

PROGRAMME
AND
ABSTRACT BOOK

2nd TRI Meeting
Together for a cure
Challenging our basic assumptions

July 17-21, 2007

Meridien Beach Plaza Hotel,
22, Avenue Princesse Grace
Principality of Monaco

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The organizers wish to express their thanks to all the persons helping
in the organization of the 2nd TRI Meeting,
especially to Chiara Merlano, Ulrike Soltani and Susanne Staudinger.

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SECOND TINNITUS RESEARCH INITIATIVE MEETING

17 - 21 July 2007, Principality of Monaco



TINNITUS RESEARCH INITIATIVE

Together for a cure

Challenging our basic assumptions

JULY 17th

18:00 Official Beginning of the Meeting
18:00 Welcome and Introduction
19:00 Welcome Cocktail

JULY 18th

8:30 Combining a fast exploratory with a solid scientific approach: trying to square the circle N. Yuan-sheng Kiang
9:15 Clinical observations which can not be explained R. Goodey
10:20 Charge to attendees
10:30 Coffee
11:00 – 12:30 Workshop session I (see workshop list)
12:30 Lunch – Buffet
13:30 – 14:30 Poster Session I
14:30 – 16:00 Workshop session II (see workshop list)
16:00 – 16:30 Coffee break
16:30 – 18:00 Workshop Session III (see workshop list)

JULY 19th

8:30 – 10:00 The path from animal models to patient treatment + discussion R. Salvi
10:00 – 10:30 Coffee break
10:30 – 12:30 Workshop Session IV (see workshop list)
12:30 Lunch – Buffet
13.30 – 14.30 Poster Session II
14:30 – 16:30 Workshop Session V (see workshop list)
16:30 – 17:00 Coffee break
17:00 – 18:00 Tinnitus clinic round table
Chair: D. Baguley
G. Searchfield
R. Tyler
T. Sanchez
R. Levine
C. Herraiz

JULY 20th

8:30 – 11:00	Workgroup meetings (parallel sessions)	
	A Somatosensory tinnitus and modulating factors	T. Sanchez
	B Subtyping tinnitus	J. Melcher
	C Pharmacology	AB. Elgoyhen, B. Langguth
	D Auditory Stimulation and Perception	G. Searchfield
	E Brain Stimulation	D. De Ridder
11:00 – 11.30	Coffee Break	
11:30 – 13:00	What we can learn from pain research	Chair: A. Møller
	Introduction	A. Møller
	Neural plasticity in pain and tinnitus	A. Møller
	Neurobiological mechanisms of chronic pain	H. Flor
	Electrical stimulation in pain and tinnitus	D. De Ridder
13.00	Lunch – Buffet	
14:00 – 17:00	Plenary session: Workgroups reports (30 minutes/Workgroup)	
17:00	Closing of the meeting	
20:00	Commitment Dinner	

Workshop session I

- A** Models for the interaction between somatosensory and auditory systems
Animal models
Susan Shore
Deafferentiation induced plasticity:
Anthony Cacace
- B** Cluster analysis of clinical characteristics
Richard Tyler
- C** Salicylate modulates arachidonic acid-sensitive NMDA receptors at the sensory inner hair cell synapse
Jean-Luc Puel
- D** Induction of brain plasticity by auditory perceptual training
Grant Searchfield
- E** Challenging our basic assumptions
Andrew Parr

Workshop session II

- A** Diagnostic approaches for somatosensory tinnitus
Robert Levine
Michael Golenhofen
- B** Psychoacoustic and Electromagnetic Properties of Residual Inhibition and Tinnitus
Larry Roberts
- C** What do we need for the development of a tinnitus-drug?
Ana Belen Elgoyhen
- D** Tinnitus and virtual reality therapy
Isabel Viaud-Delmon
- E** Mechanisms of auditory cortex stimulation
Jinsheng Zhang

Workshop session III

- A** Clinical experiences Somatosensory modulation
Tanit Ganz Sanchez
Evaluating the interesting triangle: tinnitus, cervical spine and temporo-mandibular disorders.
Eberhard Biesinger
- B** The role of non-auditory brain areas
Joseph Rauschecker
- C** Which Neurotransmitter systems should be addressed?
Aage Møller
- D** Hearing devices: state of the art and future expectations
Luca Del Bo
- E** TMS and Tinnitus
Berthold Langguth

Workshop session IV

- A** Therapies for somatosensory tinnitus Drugs:
Carlos Herraiz
Trigger-point based treatment:
Marjia Estola-Partanen
- B** fMRI and tinnitus
Jennifer Melcher
Increased neural response to auditory stimulation in tinnitus patients
Pim van Dijk
- C** Animal models of tinnitus: current state and future perspectives
Edward Lobarinas
Monitoring of activity dependent genes in animal models of tinnitus
Marlies Knipper
- D** Cochlear electrical stimulation for the treatment of tinnitus
Bruno Frachet
- E** A comprehensive brain model of tinnitus
Dirk De Ridder

Workshop session V

- A** Metabolic and nutritional factors in tinnitus: concepts and facts
Manuela Mazzoli
Oral neurotransmitters and Kenogenic diet
Miguel Lopez Gonzales
- B** Oscillatory activity as neural code of tinnitus
Nathan Weisz
- C** Drugs brainstorming: which drugs should be tested?
Miguel Lainez
- D** Computational models of Tinnitus: implications for therapy
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Roland Schaette

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Abstracts of workshops

EVALUATING THE INTERESTING TRIANGLE: TINNITUS, CERVICAL SPINE AND TEMPOROMANDIBULAR DISORDERS.

Eberhard Biesinger, Traunstein

Based on long lasting experiences with somatosensory phenomena in head and neck, the author describes his audiologic and functional findings and therapeutic procedures in Tinnitus patients. After showing the special anatomical situation of the upper cervical spine and the temporomandibular joint (TMJ), the physiology of this region is discussed and physiological models of somatosensory interactions to the nuclei of the trigeminal, cochlear and vestibular systems are shown.

The presentation may lead to a structured protocol of assessment, showing screening tools for somatic and sensorineural Tinnitus and provocation tests on a functional base. Typical findings in X-ray are also described.

HEARING DEVICES: STATE OF THE ART AND FUTURE EXPECTATIONS

Luca Del Bo¹, Stella Forti²

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² *Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy*

Clinical evidence shows that the use of hearing stimulation in tinnitus makes the patient less aware of the tinnitus and it improves communication by reducing the annoying sensation that sounds and voices are masked by the tinnitus.

But tinnitus is often caused by expression of neural plasticity evoked by deprivation of auditory input. With hearing stimulation sounds can provide sufficient activation of the auditory nervous system to reduce the tinnitus perception and it may elicit expression of neural plasticity that can reprogram the auditory nervous system and thereby have a long-term beneficial effect on tinnitus by restoring neural function. To obtain the best results can be used hearing aids preferably in open ear version (results are presented), combination instruments or stimulation via headset and mp3 players. In the next future new and more flexible combination device are expected but also wide band hearing aids and sound generators with customized sounds.

CAN 3D SPINE SCAN SUPPORT THE DIAGNOSIS OF SOMATOSENSORY TINNITUS?

Michael P. Golenhofen

Background of the study is the complexity of malfunction in the craniomandibular and craniovertebral system, that trigger the appearance of somatosensory tinnitus. Meanwhile it is relatively easy to diagnose this form of tinnitus for the experienced doctor, we still lack objective diagnostic tools. The aim of this study was to investigate the value of 3D spine scans for the diagnosis of somatosensory tinnitus. The results showed a high sensitivity of this method for malfunctions in the craniomandibular system and in the follow up of somatic therapies. However no specific results for somatosensory tinnitus could be shown, since control patients without tinnitus behaved in the same way.

Conclusion of the performed study is, that 3D spine scan can not serve as an objective diagnostic tool for somatosensory tinnitus.

MONITORING OF ACTIVITY DEPENDENT GENES IN ANIMAL MODELS OF TINNITUS: A NEW METHOD TO ADVANCE THE PROCESS OF FINDING TINNITUS DRUGS?

Panford-Walsh R^{1*}, Rüttiger L^{1*}, Singer W^{1*}, Tan, J¹, Kilian, S¹, Schulze H², Geisler H¹, Köpschall I¹, Rohbock K¹, Zimmermann U¹, Knipper M¹

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Aberrant neuronal activity is known to lead to changes in neuronal plasticity. However, the molecular changes following sensory trauma and the subsequent response of the central nervous system are only poorly understood. We focused on finding a molecular tool for monitoring the features of excitability which occur following acoustic and ototoxic trauma to the auditory system. Of particular interest are genes that alter their expression pattern during activity-induced changes in synaptic efficacy and plasticity. The expression of brain-derived neurotrophic factor (BDNF) and the activity-dependent cytoskeletal protein (Arg3.1/arc) were monitored in the peripheral and central auditory system hours and days following tinnitus-inducing traumatic stimuli or salicylate treatment. Tinnitus induction was monitored in a rodent animal behavior model. Excitatory input to the rat AI were investigated by local field potential (LFP) post pure-tone acoustic trauma using chronic implantation of 8 channel microelectrode arrays. BDNF and Arg3, were monitored at the mRNA and protein level in the cochlea and subcortical and cortical areas. We present here a summary of recent findings comparing and correlating the expression of activity dependent genes with tinnitus-behavior. The data are discussed in the context of using the monitoring of activity-dependent genes to screen for the pharmacological reversal of tinnitus.

Supported by a grant from the Deutsche Forschungsgemeinschaft Kni-316/3-3.

TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF TINNITUS

Berthold Langguth, Tobias Kleinjung, Michael Landgrebe, Peter Eichhammer,
Göran Hajak

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An increasing amount of electrophysiologic and functional imaging data indicate that subjective tinnitus is related to functional alterations in the central nervous system. PET studies have demonstrated metabolic hyperactivity in the primary auditory cortex.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive method for altering cortical excitability, receives increasing attention as a therapeutical tool in a broad range of neuropsychiatric diseases. Applied in a low-frequency range (≤ 1 Hz), rTMS reduces brain activity in directly stimulated regions as well as in functionally connected brain areas and enables to modulate neuroplasticity in cortical circuits including thalamocortical networks.

Based on these properties repetitive transcranial magnetic stimulation (rTMS) applied over the auditory cortex has been proposed as new therapeutic tool to relieve tinnitus by reducing auditory cortex hyperexcitability. There is increasing evidence from a growing amount of studies that low frequency rTMS results in reduction of tinnitus sensation in a subgroup of patients. However treatment results are characterized by high interindividual variability and only moderate effect sizes. Furthermore the mechanisms by which rTMS effects are mediated are far from being entirely understood.

After presenting available data and discussing potential mechanisms, the workshop will focus on the development of future research strategies in order to optimize treatment results.

ANIMAL MODELS OF TINNITUS: CURRENT STATE AND FUTURE PERSPECTIVES.

Edward Lobarinas Ph.D. CCC-A

Several behavioral animal models of tinnitus have been proposed over the last twenty years. The first model was introduced by Jastreboff in the late 1980's and soon after, several variants of this lick suppression paradigm followed. Initial and some current models were developed to detect the presence of tinnitus and to potentially study the time course of the tinnitus phenomenon. However, some of these models are ill suited for the screening of pharmacological agents because of long training times or extinction of the behavior once tinnitus starts. As new drugs or potential treatments become available, rapid screening tools to detect the presence of tinnitus and evaluate treatment efficacy are needed. Currently, our laboratory uses two distinct models, Schedule Induced Polydipsa-Avoidance Conditioning (SIP-AC) and Gap Prepulse Inhibition of the Acoustic Startle (GPIAS) to study transient and permanent tinnitus. Both of these animal models are completely automated. Over the last four years, both SIP-AC and GPIAS have been used extensively to study the effects of Salicylate, Quinine, and Noise-induced tinnitus and to study the therapeutic effects of Mementine and Scopalomine as tinnitus reducing agents. Correlation studies have shown both techniques are effective and correlate strongly across tinnitus inducing conditions. The advantages and disadvantages of these models relative to traditional operant models will be discussed.

ILLUSORY PERCEPTS FROM AUDITORY ADAPTATION

Lucas C. Parra and Barak Pearlmutter

Abstract : Phenomena resembling tinnitus and Zwicker phantom tone are seen to result from an auditory gain adaptation mechanism that attempts to make full use of a fixed-capacity channel. In the case of tinnitus, the gain adaptation enhances internal noise of a frequency band otherwise silent due to damage. This generates a percept of a phantom sound as a consequence of hearing loss. In the case of Zwicker tone, a frequency band is temporarily silent during the presentation of a notched broadband sound, resulting in a percept of a tone at the notched frequency. The model suggests a link between tinnitus and the Zwicker tone percept, in that it predicts different results for normal and tinnitus subjects due to a loss of instantaneous nonlinear compression. Listening experiments on 44 subjects show that tinnitus subjects (11 of 44) are significantly more likely to hear the Zwicker tone. This psychoacoustic experiment establishes the first empirical link between the Zwicker tone percept and tinnitus. Together with the modeling results, this supports the hypothesis that the phantom percept is a consequence of a central adaptation mechanism confronted with a degraded sensory apparatus.

