hearing loss. No differences were observed for two age groups with unilateral and bilateral hearing loss. Analyses by sex showed no differences.

Conclusions: Tinnitus in children is not a common problem as it was previously published. Risk factor of tinnitus in children is hearing loss.

56 - OBJECTIVE ACCOUPHENOMETRY (OA)

R. Vergara, A. Gamba

Fundacion Ciencia y Tecnologia, Bogotá, Colombia

Objectives- To demonstrate that what tinnitus patient tells to be hearing, is a true sound signal. In the literature there are few proposals like this, but we know Sayed Twefick (1974), who intended to capture the sound of tinnitus with a Phonocefalograph; Salvi et alls. 1999, demonstrated teeth clenching, which is one of the SAM, increase metabolic activity in primary auditory cortex (PAC) and this only happen when PAC is perceiving a noise or when it is remebering a noise.

Materials and Methods- Through clinical examination with the sound active maneouvers (SAM), we were able to demonstrate that what tinntius patient tells to be hearing, behaves in accordance with the laws of physics of sound; so we tried to capture such a sonorous phenomenon with an electronic and computarized device called Objective Accouphenometer (OA). We took 100 tinnitus patients in which we performed an ENT clinical examination, emphasizing in SAM and the interrogation about the similarities of the signal they tell to be hearing; age of patients from 16 to 73, 63 females 47 males, excluded those with accute or chronic otitis media, hearing level was not taken into account because tinnitus is independent of hearing. The OA was performed in a damping room. The OA is constituted by a hardware and a software; the hardware is made of a sound sensor, a wireless connection with the amplifier which is connected to the computer; inside this one is installed a software for sound signals, which displays the shape of the tinnitus soundwave. Then we reproduced it to be heard by the examiner first and then by the patient, who will tell us how similar to his tinnitus it is.

Results- From 100 tinnitus patients, 63 described the showed sound signal as simliar to their tinnitus, which means 63% efficiency of the OA. Most were below 2.000 hertz, a few higher than 4.000 hertz. A sample of these recorded sound signals will be showed at the meeting.

Conclusions- 1. We have been able to demonstrate that what tinnitus patient tells us to be hearing, is a true sound signal. 2. We have been able to capture, to record and reproduce it with appropriate technology. 3. If this is true, as it is, then there must be some anatomical elements around the ear, which are able to act as a sound source. 3. Research activity must now to be devoted to the aim to identify such a sound source. 4. It is also the compromise of research community to change its behavior and to focus treatment toward the tinnitus sound source.

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57 - COMPLEMENTARY SURVEYS OF AUDIOLOGISTS AND PATIENTS TO ASSESS TINNITUS TREATMENT EXPECTATIONS

F. Husain^{1,2,3}, J. Jansen¹, P. Gander⁴

1Department of Speech and Hearing Science

2Neuroscience Program

3Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign,

4Department of Neurosurgery, University of Iowa.

Aims: Roughly 10-15% of the general population is affected by tinnitus and the numbers are estimated to rise in future. Because there is currently no cure for tinnitus, treatment is limited and is primarily achieved through management of symptoms and counseling. This study compared audiologists' and patients' responses to similar survey questions about their expectations regarding tinnitus treatment. Two separate surveys were created, one for patients with tinnitus, and one for practicing audiologists who may treat such patients, and included many similar questions, such that comparison of the two could reveal where patients' and audiologists' expectations for tinnitus care were in agreement and areas in which they differed.

Methods: The survey for audiologists and those with tinnitus was a 31 and 38-item questionnaire respectively. Both surveys were comprised of demographic questions followed by several tinnitus-related questions in multiple choice or Likert scale format. All survey recruitment was completed online. Responses were collected via the Survey Monkey (<http://www.surveymonkey.com/>) webtool. We received 230 completed patient and 68 completed audiologist surveys. Responses were analyzed within and between surveys and grouped into topical categories (assessment, counseling, current available tinnitus information, satisfaction and expectations, improving tinnitus management). For data within surveys, descriptive statistics and correlation analyses were used. All correlations were generated with SPSS software. The primary means for analyzing data across surveys was by comparison of frequency counts and descriptive statistics from the individual surveys. In some cases independent *t*-tests were also used to compare data generated from both participant groups.

Results: An important difference was found between the two groups' responses to the question on the definition of treatment success; audiologists reported decreased awareness (77%), stress/anxiety relief (63%) and increased knowledge of tinnitus (63%) most commonly, while patients reported reduction of tinnitus loudness (63%) and complete elimination of tinnitus (57%) most often. The focus by patients on perceptual factors rather than reactions to the tinnitus demonstrates that patients may have unrealistic expectations of current treatments for tinnitus. This discrepancy is likely based more on desires than acceptance of the current lack for a cure. The topic of greatest agreement was the desire for more information on tinnitus; 62% of patients felt more information from their healthcare provider would be the most important for improved tinnitus management, and 67% of audiologists reported 'some access' or less to appropriate resources for tinnitus treatment.

Conclusion: A very simple means of improving patient satisfaction with tinnitus treatment is through more information. In particular, patients should be provided with more information about current tinnitus treatment options, and how these focus on the patient's reaction to the tinnitus rather than the percept itself. Providing credible tinnitus information resources to audiologists, and focusing resources on training a small number of tinnitus specialist audiologists could greatly improve patient satisfaction with the current state of tinnitus palliative care.

58 - EVALUATION OF A MULTIDISCIPLINARY MANAGEMENT ON THE DISABILITY OF TINNITUS PATIENTS

Chenebaux M., Bakhos D., Lescanne E., Robier A., Pondaven S.

Department of Otolaryngology and Neck Surgery, University Hospital of Tours, 37044 Tours, France.

Faculty of Medicine, University François Rabelais, 37044 Tours, France.

Aims/Objectives: Tinnitus is a common debilitating symptom, often leading to multiple medical consultations. ENT doctors are frequently asked for medical advice, having to decide between various treatments which frequently remain suboptimal. We aimed at evaluating the efficacy of a multidisciplinary team management on patients' disability.

Methods: From January to December 2013, all the patients referred to our ENT department for debilitating tinnitus were prospectively enrolled and managed by a multidisciplinary team including ENT doctors, audiologists, sophrologists, and psychologists.

Patients were clinically evaluated to confirm the diagnosis of tinnitus and rule out surgical and/or psychiatric aetiologies. The presence of a hearing loss was assessed by performing an audiometry. Then, disability was estimated by a dedicated questionnaire, the Tinnitus Handicap Inventory (THI). Five grades of tinnitus severity were considered: slight (grade 1, score 0-16), mild (grade 2, score 18-36), moderate (grade 3, score 38-56), severe (grade 4, score 58-76) and catastrophic (grade 5, score 78-100).

Five different therapeutic options were subsequently proposed by the ENT, depending on tinnitus severity, the presence of a hearing loss and/or associated symptoms and patients' preferences: counselling, sophrology sessions, hearing aids, psychological support, and sophrology sessions/hearing aids.

A second THI was performed 6 months later. Patients were considered as improved if THI grade decreased by at least 1 point. Primary endpoints were the rate of patients improved and the evolution of THI after therapy. Secondary endpoints were the efficacy of each therapy and predictive factors of improvement.

Results: Seventy-two patients were enrolled (56.2±13.5 years old, 37 men). Tinnitus history started a median time of 30 months before inclusion [IQR 12-108 months]. Mean right and left hearing losses were 21.8±16.4 dB and 23.5±22.3 dB, respectively. Initial THI score and grade were 51.9±27.4 and 3.2±1.4, respectively.

Patients were managed with counselling (n=29, 40.3%), sophrology sessions (n=22, 30.5%), hearing aids (n=12, 16.7%), psychological support (n=6, 8.3%) or sophrology sessions/hearing aids (n=3, 4.2%).