SALICYLATE MODULATES ARACHIDONIC ACID-SENSITIVE NMDA RECEPTORS AT THE SENSORY INNER HAIR CELL SYNAPSE

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Aspirin is one of the most consumed drugs in the world. A overdose of aspirin, and its metabolites sodium salicylate, provoked tinnitus (*i.e.* ringing in the ears) and hearing loss. Behavioral study showed that the occurrence of tinnitus induced by salicylate was mediated by cochlear N-Methyl-D-Aspartate (NMDA) receptors. Here, we report that NMDAR1 and NMDAR2 subunit receptors formed small clusters at the postsynaptic zones below the sensory inner hair cells. Pharmacological characterization of NMDA responses to salicylate, mefenate and arachidonic acid was addressed by patch-clamp recordings and two-photon calcium imaging on whole cochlear slice. Together with functional assessment, cyclooxygenase activity and arachidonic acid level measurements *in vivo* demonstrate that salicylate modulates arachidonic acid-sensitive NMDA receptors via cyclooxygenase inhibition. We thus provide direct evidence for a new pharmacological profile of salicylate, and the first molecular mechanisms underlying the occurrence of tinnitus in the inner ear.

Key Words: salicylate – NMDA receptor – arachidonic acid – cyclooxygenase activity - tinnitus.

THE ROLE OF NONAUDITORY BRAIN AREAS IN TINNITUS

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It has long been known that tinnitus is modulated by non-auditory factors, such as stress and sleep deprivation, and there is high co-morbidity of tinnitus with insomnia and depression. Rather than assuming that these conditions are a consequence of tinnitus, one has to consider the possibility that tinnitus and other related disorders share an underlying common cause, which involves non-auditory brain areas. Indeed, various components of the limbic system, such as the amygdala, have been discussed in the past as possible candidate structures for the involvement of non-auditory brain areas in tinnitus. A recent finding from voxel-based morphometry (VBM) on the basis of high-resolution magnetic resonance imaging (MRI) has identified the subcallosal region in the “limbic-related” ventral striatum as such a possible brain area (Mühlau et al., 2006). It includes as an essential element the nucleus accumbens (NAc), which receives glutamatergic input from the amygdala and serotonergic input from the sleep-related raphe nuclei in the brainstem. The volume of grey matter in the subcallosal area of tinnitus patients was significantly reduced as compared to normal controls. As a consequence, we propose to examine the concentration of various neurotransmitters and their precursors in the NAc of patients with and without tinnitus, using magnetic resonance spectroscopy (MRS). In particular, we plan to study patients with intermittent tinnitus, whose tinnitus strength on different days can fluctuate between “severe” and “completely absent”. Such patients can be tested during both states and effectively serve as their own controls. Identification of a deficit in a particular transmitter system of tinnitus patients, such as the glutamate, serotonin, or GABA systems, would narrow the options for pharmacological treatment. In very severe cases, deep-brain stimulation of the NAc, which is successfully done in patients with severe depression, may become another option.

PSYCHOACOUSTIC AND ELECTROMAGNETIC PROPERTIES OF RESIDUAL INHIBITION AND TINNITUS

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Animals exposed to noise trauma show augmented synchronous neural activity in auditory cortical tonotopic regions affected by hearing loss. Diminished intracortical inhibition in this region may set the stage for synchronous network activity which develops when deafferented neurons begin to respond to input via their lateral connections, generating a phantom sound (tinnitus) that is perceived in accordance with the location of the neurons in the cortical place map. This hypothesis implies that tinnitus spectra and “residual inhibition functions” which relate tinnitus suppression to the center frequency of masking sounds should cover the region of hearing loss in the audiogram. We confirmed these predictions in a baseline cohort of 90 subjects using three computer-based tools designed to assess the psychoacoustic properties of tinnitus. Research in progress indicates that masking sounds that give residual inhibition enhance the 40-Hz auditory steady state response in tinnitus but not in control subjects, suggesting a persisting inhibitory deficit in the region of the auditory core. (Supported by CIHR and NSERC of Canada and the American Tinnitus Association)

THE PATH FROM ANIMAL MODELS TO PATIENT TREATMENT

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The goal of my presentation is to review our research on tinnitus with humans and animals over the past two decades and to discuss the interplay between the basic sciences and clinical research. Our initial electrophysiological studies on tinnitus using animals prompted us to carry out a series of brain imaging studies with humans. Our human brain imaging studies then led us back to studies with animals that were trained to reliably report on the presence or absence of tinnitus. In the past few years, we have used animal models to investigate the mechanisms of tinnitus at the cellular and molecular level and evaluate potentially useful drugs to treat tinnitus.

The phantom sound of tinnitus was traditionally believed to originate from damage-induced hyperactivity in the auditory nerve. However, the neural activity in damaged ears is generally unchanged or hypoactive in cases of severe damage to the inner hair cells. Despite a reduced neural output from damaged cochleas, the neural activity in the central auditory system is often hyperactive. This led to the hypothesis that the tinnitus generator(s) might reside in the central auditory pathway and possibly involve nonauditory regions.

To test this hypothesis, we used positron emission tomography (PET) to map the sites of brain activity in: (1) Subjects with somatic tinnitus that could modulate the loudness of their tinnitus with an oral facial movement (OFM). (2) Acoustic neuroma patients that could modulate the loudness and pitch of their tinnitus by eye movements (gaze-evoked tinnitus, GET). (3) Subjects whose tinnitus loudness increased or decreased in response to intravenous lidocaine treatment.

Using PET imaging, we showed that OFM produced a significant increase in activity only in the auditory cortex contralateral to the ear in which the tinnitus was perceived. In contrast, a real sound presented to normal subjects activated both the left and right auditory cortex. Since the pattern of neural activity from OFM-induced tinnitus was fundamentally different from that evoked by a real sound, we hypothesized that the tinnitus generator was in the central auditory pathway. Similar conclusions were drawn from studies of GET and lidocaine studies. In GET patients, who experience tinnitus in their dead ear, lateral eye gaze evoked activity in the auditory brainstem or in regions adjacent to auditory cortex.

In the auditory literature, lidocaine is touted as a drug that can temporarily suppress tinnitus; however, in the cardiology literature, tinnitus is listed as a potential sideeffect of intravenous lidocaine. In our study with normal and tinnitus subjects, intra-

venous lidocaine produced bidirectional effects, in some subjects tinnitus became quieter while in others it became louder. Increases in tinnitus loudness were associated with increased activity in right auditory cortex whereas decreases were associated with decreased activity in auditory cortex. Collectively, these three studies suggest that tinnitus arises from aberrant activity in the central auditory brain system brought about by the loss of input from the cochlea.

To investigate the mechanisms of tinnitus in more detail, we developed a behavioral technique, schedule-induced polydipsia avoidance conditioning (SIPAC) to measure tinnitus-like behavior in individual rats. Reliable measurements of tinnitus-like behavior can be obtained from individual subjects over many weeks or months. All rats reliably developed behavioral evidence of tinnitus when treated with high doses of salicylate and quinine, but not with low doses or placebo. The tinnitus-like behavior disappeared after 1-2 days after terminating these treatments.

Memantine (Namenda), an anti-glutamatergic drug that acts on NMDA receptors, and scopolamine (SC), an anti-cholinergic drug, have been proposed as possible pharmacologic treatments for tinnitus. To determine if memantine and scopolamine could block the effects of salicylate-induced tinnitus, we tested the ability of memantine and scopolamine to suppress salicylate-induced tinnitus using the SIPAC paradigm. Neither memantine nor scopolamine completely suppressed salicylate-induced tinnitus at drug doses.

Exposure to high intensity noise is one of the most common causes of tinnitus in humans; however, not all humans exposed to intense sounds develop tinnitus. When we unilaterally exposed rats to high-level noise, some rats developed behavioral evidence of tinnitus after the noise exposure; in some cases the tinnitus-like behavior persisted, but in other cases, it disappeared after a day or two. Some rats never developed tinnitus.

SIPAC is an extremely useful behavioral paradigm for assessing tinnitus; however, it takes approximately three weeks to train an animal. To speed up our behavioral assay to assess tinnitus, we implemented a second paradigm, gap pre-pulse inhibition of acoustic startle (GPIAS). We evaluated salicylate-induced tinnitus in rats that had been tested with both SIPAC and GPIAS paradigms. Rats that developed salicylate-induced behavior with the SIPAC paradigm also showed tinnitus-like behavior with GPIAS. The concordance between the methods helps to establish the validity of SIPAC and GPIAS paradigms.

To identify the neural correlates of tinnitus, 16-channel, chronic microwire electrode arrays were implanted in the auditory cortex to measure single unit or local field potentials from awake rats before and after treatment with high doses of salicylate that reliably induce tinnitus. The local field potentials from the auditory cortex increased in amplitude after salicylate, especially at high frequencies. In pre-

liminary studies, high doses of salicylate unexpectedly caused a significant decrease in spontaneous activity in awake rats.

To obtain an overview of the activity in the rat brain during salicylate-induced tinnitus, we used a microPET camera and fluoro-deoxyglucose tracer (FDG) to study the changes in metabolic activity in rats with salicylate-induced tinnitus. Uptake of FDG tracer into the brain was measured in the same rat under normal baseline conditions and after the induction of tinnitus with 250 mg/kg of salicylate. During salicylate induced tinnitus, inferior colliculi ($P=0.03$) and auditory cortices ($P=0.003$) showed significant increase in FDG activities, whereas there was no significant difference in thalamic activity ($P=0.07$) from the pre-salicylate, baseline state.

Subjective tinnitus was once considered a difficult if not impossible problem to investigate. However, over the past two decade, rapid advances in brain imaging, behavioral models and techniques for recording from awake subjects experiencing tinnitus have advanced our understanding of the biological mechanisms that may be involved in tinnitus. Animal models have the potential to reveal the biological mechanisms that give rise to tinnitus and offer the potential to screen existing or new therapeutic compounds that may suppress tinnitus.

Acknowledgments: Research supported in part by grants from the American Tinnitus Association and Tinnitus Research Consortium.

A COMPUTATIONAL MODEL FOR THE DEVELOPMENT OF TINNITUS-RELATED HYPERACTIVITY: REDUCTION OF HYPERACTIVITY THROUGH ADDITIONAL ACOUSTIC STIMULATION

Roland Schaette and Richard Kempter

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Hearing loss through cochlear damage can lead to the development of increased spontaneous firing rates in central auditory neurons. This hyperactivity has been interpreted as a neurophysiological correlate of tinnitus. The earliest stage in the auditory pathway where tinnitus-related changes have been observed is the dorsal cochlear nucleus (DCN), which receives feedforward input from the auditory nerve (AN).

To address the question of how peripheral hearing loss may lead to tinnitus-related hyperactivity of neurons in the auditory brainstem, we utilize a phenomenological model of the responses of AN fibers and DCN neurons. Noise-induced hearing loss reduces the mean activity of the model AN fibers and DCN neurons. We assume that a persistent reduction of the mean firing rate of DCN neurons activates homeostatic plasticity, a plasticity mechanism that stabilizes neuronal activity on time scales of hours to days by scaling synaptic strengths and adjusting intrinsic neuronal excitability.

When homeostasis increases the response gain of DCN neurons after hearing loss, the mean firing rate can be restored to its pre-lesion values, but the spontaneous firing rate may be increased above the normal level. Thus, in our model, hyperactivity is a consequence of a central compensation for decreased AN activity, implying that hyperactivity could be decreased through additional acoustic stimulation.

When additional acoustic stimulation increases the activity of model AN fibers and DCN neurons, the pathologically increased response gain of DCN neurons is lowered, and hyperactivity is reduced. The duration of hyperactivity suppression in the model depends on the time-scale of the gain adaptation. As homeostatic plasticity is a slow process, a long-lasting reduction of hyperactivity after stimulation could be possible.

NEURAL MECHANISMS UNDERLYING SOMATIC TINNITUS

Shore et al.

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

Somatic tinnitus patients can modulate both the intensity and pitch of their tinnitus by manipulating facial regions including their jaws and teeth, areas innervated by the trigeminal nerve. Over the past several years, we have demonstrated functional connections between the trigeminal system and the auditory brainstem and mid-brain. Stimulation of trigeminal neurons can produce changes in the spontaneous and sound driven firing *rates* of cochlear nucleus (CN) and inferior colliculus (IC) neurons. These changes in firing rate could account for the *intensity* changes in their tinnitus perceived by patients. New data indicate that trigeminal neurons can also modify the *temporal* patterns of spontaneous and sound driven responses of CN neurons, often making the firing patterns more regular. Regular firing of neurons in the CN has been proposed as a model for pitch perception. Thus, if trigeminal neurons can change the *regularity* of auditory neurons' firing patterns, they could alter the perceived pitch generated by those firing patterns.

We will also present evidence that after sound over-exposure, there are compensatory changes in non-auditory innervation of the CN. Our studies so far indicate that following deafness, these compensatory changes result in *enhanced* effects of trigeminal stimulation on the firing patterns in CN, as exhibited by lower thresholds and latencies in response to this stimulation. The physiological results reflect increases in glutamatergic inputs from non-auditory regions of the brain.

Understanding how somatic tinnitus occurs will help us to understand how tinnitus itself is generated. Only then can we hope to develop methods to alleviate this distressing condition.

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TINNITUS TREATMENT WITH COCHLEAR IMPLANTATION IN UNILATERAL SENSORINEURAL DEAFNESS

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Background: In the majority of patients with bilateral profound hearing loss treated with cochlear implantation (CI), a significant reduction of their experienced tinnitus occurred.

Objectives: To assess the effectiveness of cochlear implantation to reduce tinnitus loudness and tinnitus suffering of patients in whom unilateral profound hearing loss provoked incapacitating tinnitus.

Methods: 22 patients were selected for cochlear implantation in the deaf ear in which the tinnitus was perceived.

Tinnitus was assessed using a comprehensive tinnitus assessment schedule comprising tinnitus characterization, pitch sensation, sensation level, visual analogue scale (VAS) for loudness, and the tinnitus questionnaire (TQ) following Hallam, which is a tinnitus specific quality of life questionnaire.

Evaluation was performed preoperatively, 1,3,6,12, 18 and 24 months post fitting. Patients were implanted with a COMBI 40+ M implant or a PULSARCI¹⁰⁰ FLEX^{soft} implant, with the electrode fully inserted in the scala tympani.

Results: All 22 patients used their cochlear implant every day, the whole day. A significant tinnitus reduction was realized in all patients.

Conclusions: The preliminary results of these 22 cochlear implantations suggest that CI is an adequate treatment for incapacitating tinnitus can significantly decrease or even abolish unilateral continuous tinnitus in a deaf ear. There was no conflict between the hearing with CI and the hearing in the opposite ear. These results support the hypothesis that tinnitus is a deafferentiation type of sensation in these patients and that this physiopathological mechanism is reversible.

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INCREASED NEURAL RESPONSE TO AUDITORY STIMULATION IN UNILATERAL TINNITUS, AN FMRI STUDY OF THE INFERIOR COLLICULUS AND THE AUDITORY CORTEX

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Background:

Tinnitus is believed to be related to abnormal patterns of spontaneous neural activity in the central auditory system. These abnormal patterns may result from a decreased effectiveness of neural inhibitory mechanisms. Functional MRI provides a measure of neural activity. Here we investigated whether tinnitus is related to abnormal neural responses to auditory stimulation.

Study design:

Functional MRI was performed in 10 normal hearing controls and 8 patients with unilateral tinnitus (4 left-sided, 4 right-sided). The stimuli were 6-octave wide dynamically-rippled Gaussian noise, presented to the right and left ear, respectively. Stimulus levels were 40 and 70 dB SPL. Together, this provides 4 stimulus conditions. A sparse sampling MRI protocol was used to acquire functional images (TR=10 s, scan duration 2 s). A region-of-interest analysis was performed on the left and right inferior colliculus and the left and right auditory cortex.

Results:

In normal hearing controls, the average relative response amplitude in the inferior colliculi ranged from 0.21% for sound at 40 dB in the ipsilateral ear, to 0.60% for a stimulus at 70 dB in the contralateral ear. In the cortex, these numbers were 0.34% (ipsilateral ear, 40 dB) and 1.40% (contralateral ear, 70 dB). In tinnitus patients, the average responses to the 4 stimulus conditions were larger, ranging over 0.49-0.79% in the colliculi and 0.50-1.55% in the cortex.

Conclusions:

The neural response to sound is enlarged in the inferior colliculi and the auditory cortex of patients with unilateral tinnitus. This finding is consistent with reduced effectiveness of neural inhibition in tinnitus patients.

TINNITUS AND VIRTUAL REALITY THERAPY

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Symptoms of chronic tinnitus are similar to those observed in chronic pain following amputation. Drawing from the successful use of cognitive behavioural therapy (CBT) for chronic pain, recent studies have demonstrated that CBT is also an effective treatment for tinnitus. The use of CBT aims at limiting the presence of exacerbating factors induced by inappropriate behavioural reactions and/or harmful cognitive processes. Thus, this approach should improve the quality of life of patients who willingly adhere to this therapeutic rationale.

Following this analogy, and because techniques of immersion in virtual reality have demonstrated theoretical and practical value in the treatment of chronic pain, we will adapt these techniques for patients with tinnitus. We will evaluate the efficacy of exposure to a 3D virtually reality (visual and auditory) environment on the discomfort induced by subjective unilateral tinnitus. The aim is to develop the patient's ability for assuming an active role in controlling tinnitus (sense of agency). The purpose is to act on the sub-cortical mechanisms of integration, thus allowing the patient to willingly manipulate the tinnitus in a visual and auditory 3D virtual environment to control or "master" tinnitus. It is a question of working on a psycho-sensory level to trigger low level "recalibration" allowing the patient to separate the representation of tinnitus from its perception. The underlying idea is based on the existence of specific hyperactivation associated with tinnitus as demonstrated by brain imaging. Such neural hyperactivity then becomes a target for any kind of modulation based on neural plasticity.

MECHANISMS OF AUDITORY CORTEX STIMULATION

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The accumulated evidence from the past decade of investigation supports the notion that tinnitus generally results from hyperactivity in the central auditory system and involves activation of certain non-auditory pathways. Following sound exposure or administration of salicylate and quinine, it has been reported that hyperactivity develops in the dorsal cochlear nucleus (DCN), inferior colliculus (IC), and auditory cortex (AC). Using the same conditions that induce tinnitus, it has been found that there is an increase in the number of Fos-positive neurons in certain auditory and non-auditory structures, which include the locus coeruleus, lateral parabrachial nucleus, certain subregions of the hypothalamus, and amygdala. In combination with behavioral methods, it has been reported that the sound exposure condition that causes animals to develop tinnitus also induces hyperactivity and increases c-Fos expression in certain auditory and non-auditory brain regions. This suggests that the hyperactivity and increases in c-Fos expression in those structures may represent neural substrates of tinnitus. It is conceivable that modulation or suppression of the hyperactivity and increased c-Fos expression may be an effective way of treating tinnitus.

We electrically stimulated the primary AC to investigate the modulatory effects of cortical electrical stimulation (CES) on tinnitus-related activity in both auditory and non-auditory structures. The rationale of stimulating the AC is that clinical CES or transcranial magnetic stimulation of certain areas of the primary AC in humans can mitigate the perception of tinnitus (Seidman et al. submitted, De Ridder et al. 2006; Richter et al. 2006; Londero et al. 2006; Langguth et al., 2006). Anatomically, the AC has direct projections to a number of auditory and non-auditory structures. In our recent study, we used adult rats and Syrian hamsters to electrophysiologically investigate the modulatory effects of CES on neural activity in the DCN and IC. We also performed *c-fos* immunocytochemistry and examined the effects of CES on c-

Fos expression in several auditory and non-auditory structures. The stimulation was single charge-balanced biphasic electrical pulses (40 ms wide), delivered at intensities of 0-50 mA and at a rate of 100 pps. Our preliminary results showed stimulation of the right AC induced onset suppression, residual inhibition and excitation in the left DCN, but with a higher incidence of suppression. We also found that CES affected neural activity in the right IC. In experiments using *c-fos* immunocytochemistry, we observed that CES induced changes in the number of Fos-positive neurons in some structures including decreased Fos-labeling in the left DCN and right amygdala. The results suggest that stimulation of certain areas of the CES may have modulatory effects on neural activity at the brainstem level. The results also suggest that CES may have activated the pathways between the limbic and auditory systems, possibly modulating neural activity that is involved in tinnitus perception. Possible mechanisms will be discussed.

Abstracts of Posters

THE EFFICACY OF NMDA AND KAPPA-OPIOID RECEPTOR ANTAGONISTS IN TREATMENT OF TINNITUS

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There may be several types of tinnitus with different underlying mechanisms that respond differently to interventions. Even within one type of tinnitus there may be changes over time that can influence the efficacy of interventions. Animal models provide the ability to differentiate central versus peripheral tinnitus, to track changes and to compare the efficacy of interventions. Application of salicylate in the animal model produces a percept of tinnitus that correlates with an increase in the spontaneous firing rate of auditory nerve fibers. We define this as peripheral tinnitus. Noise overstimulation can cause a percept of tinnitus along with a permanent or temporary reduction of auditory nerve spontaneous firing rate. We define this as central tinnitus. Round window noise (RWN) provides a metric of auditory nerve activity, while gap detection – acoustic startle reflex provides a behavioral metric of the percept of tinnitus. Our preliminary results found that Gacyclidine (GA), an NMDA glutamate receptor antagonist with low neurotoxicity, applied to the round window membrane in the guinea pig cochlea reduced the salicylate-induced increase in RWN without affecting cochlear sensitivity. Nor-Binaltophimine (nor-BNI), a kappa-opioid receptor antagonist (dynorphin receptor), was even more effective in reducing the salicylate-induced increase in RWN. Our ongoing experiments will test the hypothesis that a reduction in the salicylate-induced increase in RWN by application of GA or nor-BNI is correlated with amelioration in the perception (gap detection) of tinnitus. We will also test the hypothesis that GA or nor-BNI will reduce the perception of tinnitus when associated with increased RWN (peripheral tinnitus) but not when the perception occurs without increased RWN (central tinnitus) by comparing their efficacy in SA-induced versus noise-induced tinnitus.

MEMANTINE

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Introduction: Nowadays, the treatment of tinnitus is still a great challenge for the otolaryngologists. Many facts remain unknown in its pathophysiology, leading to many different therapies, with irregular results. Memantine is a drug used in Alzheimer's disease, due to its action in blockage of the NMDA receptor.

Aim: To evaluate efficacy and safety of memantine in the treatment of sensorineural tinnitus.

Materials and method: 60 patients with sensorineural tinnitus were divided in 2 groups in a double-blind prospective cross-over study against placebo, with evaluation of the therapeutic and side effects, using the THI (Tinnitus Handicap Inventory).

Results: This study didn't show any statistically significant improvement in the THI than placebo. Meanwhile, some data suggest a possible late effect of memantine. The incidence of side effects was low (9,4 %), but led to interruption in all the cases.

Conclusion: This study didn't provide data to recommend memantine to treat sensorineural tinnitus, but a possible late effect of the drug should be evaluated in further studies.

KEY WORDS: tinnitus, memantine.

TINNITUS IN CHINCHILLAS RELATED TO THREE DISTINCT PATTERNS OF COCHLEAR TRAUMA

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A long-standing hypothesis is that tinnitus, the perception of sound without an external acoustic source, is triggered by a distinctive pattern of cochlear hair cell (HC) damage. This hypothesis was tested using controlled damage of inner (IHC) and outer (OHC) hair cells. Chinchillas were assigned to 4 groups matched for performance on a psychophysical task sensitive to tinnitus: 1) acoustic exposure (AEx); 2) round window cisplatin (CisEx), an OHC toxin; 3) round window carboplatin (CarbEx), an IHC toxin; 4) unexposed controls. After testing for chronic tinnitus, single-neuron spontaneous activity was recorded in the inferior colliculus (IC) using multi-channel electrodes. Each cochlear treatment produced a distinctive pattern of HC damage. AEx: Sparse low-frequency IHC and OHC loss; CisEx: pronounced OHC loss; CarbEx: pronounced IHC loss; control: no loss. Compared to controls, all experimental groups displayed significant and similar tinnitus with features resembling a 1 kHz tone. IC spontaneous activity was affected as follows: All experimental groups showed decreased inter-spike-interval (ISI) variance; AEx and CisEx showed increased contralateral spiking and cross-fiber synchrony; AEx showed elevated ipsilateral bursting. A multi-dimensional analysis identified a sub-population of neurons more prevalent in subjects with tinnitus. Predominantly located in the IC shell, they were characterized by high bursting, low ISI variance, and within-burst peak spiking of approximately 1000/sec. It was concluded that cochlear trauma in general, rather than its specific features, leads to multiple changes in central activity that underpin tinnitus. Particularly affected was a sub-population of neurons with a unique triad of features.

BRAIN PATHOPHYSIOLOGY IN TINNITUS PATIENTS

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Brain neurosensorial disorders, i.e: tinnitus, represents one of most reasons of disability.

The most often used methods for functional imaging of the human brain are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

These tomographies provide three-dimensional (3D) images comprising information on metabolism. Although the spatial resolution of these images is excellent, the temporal resolution is not high enough to keep up with the speed at which neuronal processes occur.

During year 2000, we have started studying our patients by means of Brain Electric Tomography (LORETA) – Pascual Marqui – 1994.

Through LORETA, it is not only possible to study spatial distribution but also knowing the different cerebral activity areas.

200 patients presenting tinnitus symptoms have been studied and results were compared vs. those obtained in 40 normal patients.

In the group of tinnitus patients a common pattern of pathology is observed:

1. - Compromised BA 21 and 22
2. - Compromised BA 47

Through neuroimaging diagnoses metabolic alterations are detected due to consuming Oxygen or Glucose. These alterations could respond to hypo or hyper neuronal function, being unable to establish a diagnosis of the type of neuronal electrical alteration of the area.

To order to establish an specific treatment for tinnitus it is necessary to count on methods sensitive enough capable of demonstrating total or partial therapeutic modifications produced in patients under the established therapy.

VIBRANT SOUNDBRIDGE® AMPLIFICATION OF HIGH FREQUENCIES AND IT'S EFFECT ON TINNITUS

Dr. Eberhard Biesinger Traunstein

Supported by Tinnitus Research Initiative 2007

BACKGROUND

Many patients who experience tinnitus also suffer from high frequency sensorineural hearing loss. The newest generation of acoustic hearing aids, very small behind-the-ear hearing aids used in conjunction with an open earmold (open ear hearing solutions), are often offered as the first line of treatment in this population. Although open ear hearing solutions may provide a viable option to address both hearing and cosmetic needs in some patients, these hearing aids may not provide adequate amplification of frequencies above 6 kHz (technical datasheets of hearing aid manufacturer). Because of this technical limitation, many patients' hearing needs may not be met. In addition, they may continue to suffer the annoying consequences of tinnitus and may be dissatisfied with their hearing aids.

The Vibrant Soundbridge® is an active implantable middle ear hearing device used to treat sensorineural hearing losses ranging from mild to severe in degree. The device is designed to directly drive the ossicles, thereby amplifying the natural motion of the ossicular chain.