The overall THI score decreased from 51.9±27.4 to 42.3±27.6 ($p<0.001$). Among the study patients, 30 (41.7%) decreased their THI grade of at least 1 point and were considered improved, whereas 38 (52.8%) patients remained stable and 4 (5.5%) impaired. Among improved patients, the most frequent therapeutic option was sophrology (43.3%, $p=0.096$). The THI score significantly decreased in both counselling and sophrology groups (from 35.4±24.0 to 27.9±25.6, $p=0.002$, and 61.8±22.3 to 43.3±17.5 for observant patients, $p=0.004$, respectively) while remaining stable in the other therapy groups.

In the overall population, predictive factors of improvement were prior medical management of tinnitus (HR=3.67, 95%CI:1.18-11.4; $p=0.025$) and lower mean left-sided hearing loss (HR=0.97, 95%CI:0.94-0.99, $p=0.030$).

Conclusion: Multidisciplinary team management of patients with disabling tinnitus leads to a significant decrease of THI grade and improves more than one third of them. Medical attention, in coordination with other specifically trained healthcare providers offers new perspectives in the management of this complex symptom.

59 - COMPLEXITY AND MISSING INFORMATION MEASURES IN TINNITUS

T. K. Das^{*1}, S. Vanneste^{*2}, A. Piarulli³, Q. Noirhomme³, S. Laureys^{3,4}, A. M. Owen⁵, D. De Ridder^{6,7}, A. Soddu¹

* equally contributed + equally contributed

1 *Physics & Astronomy Department, Brain & Mind Institute, Western University, London, ON, N6A 3K7, Canada*

2 *School of Behavioral and Brain Sciences, The University of Texas at Dallas, Dallas, Texas*

3 *Cyclotron Research Center and University Hospital of Liège, University of Liège, Liège, Belgium*

4 *Department of Neurology, CHU Sart Tilman Hospital, University of Liège, Liège, Belgium*

5 *Department of Psychology, Brain & Mind Institute, Western University, London, ON, N6A 5B7, Canada*

6 *Department of Surgical Sciences, Section of Neurosurgery, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand*

7 *BRAI²N, Sint Augustinus Hospital, Antwerp, Belgium*

Introduction: The most common cause for tinnitus is auditory deafferentation with or without hearing loss. It has been proposed that tinnitus is the result of a filling in mechanism in order to reduce the auditory uncertainty related to the missing auditory information [1, 2]. Little is known on how this auditory deprivation influences global information processing in the brain. Here we address the study of understanding complexity present in multiple dynamically active brain regions, and its relation to identify the missing information that could be used to characterize the disease state of tinnitus.

Methods: Information entropy is a reflection of “missing” information or higher uncertainty due to more complexity. Two types of information entropy measures are used in this analysis: (1) spectral entropy (SE) evaluating missing information or higher uncertainty in different frequency bands and (2) permutation entropy (PE), which is a measure of complexity accounting for higher richness of patterns in time with different time delays, are calculated on EEG data of 264 healthy controls and 129 tinnitus patients. We compute the shorttime Fourier transform based spectral power first in order to obtain the sub-band SE. Including temporal orders 3, 4 and 5 (higher number of possible patterns with higher order) in EEG time series data, we generate different ordinal patterns, and investigate the presence of these patterns in the time series data to calculate the PE with delays from 1 to 13 (i.e. more spread out in time).

Results: In our SE calculations, increased normalized spectral power and SE scores in low frequency theta band indicate the recruitment of large scale spatial cortical networks present in the healthy control group, which is absent in the tinnitus group. In contrast to the theta band activity, high frequency beta and gamma band activities in tinnitus demonstrate the increasing degree of complexity in temporal, frontal and occipital lobes. On the other hand, our PE calculations with delay 1 and 2, possibly reflecting high frequency activity, imply less complexity and less information entropy in temporal and occipital areas of the control group, compared to the group of tinnitus patients. Instead, when we look at higher delay (in particular, delay 8), controls have more information entropy in central lobe areas than tinnitus patients, confirming the results for the theta band. In other words, in tinnitus patients a less entropic or “more informative” content could be extracted from central areas in the theta band or high delays, compared to temporal and occipital areas in the high beta-gamma bands or lower delays. Also, PE increases with increasing neighboring order in both controls and tinnitus patients due to the richness of temporal patterns in the time series data.