The implant consists of two major components: 1) the implant, called the Vibrating Ossicular Prosthesis (VORP), and 2) the external portion, called the Audio Processor, which is programmable to provide appropriate amplification. The implant system is capable of good fidelity up to 8 kHz (G. R. Ball, Alex Huber, Richard L. Goode; Scanning Laser Doppler Vibrometry of the Middle Ear Ossicles).

MOTIVATION

Over the past eight years, 18 patients were implanted with the Vibrant Soundbridge at the Klinikum Traunstein clinic as a treatment for sensorineural hearing loss. All patients chose the implant system because they were dissatisfied with traditional acoustic amplification. Of the 18 patients, 11 patients reported experiencing tinnitus pre-operatively. All 11 patients reported a post-operative reduction in tinnitus when the external Audio Processor was activated. One patient, implanted bilaterally, was able to completely eliminate his tinnitus when both Audio Processors were turned on. As a consequence of these encouraging observations, a prospective study of the effect of amplification provided by the Vibrant Soundbridge on tinnitus in persons with sensorineural hearing loss was designed.

SUBJECTS AND METHODS

4 adult subjects with sensorineural hearing loss fitting the current indications for the Vibrant Soundbridge will be implanted unilaterally and 1 bilaterally. The effect of amplification on subjective reports of tinnitus will be observed at 4 weeks, 12 weeks, 6 months, 1 year, and 2 years post initial activation of the implant system. Measures to characterize tinnitus and the subjects will include Questionnaire TBF-12, Questionnaire Goebel & Hiller, Visual-Analogue Scale, Symptom Checklist SCL-90, THI (Newman), BDI (Depression) and Insomnia-Index (Regensburg). In addition, audiologic performance and psychophysical tinnitus matching will be documented according to the consensus of TRI (Tinnitus Research Initiative), as well as subjective hearing benefit with the APHAB.

ACKNOWLEDGEMENTS

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STRUCTURAL AND NEUROBIOCHEMICAL CORRELATES OF NOISE-INDUCED TINNITUS: A MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY STUDY

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Using single voxel or multi-voxel magnetic resonance spectroscopy (MRS), this research is designed to develop neurobiochemical biomarkers of noise-induced tinnitus within the auditory centers of the human brain in the left and right hemispheres. Being able to detect and measure metabolites in the millimolar range, such as *N*-acetyl aspartate (NAA), choline (Cho), creatine (Cr), glutamate (Glu), gamma-aminobutyric acid (GABA) and or glycine (Gly), we can begin to understand if and or how tinnitus and hearing loss, either alone or in combination, alters the neurobiochemical environment of these auditory cortical areas. Two groups of individuals matched for age, gender, and hearing loss will be studied: Group 1 will include individuals with noise induced hearing loss *with* tinnitus and Group 2 will include individuals with noise induced hearing loss *without* tinnitus. Controlling for hearing loss is an imperative core issue that has confounded many previous studies in this area, making interpretation of results difficult if not impossible. Additionally, using voxel-based morphometry (VBM), we will determine the extent to which structural brain anatomy in the form of grey and/or white matter volumes are different between groups and possibly correlated with the MRS. Taken together, MRS and VBM has the potential to enhance our understanding of tinnitus that is currently unavailable by any other methodologies. If successful, this conceptual framework will add to the available body of tinnitus research by: 1) contributing to understanding underlying mechanisms, 2) aid in developing structural and/or neurobiochemical models of noise-induced tinnitus, 3) help in monitoring treatment options, 4) aid in diagnosis, and 5) act as a segue towards a cure. Indeed, MRS in particular is uniquely positioned as a research tool between the domains of neurochemistry and structural brain imaging that is well suited for studying humans in a non-invasive manner.

ANXIETY AND DEPRESSIVE SYMPTOMS IN TINNITUS PATIENTS

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The aim of this study is to investigate any correlation between tinnitus and anxiety and depressive symptoms.

The assessment is composed of: Visual Analogical Scales (VAS) for the evaluation of tinnitus induced problems; Tinnitus Handicap Inventory (THI); State and Trait Anxiety Inventory-Y (STAI); Beck Depression Inventory (BDI).

These instruments were chosen based on their psychometric properties, time of administration and validity in many languages; the sample consists of 108 patients. Correlation between anxiety symptoms and THI score is significant ($p < 0.001$); significance was found between depressive symptoms and THI ($p = 0.011$) as well as between STAI-T and BDI. Significant correlation was also found between these questionnaires and the intensity of tinnitus, annoyance and effect on life evaluated by the VAS scale.

24% of the sample had severe tinnitus. Mean anxiety is at 67th percentile for male patients and 86th for female patients; 35% of the total sample having an anxiety disorder. 13% of the sample shows a depressive pathology. 12% have both anxiety and depression symptoms. Although about 1/3 of patients are suspected of suffering from anxiety, a pathological level of anxiety and depression was found in about 10% of the sample. The THI questionnaire is a good predictor for patients with higher levels of depression and anxiety.

FUNCTIONAL CORRELATES OF UNILATERAL TINNITUS IN AUDITORY CORTEX

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Introduction

Often, tinnitus is associated with some extent of high-frequency hearing loss. The tinnitus frequency is usually higher than the “audiometric edge” frequency above which hearing starts to fall off. Tinnitus is related to hyperactivity and hyperresponsivity of several structures of the afferent auditory pathway including the auditory cortex. Here we focus on the functional differences, assessed by evoked magnetic fields, between the auditory cortices contralateral and ipsilateral to the tinnitus ear in patients with unilateral tinnitus.

Methods

25 tinnitus patients and 22 controls participated in the study. 10 of the tinnitus patients and 15 of the controls were professional musicians, including orchestra musicians. Stimuli were amplitude-modulated tones with two modulation frequencies (39.1 Hz, 41.1 Hz) and three carrier frequencies matching the tinnitus frequency (the frequency 1? octaves above the audiometric edge frequency in controls), the audiometric edge frequency, and a frequency below the audiometric edge. Stimulation was binaural regarding carrier frequency and dichotic regarding modulation frequency. The MEG was recorded using a Neuromag122 system. The steady-state response was averaged across all stimulus conditions and projected into the source domain using a bilaterally symmetric source model. Source amplitude, inter-trial phase source coherence, and within and across frequency inter-source phase coherence were computed for each carrier and modulation frequency. Source amplitude was also determined for spontaneous activity in the modulation frequency bands.

Results

Spontaneous source activity in the modulation frequency bands was larger for tinnitus patients than for controls. Inter-trial phase source coherence and source amplitude of the steady-state response were larger for contralateral than for ipsilateral stimulus input in both hemispheres. In tinnitus patients who were not musicians the laterality of input interacted with hemisphere and carrier frequency in such a way that the laterality of input effect was largest for the tinnitus frequency in the

hemisphere contralateral and smallest for the tinnitus frequency in the hemisphere ipsilateral to the tinnitus ear. In musicians with tinnitus the source amplitude of the steady-state response was larger in the hemisphere ipsilateral than in the hemisphere contralateral to the tinnitus ear. Within-hemisphere cross-frequency source phase coherence of the response was inversely related to stimulus carrier frequency, but did not show an effect for tinnitus status. However, the within-hemisphere cross-frequency source phase difference was smaller for tinnitus patients than for controls.

Conclusions

Tinnitus patients show enhanced spontaneous activity in the frequency bands investigated, a reduced within-hemisphere cross-frequency source phase difference, and altered patterns of inter-trial phase coherence and steady-state response amplitude across hemispheres, laterality of input, and carrier frequency. The inter-trial phase coherence and response amplitude patterns are different for musicians and non-musicians with tinnitus. Together, these findings suggest that tinnitus is associated with a reorganization of the phase relationship between rhythms of neighboring frequencies, albeit in a way that differs between musicians and non-musicians.

Research was supported by DFG grant Di497/3-2.

ALTERED RESTING-STATE BRAIN CONNECTIVITY IN TINNITUS PATIENTS REVEALED BY PHASE-SYNCHRONY ANALYSIS

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Phase synchronization between neuronal signals can be used to investigate long-range interactions in the human brain. We examined differences of brain connectivity between 21 chronic tinnitus patients and 20 healthy control subjects in during the resting-state, using MEG (Magnetoencephalography) recordings. Based on a source-space-projection we estimated source activations in major brain regions of interest. Instantaneous phase was estimated with a wavelet convolution in the frequency range of 1-90 Hz.

A highly significant group difference was prominent in brain connectivity measures within the alpha- and the gamma band. Inter-regional phase synchronization in 9-12 Hz band was reduced for the tinnitus patients. In contrast, there was a pronounced enhancement of phase synchronization in the 48-54 Hz frequency range, relative to the one in control subjects. We estimated the architecture of the connections that gave rise to the group difference in both frequency bands. The activation of these networks separated the tinnitus group from the control group with an accuracy of 83%.

Findings suggest that enhanced gamma activity comprises a neuronal correlate of the tinnitus sensation. Reduced alpha band activity might be seen as a weakening of correlated tau-rhythms, generated in auditory regions. Phase synchronizations in these bands as revealed in the present study could therefore indicate the top-down involvement of distant non-auditory brain regions.

PIRIBEDIL

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Tinnitus is still a great challenge to Otolaryngologists, due to the facts that its pathophysiology is still largely unknown and that there are no well established treatment methods.

Any new therapeutic perspective is a new hope for millions of tinnitus` sufferers around the world. One of the facts that lead to therapeutic failure is that there are no methods available to delineate different subtypes of tinnitus and to predict response to distinct pharmacological treatments. The presented study aims to investigate whether ECoCh and DPAOE may be helpful to predict treatment outcome for therapy with a dopamine agonist.

Piribedil is a dopamin agonist that acts at the lateral olivo-cochlear bundle: 100 patients with tinnitus of sensorineural origin will be included and divided in two groups, according to the results of the ECoCh and DPAOE: 50 patients with abnormal eletrocochleography (ECoCh) and normal DPAOE and 50 patients with normal ECoCh and abnormal DPAOE. Each group will be subdivided in two 25 patients subgroup, one of them taking piribedil 50 mg once a day and the other placebo, also once a day, for 3 months. After a 1 month wash out interval, groups will change as a double blind cross-over study. Tinnitus will be evaluated at the beginning of the study and monthly until 7 months with the Tinnitus Handicap Inventory (THI). Current status: clinical evaluation, with 74 patients taking the drug in Phase 1. An interesting finding is the high incidence of double peak at the action potential in eletrocochleography. There are no references about this finding and its relevance is yet to be established.

TINNITUS SOUND THERAPY WITH OPEN EAR HEARING INSTRUMENTS: WHICH PARAMETERS COULD AFFECT THE RESULTS?

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Abstract

In a previous study, tinnitus treatment with sound enrichment delivered by open ear hearing instruments was investigated. Aim of this study was to evaluate if some factor (gender, age, tinnitus characteristics, duration of the therapy, use of drugs, PTA, DPOAE, MML, OHI gain) can be significative in therapy outcome. We recruited 46 patients with ski slope and with mild hearing loss. THI questionnaire was used. No correlations were founded, but the improvement was statistically significative.

TINNITUS MODULATION BY MUSCLES PRESSURE OR CONTRACTION CAN BE REDUCED USING THE SAME MOVEMENTS THAT EVOKE IT

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Introduction: Different stimuli on non auditory nature – especially muscle contractions, gaze or tactile - can interfere with the auditory pathways, evoking tinnitus modulation while such stimuli are present. This modulation pattern – usually tinnitus worsening - seems to be a result of neural plasticity, especially involving the activity of dorsal cochlear nucleus.

Objective: Observe whether a personalized training with daily repetition of the muscle movements that evoke tinnitus modulation can reduce this modulation in a two-month period.

Methods: Seven patients (mean age: 53, ranging from 22 to 72 years-old) who spontaneously complained about the onset of a new tinnitus or changes in loudness or pitch of their preexistent tinnitus by pressure or contraction of head and neck muscles were enrolled. One subject also presented tinnitus modulation by upper and lower limbs movements. All patients were asked to perform a personalized training involving repetitive pressures or contractions of the own muscles that evoked their modulation. Training was suggested to start with 10 repetitions of each movement, two or three times a day. The medical follow-up was scheduled every fortnight for two months.

Results: Four subjects (57.1%) showed reduction of tinnitus modulation pattern after 30 days of training, including one patient who also improved his preexistent tinnitus after 4 months. On the other side, two patients (28.5%) showed no change and one impaired his modulation pattern after 30 days. Additional head and neck muscles modulating tinnitus were identified after repetitive contractions in two patients.

Conclusions: It is possible to change the tinnitus modulation caused by muscular contractions using the repetition of the same movements that evoke the modulation. Such changes start to occur about 30 days of training. Future controlled studies with prolonged periods of repetitive modulation movements should be performed to check improvement of the preexistent tinnitus.

GAZE-EVOKED TINNITUS CAN RESOLVE WITH A GAZE-EXERCISE PROGRAM

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Introduction: Gaze-evoked tinnitus (GET), usually a sequela of posterior fossa surgery, refers to tinnitus associated with eye movements. It seems to be related to anomalous interactions among auditory, vestibular, visual and somatosensory pathways. No effective treatments for GET have yet been described.

Objective: Describe an effective treatment that allowed the complete resolution of a GET.

Case report: A 39-year-old woman with bilateral profound hearing loss [right ear unknown cause (age 16)]; left ear acoustic neuroma surgery (age 33); right cochlear implant and second left acoustic neuroma surgery both age 35] developed monaural GET whenever her cochlear implant was activated. With her implant off, she had no tinnitus even with eye movements. Whenever her implant was on, she had no tinnitus in the primary position of gaze but, with down or right gaze, right tinnitus was heard, and, with up or left gaze, left tinnitus was heard. Within 2 weeks of a specific and personalized gaze exercise program, up gaze tinnitus completely resolved. After 16 weeks of a progressively more intense gaze exercise program all tinnitus resolved.