Conclusions: The measure of complexity or “missing” information in terms of PE with delay 1 and 2 shows the direct correspondence with SE calculations in high beta and gamma bands while delay 8 for PE corresponds to the theta band for SE. This suggests that short time delays represent high frequency activity while long time delays correspond to lower frequencies. Tinnitus patients extract more information via carrier waves (theta) from central brain areas than controls, whereas controls can extract more information from sensory areas (temporal, occipital), presumably picking up changing information (gamma).

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60 - SUSTAINED BENEFIT OF MINDFULNESS BASED TINNITUS STRESS REDUCTION (MBTSR) IN ADULTS WITH CHRONIC TINNITUS

Jennifer J. Gans & Michael A. Cole

This 12-month follow-up aims to evaluate the long-term effects of an 8-week Mindfulness Based Tinnitus Stress Reduction (MBTSR) course on tinnitus handicap in adults with chronic tinnitus. Seven individuals with chronic tinnitus who had participated in an 8-week Mindfulness Based Tinnitus Stress Reduction (MBTSR) pilot study were assessed in a subsequent 12-month follow-up. After 12 months, continued reduction in tinnitus handicap was observed across all subjects. Mean THI scores immediately at post MBTSR intervention were 41.7. Mean THI scores at 12-months post MBTSR intervention were 22.8. Effect sizes are clinically significant and demonstrate a substantial decrease for items measuring perceived tinnitus handicap ($d=1.25$) at 12-months post-intervention. In adults with chronic tinnitus, benefits in perceived tinnitus handicap from the mindfulness skills taught in an 8-week MBTSR program can be sustained showing continued improvement for 12-months.

61 - IMPACT OF TINNITUS ON DAILY LIFE: ANALYSIS USING THE TINNITUS HANDICAP INVENTORY

N Oishi, S Wakabayashi, S Shinden, K Ogawa

Department of Otolaryngology, Head and Neck Surgery, Keio University School of Medicine, Tokyo, Japan

Aims/Objectives: The Tinnitus Handicap Inventory (THI) is one of the best established questionnaires to assess different aspects of the impairment and distress associated with tinnitus. The total THI score has been typically used, but a recent paper has also reported the usefulness of the postulated three-factor structure (functional: F, emotional: E, and atastrophic: C). However, a detailed analysis of each item of THI may be useful to better understand the psychological state and living situation of patients with tinnitus. Therefore, we attempted to understand the impact of tinnitus on daily life by analyzing each item of THI.

Methods: THI was administered to 1,332 patients with tinnitus at their first visit to our clinic

from 2004 to 2011. The average of the total score was 54.2 ± 26.1 , including 119 patients with “no handicap,” 265 patients with “mild handicap,” 321 patients with “moderate handicap,” 303 patients with “severe handicap,” and 324 patients with “catastrophic handicap.” We calculated the number of patients who answered “yes” to each item in THI; when more than 10% answered “yes” to an item, the content of the item was regarded as the distressing aspect of the daily life by tinnitus.

Results: In the “no handicap” group, none of the items were answered “yes” by over 10% of the patients. In the “mild handicap” group, the following 6 items were answered “yes” by more than 10% of the patients: difficult to hear people (F); difficulty in falling asleep (F); gets worse under stress (F); feeling angry (E); unable to escape (C); and no control over tinnitus (C). In the “moderate handicap” group, many items were answered “yes.” The following 6 items were answered “yes” by more than 10% of the patients only in the “severe and catastrophic handicap” group: confused (F); difficulty in reading (F); frustration (E); upset (E); stress on relationships with family and friends (E); desperate (C); and feeling of having a terrible disease (C). These results indicated that patients with tinnitus might start by having difficulties in falling asleep and hearing and feeling angry, in early stages of tinnitus-related distress. In a more distressed stage, various daily activities of patients are affected, including difficulty to concentrate and to enjoy life; interruption in social activities and work; and feeling tired, irritable, depressed, anxious, and insecure. They might finally progress to severe functionally and emotionally distressing conditions such as confusion, frustration, and desperation.