Conclusion: Gaze-evoked tinnitus can resolve with exercises designed to elicit the tinnitus. All patients with GET should have a trial of a gaze-exercise program.

TINNITUS MODULATION BY MYOFASCIAL TRIGGER POINTS AND ITS DISAPPEARANCE BY TREATMENT OF THE MYOFASCIAL PAIN SYNDROME: AN INTERESTING RESULT

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Introduction: Tinnitus and pain have several similarities and both are common symptoms. However, professionals are not used to search for pain complaints nor for modulation pattern when attending tinnitus patients. Both symptoms seem to be especially related when tinnitus modulates during trigger points palpation.

Objective: describe a patient with chronic tinnitus, dizziness and pain who showed tinnitus modulation during palpation of some myofascial trigger points (MTP) and was cured of all symptoms by the treatment of her myofascial pain syndrome.

Case report: a 51 year-old female presented with bilateral tinnitus for the last 4 years, worse on the left ear. She scored his annoyance as 10 in a 0-10 visual analogue scale. She also complained of dizziness and chronic pain in upper limbs, cervical spine and left side of the head for the last 4 years, which she scored as 9. Other complaints included daily bruxism, subjective hearing loss and depression. The physical ENT examination was normal. Because of her clinical pain feature, she was forwarded to the physiotherapist. MTP were found in nine muscles of the head, neck and shoulder girdle, most of them related with her previous pain. During palpation of MTP of the left sternocleidomastoid, she noticed a complete tinnitus remission, although it returned to the basal after pressure withdrawal; during palpation of MTP of the right trapezius, the patient suddenly reported a change in tinnitus pitch; eventually, in the left trapezius she had a temporary sensation of dizziness. The proposed treatment was directed to her myofascial pain syndrome through digital deactivation of MTP, muscle stretching and strengthening, postural corrections during daily activities and sleep positions, as well as self-massage. Weekly sessions were performed for six months, with a gradual improvement of the three symptoms (pain, tinnitus and dizziness) up to the total cure.

Conclusion: Tinnitus patients should be alert to the relation between tinnitus and myofascial pain syndrome, especially when tinnitus can be modulated by the pressure of trigger points. Treating the pain through deactivation of trigger points seems to be the most important factor of the tinnitus cure in such cases.

A VERY UNIQUE CASE OF TINNITUS MODULATION BY TACTILE STIMULI IN A PATIENT WITH PULSATILE TINNITUS

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Introduction: Tinnitus modulation is a clinical sign of the interference of other pathways upon the auditory pathways

Objective: to describe a very different clinical pattern of tinnitus modulation in a patient with pulsatile tinnitus

Case report: a 54-year-old male patient complained of constant bilateral pulsatile tinnitus for the last 4 years, worse on the left side. He scored his annoyance as 10 in a 0-10 visual analogue scale. He also complained of subjective bilateral hypoaacusis for the last 20 years, worse on the left side. Although he has had episodes of depression, anxiety and panic syndrome, he was currently symptom-free. He came to the first visit with an audiologic screening showing a moderate high frequency SNHL in the left ear and a temporal bone CT scan showing bilateral non-dehiscent high jugular bulb. Additional exams such as blood biochemistry and MRI were normal. The high frequency audiometry showed severe SNHL in 10kHz and profound hearing loss in 12, 14.5 and 16kHz in both ears. Tinnitus seemed to have a 12kHz pitch, but loudness was not possible to detect.

His regular ENT physical exam was normal. However, his tinnitus presented a specific and repeatable pattern of temporary modulation with tactile stimuli in his head: a light worsening occurred when he touched the left side of his face in the corresponding area innervated by the three branches of trigeminal nerve, mainly in the maxillary branch. Moreover, when the tactile stimulus was changed to a pressure of the same region, he complained of a greater worsening than when he just touched it. As he rated his regular tinnitus as a 10, it was impossible to rate the amount of worsening. On the other side, he has a tinnitus improvement with tactile stimuli in ipsilateral retroauricular area following a similar pattern: a light improvement during touching and a greater improvement after pressuring the region (score 2 in the VAS).

Besides all tactile stimuli, he also presented modulation by muscular contractions, such as the improvement with head rotation to the right and to the left (improving only the contralateral tinnitus), maximum opening of the mouth and clenching teeth (bilateral improvement) and mandible lateralization to the right and to the left (improving only the contralateral tinnitus).

The patient underwent 3 SPECTs: in a basal situation, after pressuring his left cheek (worst tinnitus) and after pressuring his left postauricular area (lowest tinnitus). Comparing the first and the second SPECTs, reduction of blood flow was observed in the left cerebral hemisphere, in the limbic lobe, in the uncus and in Brodmann area 36. Comparing the first and the third exams, improvement was observed in blood flow in the right temporal lobe, in the superior temporal gyrus and in Brodmann area 22. Decrease was observed in the left limbic lobe, in the uncus and in Brodmann area 36.

Conclusion: the bilateral pulsatile tinnitus in this case maybe associated with the blood flow in the bilateral non-dehiscent high jugular bulb, which improved immediately during the pressure of the post auricular area. However, the patient showed a very unique pattern on tinnitus modulation with tactile stimuli in the trigeminal area of the face, with different degrees of response when he touched the areas and when he pressured them.

A TINNITUS DATABASE.

Ron Goodey & Sally Wheater, July 2007

Tinnitus Research Initiative is focused on finding treatments for tinnitus. It does not want any potential resource overlooked. Online databases are restricted mainly to articles in peer reviewed journals and are relatively slow to access. Old research may include projects which were never completed or may have been overlooked yet have potential. Book chapters often include material not readily found in journal articles. Presentations and posters include ideas which have not yet reached peer reviewed journals and may never do so. Claims made in newspaper articles, magazines and advertisements may include ideas of merit.

Therefore, with the encouragement of Dr de Nora, I decided to set up a tinnitus database which would incorporate items from these various sources & be quicker and easier to use than numerous online databases. My plan was to identify incomplete or forgotten projects with potential & then bring them to the attention of the TRI executive. I reviewed available reference management systems. I decided to use EndNote on the basis that it is used by two to three times the number of people who use all the other reference management systems added together.

I decided to limit the database to items which include “tinnitus” in the heading and/or the abstract. I realise this excludes many other articles which may also be relevant to some tinnitus studies. These articles need to be saved in other databases so as to avoid making this one unmanageably large.

I limited the number of reference types to which items are allocated so as to help keep the database manageable. The reference types used are shown in table 1. Each user has to select them on their own computer because EndNote stores them in a Windows program and not in EndNote itself. Extra reference types could be added for a user’s private use (Personal Communication, Grant Application).

To search a wide variety of data sources, create an abstract where there is none, enter items & then keep upgrading the database is a major undertaking. I was fortunate to enlist Ms Sally Wheater as co-worker. Sally is a trained research librarian & previously lectured on the use of EndNote.

This database was assembled for my personal use. However it may also be a useful tool for others working with TRI to help them identify resources which might otherwise be overlooked. This database should not itself be treated or quoted as a source. Original sources must always be referred to.

Most potential users probably already have EndNote available through their academic institutions. We are using version 9 rather than the newer version 10 which at the time of its release was said to contain some bugs.

For those who must have their reference management system on a network we are

assured that EndNote can easily be converted to RefMan.

In the version for my personal use I have attached where possible a PDF of the original document either through downloading it or by scanning it as a searchable PDF file. If I have the original article then this is indicated by a 'paper clip' against the citation in the EndNote tinnitus library.

Having provided the database of tinnitus citations on CD or DVD for personal use of those TRI associates who want to use it, we plan subsequently to provide an update at appropriate intervals. The recipient can then merge the database update with the existing database. From time to time we shall need to re-issue the full up-to-date database.

When users identify articles (including their own) which meet inclusion criteria and are missing then please send them to us for subsequent inclusion. If an abstract is absent &/or I do not have the full article then I would be very grateful to be sent the full article in whatever form you have it whether hard copy or digital. We can then include an abstract in the next update. We want this to be a living database which helps all of us as we seek cures for tinnitus.

Following a search within an EndNote database EndNote allows the user to store the resultant collection as a Word document. An alternative way of storing a collection within EndNote itself is to tag all the collected items with a keyword unique to that collection. E.g. I have tagged all my favourite articles related to lidocaine as "1idocaine". This is suitable mostly for customising each user's own copy of the database. However as the "TRI Workgroups" evolve they may suggest tagged collections of benefit to all users.

For those who are unfamiliar with EndNote the online manual is quite daunting. A much more consumer friendly option is to purchase "EndNote 1-2-3 Easy", by Abha Agrawal, 2006 Springer Science+Business Media, Inc.

Table 1

Reference Types used in this Tinnitus Database.

Journal Article Book

Thesis

Conference Proceedings

Newspaper Article

Book Section

Magazine Article Edited Book

Patent

Electronic Source

Manuscript

Brochure/Newsletter/Advertisement (Unused 2 reallocated)

Form/Questionnaire (Unused 3 reallocated)

Electronic Book

Conference Paper/Poster

ABNORMAL SOUND-EVOKED ACTIVATION IN THE AUDITORY PATHWAY OF PEOPLE WITH TINNITUS

Jianwen Wendy Gu, Euicheol Nam, Robert A. Levine, and Jennifer R. Melcher

The present study builds on a previous report describing two abnormalities in the inferior colliculi (IC) of people with tinnitus: (1) elevated activation in response to sound compared to audiometrically-matched controls without tinnitus, and (2) reduced sound-evoked activation during ongoing background noise (Melcher et al. 2000, 2005). We hypothesize that the first abnormality is associated with the low tolerance for high level sound experienced by many people with tinnitus, while the second may reflect premature saturation of sound-driven activity. Here, we present preliminary results from an ongoing study aimed at testing these hypotheses and extending the examination of sound-evoked fMRI activation in tinnitus subjects to centers throughout the auditory pathway.

Normal-hearing tinnitus and non-tinnitus subjects (eight and eleven, respectively) underwent behavioral tests followed by fMRI. The behavioral tests included measurement of threshold and loudness growth for the sound stimulus used during fMRI (continuous broadband noise). Subjects were characterized according to whether they deemed the noise stimulus to be uncomfortably loud at levels less than 90 dB SL (reduced sound tolerance) or above 90 dB SL (normal tolerance). 10 slices were imaged in a sparse paradigm to prevent the scanner acoustic noise from contaminating the activation, and cardiac gating was used to improve detection of activity in brainstem structures. Images were acquired using a 3 T Siemens Trio scanner and 12-channel Matrix head coil. Sound levels of 50, 70, and 80 dB SPL were used. However, the present report focuses on the two sound levels tolerated by all subjects: 50 and 70 dB SPL.

The present results for 70 dB SPL replicated the previous report in showing significantly greater activation in the IC of people with tinnitus as compared to those without ($p < 0.04$). Furthermore, they indicate that the greater activation is specifically attributable to a subset of tinnitus subjects (6 of 8) with reduced tolerance for high level sound. In both ICs and at both 50 and 70 dB SPL, activation in tinnitus subjects with reduced sound tolerance was almost always greater than or equal to that in tinnitus subjects with normal tolerance. A relationship between reduced tolerance and IC activation was also apparent in subjects without tinnitus. There were two non-tinnitus subjects with reduced tolerance. One always showed activation that was greater than or equal to that of non-tinnitus, normal tolerance subjects and the other usually did.

In contrast to the IC, which showed activation for every subject, the cochlear nucleus showed detectable activation in only about half the subjects. Nevertheless, the

qualitative impression from the data so far is of elevated activation for subjects with reduced sound tolerance (both tinnitus and non-tinnitus).

Our next step is to examine the results for the auditory cortex, medial geniculate body, and superior olivary complex. In addition, because most subjects with reduced sound tolerance could not tolerate the stimulus (80 dB SPL noise) intended to drive activity into saturation, our present data are insufficient for testing our second “saturation” hypothesis. To test this hypothesis in future experiments, we will adopt a new stimulus modeled after the ongoing background sound of our previous study, a sound tolerated by all subjects.

Conclusion: The decreased tolerance for high-level sound experienced by many people with tinnitus is associated with amplified sound-evoked activity in the inferior colliculi and perhaps also the cochlear nuclei. Whether this abnormal neural amplification arises from local, bottom-up or top-down mechanisms remains unknown, but may be clarified by our as yet unanalyzed data for auditory thalamus and cortex.

OPENNFB - AN OPEN NEUROFEEDBACK ENVIRONMENT

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Our group has recently demonstrated that modifying oscillatory brain dynamics in tinnitus using neurofeedback could help to alleviate this condition. The software to perform neurofeedback however is mostly proprietary meaning that the source code is not open. Also it is usually tied to the specific hardware of the manufactures. For scientific purposes however it is desirable to implement a feedback software that is independent of one type of hardware. An open-source platform will make it furthermore easier for to implement and probe innovative methods to analyze EEG-data in real-time, giving us great flexibility to investigate various tinnitus neurofeedback treatment strategies.

OpenNFB is an open-source neurofeedback-application that aims to fill this shortcoming that we face and which will be released under the GPL . It enables everyone with knowledge in C++ to write plugins to implement new methods or access new data-sources. No programming knowledge is needed to setup a neurofeedback-training as training-paradigms are built using an easy to learn XML dialect. The first public version is planned to be released in late 2007. Future versions will also include an intuitive graphical user interface to build these paradigms.

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EVALUATION OF BOTULINUM TOXIN IN THE TREATMENT OF SOMATIC TINNITUS

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Somatic tinnitus are those tinnitus generated after a somatosensorial injure (whiplash syndrome, temporomandibular joint disorders, dental injure) or those tinnitus that can change the pitch or the loudness with orofacial movements. The botulinum toxin has demonstrated a positive effect on the autonomic nervous system (ANS). The mechanism of the toxin is performed through the peripheral nerves surrounding the aural region and act from the distal dendrites of the nerves to the ANS, all along the somatosensorial pathway. A possible action on the multimodal crossing sites could have an indirect effect on the auditory pathways, so the auditory modulation could reduce somatic tinnitus perception. The goal of the study is the evaluation of the effect of botulinum toxin in patients with somatic tinnitus compared with a placebo group.

Twenty-five patients will be included in each group. All the patients will follow a physical exploration, auditory battery tests (tonal and speech audiometry, tympanometry and study of the stapes reflex, otoacoustic emissions and distortion products, evoked brain responses) and the loudness discomfort level. Tinnitus evaluation will include a tinnitogram (psychoacoustical loudness, pitch, minimal masking level, residual inhibition), Spanish validation of the tinnitus handicap inventory (Newman 1996), visual analogue scale (VAS) on tinnitus loudness from 1 (mild) to 10 (severe) and the somatic tinnitus test. Hyperacusis evaluation will be performed through the VAS, number of activities affected due to the decreased sound tolerance from a list of 11, Spanish validation of the hypersensitivity to sound questionnaire (Geräuschüberempfindlichkeit (GÜF), Nelting 2002).

The method will be an injection of 20 units of Botulinum Toxin A, placed on three positions: superior, postero-superior, posterior-inferior of the retroauricular region. Placebo will have the same aspect of the drug and it will be injected in the same places. Follow-up evaluation has been established after 1 and 4 months

Results between the treated and the placebo group will be studied according to the tinnitus and hyperacusis symptoms.

THE EFFICACY AND LIMITATION OF TRANSTYMPANIC MICROENDOSCOPE IN THE APPROACH TO THE ROUND WINDOW MEMBRANE

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Sensorineural hearing loss is one of the most common disabilities in industrial countries. Recently, there has been increasing interest in local delivery of therapeutic agents onto the round window membrane (RWM). The drug delivery system using biodegradable hydrogel is reported to be a safe and effective candidate for the treatment of inner ear disorders. In this system, a positively charged protein is electrostatically trapped in negatively charged polymer chains composing the biodegradable hydrogel. As the polymer chains degenerate, the protein is released from the hydrogel. The released protein is conveyed into the inner ear according to the concentration gradient, so close contact between biodegradable hydrogel and RWM is important to obtain effective drug introduction. Plontke et al. (2002) reported that transtympanic microendoscope provided good visualization of RWM. He showed some representative cases and concluded that microendoscope was effective in the approach to the RWM. However, the efficacy and limitation was not examined enough. In this study, we examined the visibility of RWM with a specially prepared microendoscope in 8 temporal bones. A small fenestration (2 * 1 mm) was made in the posterior inferior quadrant of the tympanic membrane. The RWM was observed through this window using microendoscope. In all bones, some part of RWM was observed. In 3 bones, excellent access to RWM was obtained and the tip of the microendoscope was able to be advanced close to the RWM. In 3 bones, the round window niche was totally covered with false membrane. The microendoscope failed to differentiate false membrane from RWM because the resolution is not high enough and the provided image is two-dimensional. Microendoscope provides good view of RWM and is available in the local drug administration. The quality of image is still to be improved.

THE EFFECT OF SSRI ON TINNITUS SEVERITY

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Tinnitus is often associated with hearing loss, but the severity of tinnitus suffering depends on many other factors. The correlation between psychological/ psychiatric factors, and the suffering of tinnitus are strong and tinnitus suffering is often associated with anxiety and depressive disorders, as well as decreased general health. We have earlier suggested a possible common neurochemical dysfunctions in patients with severe tinnitus and patients with depressive disorders. A dysfunction in the serotonergic (5-HT) system is likely, because of its involvement in both the regulation of concentration, sleep and mood and in the modulation of the sensory processing in the auditory pathways and auditory cortex.

In the clinical practice it is important to differ the etiology of the emergence of tinnitus from the etiology to the development of a persistent tinnitus suffering, but also to identify different causes to such severe suffering. For this purpose we have constructed an evidence- based screening model for early identification of patients with high risk of developing incapacitating tinnitus and have used this model in the recruitment of patients for a prospective randomised double blind study of sertraline. Our result showed that sertraline had significant better effect on the severity of tinnitus compared to placebo.

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TINNITUS AND SLEEP

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There are many factors that influence the severity of tinnitus. Currently there is a consensus that sleep problems are among the most frequently reported concerns by tinnitus patients. These problems include falling asleep, frequent waking up during the night, poor quality of sleep and decreased duration of sleep. Many of tinnitus sufferers blame tinnitus for sleep difficulties. They are more distressed and report greater tinnitus severity. In our study the severity of tinnitus, evaluated by the total score of the Tinnitus Handicap Inventory depended in the highly statistical manner from the extent of sleep problems. It has been postulated that the processing of the tinnitus related- neuronal activity at the subconscious level plays an important role in the habituation of tinnitus. Tinnitus Retraining Therapy (TRT) includes the use of sound 24-hours per day and it seems the nighttime use of sound helps not only with tinnitus, but with sleep as well. Both, sleep problems and tinnitus severity decreased significantly during 3 months of TRT treatment and there was a highly statistically significant correlation between the extent of improvement of sleep problems and the extent of improvement of tinnitus severity. It seems that the use of sound during the night is particularly useful for tinnitus patients who have problems with sleep as well.

CORTICAL EXCITABILITY AND TRANSCALLOSAL INHIBITION IN CHRONIC TINNITUS: TRANSCRANIAL MAGNETIC STUDY

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The lack of an efficient medical or surgical therapy for chronic tinnitus is in part due to our the lack of understanding of the mechanisms underlying the condition. The development of transcranial magnetic stimulation has provided new tool to study the cortical excitability in chronic tinnitus. We assessed motor cortical excitability in chronic tinnitus patients in order to understand more about its pathophysiological mechanisms. Methods: Thirty four patients with chronic unilateral tinnitus and eleven normal age and sex matched volunteers were used as a control group. We measured resting motor threshold (rMT), cortical silent period duration (CSP), and transcallosal inhibition for both hemispheres. Intracortical inhibition (ICI) and intracortical facilitation (ICF) using paired pulse stimulation paradigm were measured in the left hemisphere (dominant). Results: There were no significant differences between patients and normals in resting and active motor threshold or cortical silent period. Similarly there were no differences in these measures between the tinnitus side or the non tinnitus side in patients with predominantly unilateral symptoms. However, there was a significant prolongation of the duration and onset latency of TCI in patients compared with normals. ($P < 0.02$, 0.04 respectively) Conclusion: The significant abnormalities of TCI duration and time could support the presence of functional abnormality of corpus callosum in chronic tinnitus.

NEW THERAPEUTIC APPROACHES TO THE TREATMENT OF CHRONIC TINNITUS: A PROSPECTIVE STUDY

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Key words: repetitive transcranial magnetic stimulation, chronic tinnitus

Running title: therapeutic role of rTMS in chronic tinnitus

Prof. John Rothwell and Professor Eman Khedr conducted the statistical analysis

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Search Terms

TMS(289)

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Abstract

Background: There have been a number of recent reports about the possible therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) for treatment of tinnitus. Objective: To compare compare the effect of 3 different frequencies (total of 1500 pulses at 100% resting motor threshold) of rTMS given daily over the left temporoparietal cortex for two weeks. Material and Methods: Sixty six consecutive patients with chronic tinnitus were randomly allocated to one of four groups; 1 Hz, 10Hz, 25Hz and sham (occipital, 1 Hz). Patients were assessed with the tinnitus handicap inventory (THI), and self-rated measures of tinnitus loudness, awareness and annoyance. In addition, audiometric measures of tinnitus matching and residual inhibition were made before, after the end of sessions and monthly thereafter for 4 consecutive months. Results: There were no significant differences in basal measures between four groups of patients. However, a two factor ANOVA

revealed significant “rTMS” x “time” interactions indicating that real and sham rTMS had different effects on the THI scale, loudness, awareness and annoyance of tinnitus. Post hoc testing showed that in the three groups of patients, real-rTMS led to a greater improvement in scales than sham-rTMS, evident even 4 months after the end of the treatment. However, there was no significant difference between the response to different frequencies of rTMS. The effectiveness of rTMS depended on the duration of tinnitus: patients who had had tinnitus the longest were the least likely to respond to treatment. Conclusions: The daily sessions of rTMS over the auditory cortex may be a useful potential treatment for tinnitus.

TINNITUS BEHAVIOR AND HEARING FUNCTION CORRELATE WITH THE RECIPROCAL EXPRESSION PATTERNS OF BDNF AND ARG3.1/ARC IN AUDITORY NEURONS FOLLOWING ACOUSTIC TRAUMA

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The molecular changes following sensory trauma and the subsequent response of the central nervous system are poorly understood. We focused on finding a molecular tool for monitoring the features of excitability which occur following acoustic trauma to the auditory system. Of particular interest are genes that alter their expression pattern during activity-induced changes in synaptic efficacy and plasticity. The expression of brain-derived neurotrophic factor (BDNF), the activity-dependent cytoskeletal protein (Arg3.1/arc), and the immediate early gene c-Fos were monitored in the peripheral and central auditory system hours and days following a traumatic acoustic stimulus that induced not only hearing loss but also phantom auditory perception (tinnitus), as shown in rodent animal behavior models. A reciprocal responsiveness of activity-dependent genes became evident between the periphery and the primary auditory cortex (AI): as c-Fos and BDNF exon IV expression was increased in spiral ganglion neurons, Arg3.1/arc and (later on) BDNF exon IV expression was reduced in AI. In line with studies indicating increased spontaneous spike activity at the level of the inferior colliculus, an increase in BDNF and GABA-positive neurons was seen in the inferior colliculus. The data clearly indicate the usefulness of Arg3.1/arc and BDNF for monitoring trauma-induced activity changes and the associated putative plasticity responses in the auditory system.

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MORPHOLOGICAL ALTERATIONS IN PATIENTS WITH CHRONIC TINNITUS – A VOXEL-BASED MORPHOMETRY STUDY

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Chronic tinnitus is a frequent auditory sensation experienced in the absence of an external or internal acoustic stimulus. There is increasing evidence from electrophysiological and functional neuroimaging studies that abnormal functioning of the central nervous system is involved in the pathophysiology of chronic tinnitus. In detail, the misprocessing of excessive neuronal firing within the auditory pathway may account for the phantom perception of sound. Current neuroimaging studies point to a pathologically overactivated, distributed cortical network involving the inferior colliculus, the thalamus and the auditory cortex. Recently, voxel-based morphometry (VBM) has been proposed for the identification of brain areas that display structural changes in tinnitus. Therefore, we used VBM to elucidate specific morphological alterations in our sample of chronic tinnitus patients to get further insight in to the pathophysiology of chronic tinnitus.

We investigated 32 patients suffering from chronic tinnitus (mean tinnitus duration 72,8 months, range 6 - 360) with VBM and compared these to 32 unaffected healthy controls which were matched according to age and sex (mean age: tinnitus sufferers 40,3 years, controls 39,2 years, 11 females in each group). All participants did not have a significant hearing loss. MRI scans were performed on a Siemens Symphony scanner operating at 1.5 T with a standard 8-channel birdcage head coil. A 3 dimensional, structural high-resolution T1 weighted magnetization prepared rapid gradient echo sequence (MPRAGE) was acquired on each subject yielding 176 sagittal slices with a defined voxel size of 1x1x1 mm. Conventional T1 images showed no morphological abnormalities or artifacts in both groups. Statistical analyses were performed using the SPM5 software (Wellcome Department of Cognitive Neurology, London, UK).

Compared to healthy controls chronic tinnitus patients showed significant gray matter increases (uncorrected on both cluster- and voxel-level) in both cerebellar hemispheres as well as right anterior cingulate cortex. No changes were detected within the auditory system despite region of interest analyses.

In line with recent studies these data show specific morphological alterations in chronic tinnitus patients compared to healthy controls.

A NEW WINDOW ON TINNITUS: EXPLORING FUNCTIONAL CONNECTIVITY IN THE CLASSICAL AND NON-CLASSICAL AUDITORY PATHWAYS

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Functional magnetic resonance imaging (fMRI) has proved to be useful for the investigation of the neural mechanisms that underlie auditory perception. However, the application of fMRI in tinnitus research is hampered by the fact that the tinnitus percept is inherently subjective. The present study begins to bring a promising new fMRI approach to bear on tinnitus.

Standard fMRI techniques involve measuring brain activity correlated with an external stimulus such as sound. The approach examined here instead detects temporal correlations of activity between brain areas. This so-called functional connectivity approach does not necessarily require an external stimulus and has the capability of revealing functional networks in the brain during “resting state”. In tinnitus patients, this method may be able to reveal functional abnormalities that are directly related to the presence of tinnitus: for instance, connections in the non-classical auditory pathway between auditory and emotional centers may be abnormally strong.

Our current goal is to assess whether it is feasible to assess functional connectivity in the central auditory system. We report preliminary outcomes of a study that has been carried out on 13 control subjects with normal hearing; in addition 4 tinnitus patients have currently been included. Data were acquired using a sparse, cardiac-gated fMRI sequence. Subjects were engaged in a simple visual task while passively listening to 32-s broadband noise fragments.