Conclusion: These results indicated that difficulty in sleeping and feeling angry can be initial symptoms in distressed patients with tinnitus, and wider aspects of daily life are affected in more distressed patients. In severely distressed patients, confusion, frustration, and desperation can occur. These findings can be used for a better management of patients with tinnitus.

62 -ARE THOSE SEEKING HELP FOR TINNITUS SATISFIED WITH THEIR INTERACTION WITH HEALTH PROVIDERS?

N Carmody and RH Eikelboom

Ear Sciences Centre, School of Surgery, The University of Western Australia

Ear Science Institute Australia, Western Australia

Background: Limited published evidence exists on the help seeking behaviour of people with tinnitus and their satisfaction with health providers. The limited research available suggests those seeking help for tinnitus report low satisfaction with health providers and report lower health status and greater tinnitus interference.^{1,2} Health providers and researchers agree that health services for tinnitus need improvement.

Aims/Objective: To determine whether people with tinnitus seeking help are satisfied with health providers considering factors such as tinnitus interference, health status and self-reported history of anxiety or depression.

Methods: Cohort 1: Volunteers, presenting with tinnitus, aged 18 years and over and; Cohort 2: Those self-reporting tinnitus in an epidemiological study of people born between 1946 - 1964. A five part survey was administered: Tinnitus Sample Case History Questionnaire – Adapted (TSCHQ), Tinnitus Reaction Questionnaire (TRQ), Glasgow Health Status Inventory – all purpose (GHSI), Patient Satisfaction with Communication (PSC) and the Functional Assessment of Chronic Illness Therapy - Treatment Satisfaction - General (FACIT-TS-G). A TRQ score of <17 indicated sub-clinical tinnitus.

Results: A total of 281 participants completed the survey; Cohort 1 ($n=150$; mean age: 58.94, SD: 13.24) and Cohort 2 ($n=131$; mean age: 59.74, SD: 5.04). TRQ scores were slightly higher for Cohort 1 (mean TRQ: 19.09, SD: 17) than for Cohort 2 (mean TRQ: 11.83, SD: 14.85). $TRQ \geq 17$ had significant associations ([chi-square test], $p < 0.05$) with Cohort 1, age category (60-65), help seeking, seeking >1 health provider, lower health status, anxiety and depression.

For those help seeking (Cohort 1 $n=90$, Cohort 2 $n=57$) few undertook treatment (Cohort 1 $n=27$, Cohort 2 $n=6$). The analysis showed help seeking was significantly associated ([chi-square test], $p < 0.05$) with $TRQ \geq 17$, Cohort 1, self-report hearing loss, those on medication and lower health status but not with anxiety or depression.

Diagnosis and treatment satisfaction ratings indicated low satisfaction with health providers. There were no significant relationships between satisfaction with diagnosis or treatment and which health provider (General Practitioner, Ear Nose and Throat specialist or audiologist) provided the service. Males were more likely to report lower satisfaction with treatment ([t-test], $p < 0.05$). Seeking >1 health provider ($n=29$) was significantly associated with Cohort 1, $TRQ \geq 17$ and anxiety ([chi-square test], $p < 0.05$).

Conclusion: People with tinnitus appear to be dissatisfied with health services. The level of interference from tinnitus and health status is associated with help seeking, it does not however influence their satisfaction of health services. Seeking help from more than one source was related to anxiety and greater tinnitus interference. Further work is required to improve clinical management of people with greater tinnitus interference and lower health status when seeking help in the initial stages, including identifying anxious patients. More research is required into the help seeking behaviour of people with tinnitus, especially how their tinnitus is affected by health status.

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