Independent component analysis was performed on the measured fMRI signals; this method extracts relevant functional networks without prior information about the stimulus paradigm. In addition, functional connectivity analysis was carried out to identify brain regions with similar functional characteristics, by correlating the fMRI signals in the entire brain with those of predefined regions of interest.

In all subjects, components could reliably be identified that comprised the bilateral auditory cortices, thalamus (medial geniculate body), midbrain (inferior colliculus) and brainstem (cochlear nucleus). In addition, correlated activity of limbic structures in the thalamus (medial dorsal nucleus) and cortex (cingulate gyrus) was observed. These structures were found to be strongly functionally connected.

Our results indicate that functional connectivity measurements are feasible in tinnitus patients and controls, without relying on prior knowledge about stimulus perception. Such measurements can reveal the classical pathway, including sub-cor-

tical processing centers. In addition, we showed that correlated activity in the non-classical pathway can be detected, which is very difficult to achieve by conventional fMRI techniques.

Therefore, our methods provide a promising alternative to complement standard fMRI analyses in the assessment of tinnitus related abnormalities. Additional measurements will be carried out to further validate our methods, and to assess differences between tinnitus subjects and controls.

CHRONIC TINNITUS AFFECTS TONOTOPIC ORGANIZATION IN HUMAN AUDITORY CORTEX.

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Despite the pervasiveness of tinnitus, little is known about its mechanisms of origin. Three factors seem to contribute to creating this auditory phantom sensation: 1) damage to the peripheral auditory system; 2) reorganization of central auditory structures; and 3) involvement of non-auditory central gating systems. In a previous study (Leaver et al., *Soc. Neurosci. Abstr.* 2006), we provided some of the first direct evidence for cortical involvement, specifically demonstrating functional reorganization of primary auditory cortex in patients with chronic tinnitus. Using high-resolution functional magnetic resonance imaging (fMRI), we monitored changes in cerebral blood oxygenation levels while tinnitus patients and control participants with normal hearing listened to narrow band-passed noise bursts. A broad range of stimulus frequencies was tested. Stimuli were either matched to the patients' tinnitus frequency, or were one-half, one, and two octaves above or below the middle/tinnitus frequency. Each tinnitus patient was matched with one control subject that heard the same range of stimulus frequencies. Results indicated a significant hyperactivity in the hemodynamic response to auditory stimulation in the auditory cortices of tinnitus patients, as compared to controls. We also observed distortion within the tonotopic map of primary auditory cortex in tinnitus patients. The distance between the tinnitus frequency and non-tinnitus frequencies was increased in patients as compared to inter-frequency spacing in controls. Thus, tinnitus results not only in hypersensitivity of primary auditory cortex, it induces plastic changes in the tonotopic organization of this area as well. With the present results, we corroborate the previous data in a larger number of patients and offer a more refined analysis of the distortions found in the tonotopic maps of tinnitus patients. Since hearing loss does not automatically result in tinnitus, we also discuss the degree to which hearing loss affects auditory cortical reorganization and to what extent thalamic gating mechanisms play a role. Taken together, our data provide strong evidence for reorganization of auditory cortex as one important factor in the origin of chronic tinnitus.

NON-LATERALIZED PULSATILE TINNITUS: PULSATILE COMPONENT SUPPRESSED BY SOMATIC TESTING

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Background: In our clinic the source for pulsatile tinnitus can be found in about 10% of cases, but in the majority of people no cause is found despite an exhaustive physical examination and ancillary investigation. The presumption with pulsatile tinnitus is that either a “somatosound” is being heard or auditory-related neural activity is being modulated by blood flow.

Convincing evidence for monaural pulsatile tinnitus originating from vascular compression of the auditory nerve has been provided from intraoperative observations during hemifacial spasm decompressive surgery. Another possible source for modulation of neural activity is through somatosensory-auditory interactions in the central auditory pathway, if the somatosensory input is pulsatile.

We report now five cases, four of whom were seen in the past year, with non-lateralized pulsatile tinnitus for whom no etiology was found from the physical examination or ancillary testing but the pulsatile component of their tinnitus could be suppressed by somatic testing.

Cases: The three women and two men ranged in age between 49 and 63. All described their pulsatile tinnitus as high pitched and localized to both ears or in the head. Audiometry was symmetric in all subjects; two had normal pure tone thresholds and three had a mild symmetric high frequency sensorineural hearing loss. Auscultation was normal in all. Jugular compression did not modulate any subject’s tinnitus. Carotid compression did suppress tinnitus in two subjects, but a similar affect occurred with sternocleidomastoid compression without carotid compression. Imaging studies were all unrevealing including cerebral angiography in one. All could suppress the pulsatile component of their tinnitus with various strong neck or jaw muscle contractions, occlusion of the ear canals, or pressure on the sternocleidomastoid muscle. In some the tinnitus was completely suppressed; in others only the pulsatile component of the tinnitus was suppressed; high pitched non-pulsatile tinnitus remained. With some maneuvers only one side was suppressed.

Conclusions: The non-lateralized quality of the pulsatile tinnitus suggests either a central somatosound or modulation of neural activity of either the central auditory

system bilaterally or a level of the auditory system that can affect bilateral auditory perception.

In consideration of (a) the negative findings with auscultation and imaging and (b) suppression of the pulsations with activation of the somatosensory system, we suggest the following: some or all of these cases perceive non-lateralized high-pitched pulsatile tinnitus from (1) cardiac modulation of the somatosensory system, which, in turn, (2) modulates the central auditory system, thereby accounting for the pulsatile quality of their high-pitched tinnitus.

EVIDENCE FOR A TINNITUS SUBGROUP RESPONSIVE TO SOMATOSENSORY BASED TREATMENT MODALITIES

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Background: Studies have established that the somatosensory system of the upper cervical region and head can be intimately involved in tinnitus. Tinnitus can arise directly from a disorder of the head and upper neck through activation of the somatosensory system. "Somatic testing" (a series of strong muscle contractions of the head and neck) can (1) modulate the tinnitus percept of about 80% of people with ongoing tinnitus, and (2) elicit a sound percept in about 50% of people with no tinnitus. These somatic phenomena are equally prevalent among people with or without functioning cochlea. Animal studies have identified neural pathways that are likely responsible for the induction and modulation of tinnitus via the somatosensory system.

Because somatic influences are fundamental to the operation of the auditory system, in general, and to tinnitus, in particular, somatic testing should be incorporated into all evaluations of tinnitus (1) to improve understanding of the role of the somatosensory system in any individual and (2) to identify subgroups of tinnitus patients who may respond to a particular treatment modality (as has already been shown for the tinnitus associated with temporomandibular disorder).

Aims: To identify a tinnitus subgroup that will likely respond to treatment modalities involving the somatosensory system from reviewing (a) our clinical experience and (b) published reports.

Results: Previous reports indicate that, at least in isolated cases, a range of treatments can be effective. In general these reports do not provide details of the isolated cases. One acupuncture report, however, studied only unilateral tinnitus patients. Their results do identify a subgroup of individuals with tinnitus who respond to acupuncture, namely, those with unilateral tinnitus but symmetric hearing, i.e. tinnitus not accounted for by a hearing impairment. This finding is supported by other studies employing treatments likely involving the somatosensory system, namely, acupuncture, electrical stimulation of the scalp and auricle, cervical

manipulation, craniosacral therapy, temporomandibular disorder treatments, and trigger point treatments, including injections.

There is a suggestion also that the subgroup of individuals with unilateral tinnitus and symmetric hearing that responds best to somatosensory treatments is those whose tinnitus is fluctuating. Two extreme kinds of fluctuating tinnitus are (a) intermittent tinnitus and (b) tinnitus that can be unilateral when quieter and non-lateralized when louder.

Conclusions: Our clinical experience and review of treatment reports supports the hypothesis that modalities directed toward the somatosensory system can benefit the subgroup that has symmetric hearing thresholds but asymmetric widely fluctuating tinnitus. These modalities should be restudied employing a design that tests this hypothesis.

IMAGING TYPEWRITER TINNITUS: IS IT NEUROCOMPRESSION AFTER ALL?

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Background: Previously we reported a subgroup of unilateral tinnitus, “typewriter-tinnitus”, which was characterized by the intermittent bursting clicks and an excellent response to carbamazepine. We speculate that the pathophysiologic mechanism of typewriter tinnitus might be aberrant neural firings from a compressed auditory nerve, because typewriter tinnitus has many similarities to other well-known neurovascular compression syndromes such as trigeminal neuralgia, hemifacial spasm and glossopharyngeal neuralgia, namely intermittent bursting unilateral symptoms, which can be triggered by corresponding physiologic stimuli, and can be successfully treated with the same medications including carbamazepine and lamotrigine.

Aims: To assess the likelihood that vascular compression is associated with typewriter tinnitus.

Subjects & Methods: Eight patients with typewriter tinnitus were imaged with heavily T2-weighted MRI imaging (CISS) and MRA protocols. The most recent six studies could be reformatted in any arbitrary plane. Two radiologists interpreted the MR images independently and were blinded to the side with typewriter tinnitus. Using a zero to one hundred scale each estimated the likelihood that the auditory nerve was compressed for each side; the estimates for the right and left sides were required to total one hundred. In addition, for the images that could be reformatted the radiologists identified any vascular structure which contacts or is nearby the auditory nerve, including their size, number, and each crossing or contacting point along the nerve.

Results: For five subjects both radiologists agreed that blood vessels contacted the auditory nerve on one side only; for four of the five, the contact was on the same side as the typewriter tinnitus. For two other subjects the radiologists detected blood vessels contacting the auditory nerves of both sides. For one of these two typewriter tinnitus subjects, both felt strongly that the evidence favored the typewriter tinnitus side. For the other subject both had difficulty favoring one side more than the other. The eighth subject had arteries looping into both internal audi-

tory canals; the images could not be analyzed in detail since reformatting was not available. Chi-square analysis of each radiologist's estimation of the relative degree of vascular compression of each auditory nerve yielded a highly significant association between the side of auditory nerve vascular compression and the side of typewriter tinnitus ($p < 0.001$).

Conclusions: Typewriter tinnitus is significantly associated with ipsilateral auditory nerve vascular compression.

THE EFFECT OF SOMATIC MODULATION ON AUDITORY BRAINSTEM-EVOKED RESPONSES IN NORMAL SUBJECTS AND TINNITUS PATIENTS

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Background: Several lines of evidence support the principle that auditory function can be modified by somatosensory input. In particular tinnitus can (a) be caused by disorders involving the somatosensory system and (b) be modulated by somatosensory activation.

Aims: To further our understanding of how the somatosensory system modulates the auditory system, we examined how the human auditory brainstem-evoked response (ABR) is modulated by changes in jaw position in both subjects with and without tinnitus.

Subjects & Methods: Seventy non-tinnitus subjects with normal hearing (28 M, 42 F; ages 20-29) and 29 tinnitus subjects (13 M, 16 F; ages 43-72) with mild hearing loss (average pure-tone threshold <40 dB) participated. Before measuring the ABR, we determined how maximal clenching and jaw opening modulated their tinnitus. The ABR to 90 dB HL, 11.3/sec, monaural rarefaction clicks was recorded with contralateral masking in a soundproof audio booth from forehead and ipsilateral mastoid electrodes under three jaw conditions: (a) at rest, (b) clenched, and (c) widely opened. The order of testing was randomized.

Results: Clenching increased wave II amplitude of all subjects ($p=0.008$), likewise for the control ($p=0.028$) and tinnitus ($p=0.046$) subjects when considered separately.

Clenching suppressed wave III amplitude ($p=0.031$) and prolonged its latency only for the group whose tinnitus was suppressed by clenching. Clenching enhanced wave III amplitude for the group whose tinnitus was unchanged by clenching

For the group whose tinnitus was enhanced with jaw opening, I-III interpeak latency was prolonged with jaw opening.

When comparing jaw opening to the resting state of the nine subjects with unilateral tinnitus, the ABR ipsilateral to the tinnitus had greater (a) wave III amplitude suppression ($p=0.020$) and (b) II-III interpeak latency prolongation ($p=0.041$), as compared to the ABR contralateral to the tinnitus.

Conclusions: Jaw position modulates the ABR, likely through the somatosensory system. In some cases how the ABR is modulated is related to how the tinnitus is modulated. Modulation of wave III is more prominent on the side with unilateral tinnitus. When taken together with our prior studies of the ABR generators, the findings in unilateral tinnitus subjects suggests that jaw opening is modulating the output of the spherical cells of the ipsilateral ventral cochlear nucleus.

SPONTANEOUS BRIEF UNILATERAL TINNITUS - PREVALENCE AND PROPERTIES

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Background: Tinnitus refers to a diverse set of phenomena. To understand tinnitus requires an understanding of each of the various types of tinnitus. Progress made in understanding one type of tinnitus may provide further insights into other types of tinnitus.

SBUTs appears to be “a blind spot” in tinnitus research. Despite being the most common form of tinnitus, there are no systematic reports of SBUTs in the medical literature. In the absence of any systematic studies, spontaneous brief unilateral tinnitus (SBUT) had been described as a “nearly universal sensation {Dobie, 2004 #2}.” From questioning normal hearing volunteers, we have previously reported that in fact the prevalence of SBUTs is not “nearly universal” but has a prevalence of about 76% in normal hearing subjects {Levine, 2005 #1}. We also obtained prospective data on five subjects who had indicated that they previously had experienced SBUTs; three of the five experienced no SBUTs during four months of logging their SBUTs. In the other two subjects an ipsilateral ear fullness usually accompanied the SBUTs and their duration ranged between 5 and 60 seconds with a mean of 20 seconds. One of the subjects with relative pitch estimated the SBUTs’ as tonal whose pitch ranged between 0.1 to 1.0 kHz, with more than half at 1 kHz.

Aims: To extend our preliminary SBUT findings to a larger population, including tinnitus subjects.

Method: Adults, who reported they had experienced SBUTs previously, kept a log of their SBUTs for 4 consecutive months. For each occurrence of an SBUT they recorded its location, duration, pitch, time of occurrence, activity at the time, dominant pitch, and whether or not it was accompanied by any other symptom such as ear pressure.

Results: 34 males and 30 females between the ages of 19 and 66 (mean age 42) logged their SBUTs. Ten had chronic tinnitus in addition to their SBUTs. The total number of occurrences for an individual ranged between 0 and 15 (mean of 10.2 SBUTs/year). Despite reporting having had SBUTs, 17 (27%) experienced none during the 4 month observation period. Those with chronic tinnitus tended to have less SBUTs ($p < 0.10$). For over 75% SBUTs occurred for only one ear, with right ear only predominating (49% right only, 28% left only, $p < .01$); and yet of the 11 with bilateral SBUTs 9 had more left than right. Men had more SBUTs than women ($p < 0.05$); particularly those with more than 5 SBUTs in total during the 4 month observation period ($p < 0.025$). For each subject a pressure feeling either occurred for all SBUTs or for no SBUTs; no subject reported the pressure feeling for some but not for others. 28% of subjects reported a pressure feeling with all SBUTs, and 72% did not.

When all SBUTs from all subjects are combined, the average SBUT lasted 33 seconds (1 to 600 sec range, mode= 5secs; median = 10 secs). 67% of the events occurred in the right ear, versus 33% in the left. SBUT's were shorter the louder the ambient noise. Ear fullness was more common in the quiet.

Conclusions: One-quarter of adults have never experienced an SBUT. Of those who have experienced an SBUT about a quarter have less than one per 4 months. Most individuals hear their SBUTs in only one ear, predominantly the right. Men have more SBUTs than women. About a fourth of people have ipsilateral ear fullness with their SBUTs.

MODIFICATION OF TINNITUS PITCH PERCEPTION BY MEDICATION

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High-tone tinnitus produces annoyance, while low-tone tinnitus is better tolerated. A prospective, randomized, double-blinded, placebo-controlled study was done. Fifty patients with subjective tinnitus of high frequency were divided in two groups of 25. All of them received treatment. The control group received placebo (lactose) and the medication group received pregabalin at different dosage according to the individual tolerance, for three months. Tinnitus evaluation was done by means of tinnitometry and visual analogue scale.

Medication decreased slightly the intensity (decibels) of tinnitus and decreased greatly the tone (hertz) of tinnitus, as well as decreased also the values of the visual analogue scale (annoyance).

It is known that pregabalin potentiates the inhibitory cerebral neurotransmission. Inhibitory neurotransmitters can decrease the tone tinnitus perception and their annoyance.

(intensity=loudness=decibels). (tone=pitch=frequency=hertz).

ABSTRACT

TRI - TINNITUS CLASSIFICATION

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It is important to begin the differentiation between subtypes of subjective tinnitus. We propose a tinnitus classification to be studied in a workshop and to get a consensus about it.

The novelty of this classification is to can differentiate subtypes of subjective tinnitus. It is based in two parameters: deafness and stress.

Subjective tinnitus

	Deafness	Stress
Behavioral tinnitus	NO	YES
Auditory tinnitus	YES	NO
Auditory-Behavioral tinnitus	YES	YES

Deafness is determined by total audiometry. Stress is studied during the Clinical History (stress factors, grade of labor stress, grade of family stress, grade of irritability), questionnaires (THI), or stress hormones (cortisol, growth hormone, prolactin).

The TINNITUS CLASSIFICATION would be:

Objective tinnitus	Vascular Osteoconnectivemuscular
Subjective tinnitus	Behavioral tinnitus Auditory tinnitus Auditory-Behavioral tinnitus

This tinnitus classification gives information about pathogeny, diagnosis and treatment.

HYPERTENSION OF PERI-AURICULAR AND CERVICAL MUSCULAR GROUPS: INFLUENCE IN TINNITUS PERCEPTION AND TREATMENT WITH INTERX® OR OSTEOPATHIC MANIPULATIONS.

M. Mazzoli, A. Bonaconsa, C. Milanese, A. Magnano San Lio

Background: This clinical study was designed to evaluate the prevalence of postural and musculo-skeletal problems in tinnitus patients compared with the non symptomatic population. Furthermore, it was evaluated the benefit of osteopathic manipulation or InterX® treatment on tinnitus.

A basic concept in osteopathic evaluation and treatment is to consider the body as a whole. The spine is under two main force vectors: antero-posterior (from the anterior limit of the occipital foramen at the skull base to the coxes), and postero-anterior (from posterior limit of the occipital foramen, passing through the D2 and 2nd rib, anteriorly to L3 body, divides into two lines going to the femoral acetables). The resultant of these two force lines is a third vector (virtual). The three lines form two “pyramids” one with base at the pelvis, the second with base at the skull base. The vertex of these pyramids merge in front of D4. Therefore, there are nodal focus points such as D4 that is affected always and is a point of major stress (pivot). This way the bases of these dynamic pyramids are free to move and correspond to the movement that we do when walking. So in the treatment of a postural problem the osteopath does not focus on a single segment but works toward balancing the whole system. As D4 is the stress point of the whole spine, there are other pivot points for each segment as L5, D9 and C5. In a condition of torsion of the pelvis, the base of the inferior pyramid change the stress forces at D4 that is transmitted up to C5 and then to other vertebrae of the cervical spine. We shall remember the close anatomical connections of vertebral bodies, processes, fascial system, musculature and neural roots, cervical ganglia, vascular system. A distress at C5 can also create local oedema and inflammatory reactions. From C5 up we find the neural centres that affects the ear.

In classical osteopathy textbooks tinnitus is classified in: tinnitus auris, tinnitus cerebri and tinnitus simplex. Target of osteopathic diagnosis is the identification of “primary injuries” responsible of structural alterations (keeping in mind gravity vectors), Muscular relaxation (especially cervico-brachial), verify tensions and relax the TMJ and treating cranial lymphatic shunts.

InterX® is an interactive non invasive skin neurostimulator for pain management. The device produces biphasic impulse current indicated for symptomatic relief and management of chronic pain, post traumatic strain and pain, muscle relaxation and muscle re-education. The main difference with the traditional TENS techniques is

that InterX® is designed to sense the difference in skin potential and to adapt dynamically its stimulation to this modifying parameter through a process of interactive feedback.

Study design: 40 consecutive tinnitus patients, aged 18-65, randomly selected for treatment (2 months 1/w): 20 treated with osteopathic manipulations, 20 with InterX®, 40 controls (no tinnitus, no HL age and sex matched. All undergo the same evaluation protocol (audiogram up to 16 kHz, OAE, tinnitus pitch and loudness match, MML, THI, posturography, structured interview with special attention on postural and movement influence on tinnitus, physical evaluation and osteopathic evaluation). Tinnitus patients were re-evaluated at end of therapy (2 months). No sound/other therapies were given during participation in the study.

Preliminary results: the study is still ongoing. 48 patients were recruited until now: 24 with tinnitus, 21 controls, 3 drop outs. 13 have been treated with osteopathy, 11 with InterX®.

The prevalence of musculoskeletal strains and decreased postural control measured with the posturographic pad, is significantly higher in patients with tinnitus compared to controls. After osteopathic treatment, there was a decrease in loudness for 6 treated with osteopathy, 1 treated with InterX®, other patients reported variation of pitch and overall benefit (reduction of % of annoyance and awareness of the tinnitus), was higher in the patients who underwent osteopathic treatments. All control subjects had either no significant or little muscle strains. Only one subject with tinnitus had no significant muscle strain (he had post-traumatic tinnitus).

Conclusions: this preliminary results show that postural control and musculoskeletal strains are more frequent in the tinnitus population compared with the controls. This can be measured objectively with posturographic test and compare the pre- and post-treatment results. This could be useful in selecting which patient could benefit from osteopathy. Osteopathy seem to give greater benefit compared to InterX®. We need to increase the number of patients treated to verify the statistical significance of our preliminary results.

VOLTAGE GATED SODIUM CHANNEL BLOCKERS AS PUTATIVE TINNITOLYTICS: THE EFFECTS OF LTG ON COCHLEAR FUNCTION IN AN ACUTE NOISE MODEL.

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A number of drugs that act as Voltage Gated Sodium Channels Blockers (VGSCBs) have been investigated for their use as potential tinnitolytics. Their known mode of action is to selectively and exponentially decrease sodium conductance as membrane depolarisation increases. Members of the VGSCB family have a wide range established therapeutic applications and includes local anaesthetics, anticonvulsants and antiarrhythmics. Those investigated as tinnitolytics include lignocaine, phenytoin, carbamezepine and lamotrigine.

Whilst this family shows considerable promise as a source of tinnitolytics, there has been no systematic study of their effects within the auditory pathway. As part of a study to begin characterising the effects of VGSCBs in the auditory system, we investigated the effect of Lamotrigine (LTG) on the cochlear compound action potential (CAP) and the spectrum of neural noise (SNN) in an acute noise model in the guinea pig.

Preliminary pharmacokinetic studies supported use of 20 mg/kg of Lamotrigine given orally. These resulted in plasma levels comparable to those seen in man, with a one hour post dose peak of about 3 ug/ml. There was evidence of selective partitioning with a ratio of 2:1 into the cochlea, where peak levels of LTG at 2 hrs reached about 6 ug/ml. Half-life of LTG in both compartments was about 12 hours. Subsequent electrophysiological recordings carried out at 2 hrs post dosing showed that Lamotrigine did not appear to have any marked effect on cochlear function. No major changes were apparent in CAP threshold amplitude and latency over 8-30 kHz.

The acute noise model employed open field 100 dB SPL bandpass noise (5-15 kHz) for 15 minutes. Most notably this resulted in threshold elevation at 8 and 16 kHz of about 25 dB. When LTG was given prior to acute noise exposure, this resulted in significantly less marked threshold elevation of about 15 dB at these frequencies. Generally, changes in post-noise CAP amplitude and latency were comparable in both the Noise alone and Noise/LTG treated groups.

The SNN has a peak around 1 kHz and can be used as an index of both spontaneous and acoustically driven cochleoneural activity. The most notable change between the Noise and Noise/LTG groups was seen during noise exposure in the SNN power spectrum between 0.5 -1.5 kHz. There was a highly significant

decrease in power of about 60% in the Noise/LTG group, down to 70 μV rms from 165 μV rms in the Noise alone group.

These results provide some preliminary evidence about the action of VGSCs in the auditory pathway. Firstly, it appears that they can act to reduce acute loss of CAP threshold, most likely acting on afferent cochlear nerve fibres. Protectant effects of VGSCs elsewhere in the CNS have been shown to be related to reduction in firing rate during prolonged depolarisation, which in turn reduces metabolic demand. The marked decrease in SNN seen here during noise stimulus would also support this as an explanation for the protection seen here.

We further propose that further experimental characterisation of this drug group as potential tinnitolytics should begin with systematic consideration of the voltage dependent binding kinetics of a range of VGSCBs. This would help determine their suitability as candidates for future clinical trials.

LOCAL DRUG DELIVERY SYSTEMS FOR THE COCHLEA

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*: presenter

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Sensorineural hearing loss (SNHL) is the most common disability in our society. Most patients with SNHL also suffer tinnitus. The mechanism for generation of tinnitus is an unsolved problem. The auditory pathway is divided into seven sections sensory hair cells (inner and outer hair cells), synapses between hair cells and spiral ganglion neurons, spiral ganglion neurons, VIIIth nerve, brain stem pathway, thalamus and cortex. These sections can be the origin of tinnitus. We focus on development of therapeutic strategies for SNHL and tinnitus due to the dysfunction of peripheral systems including hair cells, synapses and spiral ganglion neurons. Local drug application is useful for pharmacological treatment of these regions. Our aim is to establish safe and effective methods for cochlear drug delivery. We examined the efficiency of two biomaterials, gelatin polymers and poly lactic/glycolic acid (PLGA) particles, for sustained delivery of drugs to the cochlea. Gelatin polymers are electrostatically complexed with drugs, and degradation of gelatin polymers by collagenases leads to release of drugs. Encapsulating drugs in PLGA polymers also enables sustained release of drugs. Biodegradation of PLGA polymers results in release of drugs. Geratin polymers are suitable for water-soluble drugs, and PLGA particles fit for delivery of water-insoluble drugs. We will present the potential of gelatin and PLGA polymers for cochlear drug delivery in animal models.

ABNORMAL SPONTANEOUS NEURAL ACTIVITY IN TINNITUS PATIENTS SUFFERERS ASSESSED WITH MEG

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Tinnitus, the perception of sound in the absence of physical sound, is a common clinical problem for which there are no effective treatments and no proven objective measures. Numerous imaging studies have reported physiological differences between people with and without tinnitus, but none has been replicated. Here we present the first such replication by confirming that tinnitus patients show an abnormal spectral pattern of spontaneous magnetoencephalographic (MEG) activity (Weisz et al., 2005). Spontaneous MEG activity was measured in seven normal hearing tinnitus subjects and eight audiometrically-matched controls using a 306-channel Neuromag Vectorview system housed in an electrically and magnetically shielded room. MEG signals were recorded for 10 minutes at a sampling rate of 600 Hz while subjects sat quietly with their eyes fixated on a cross. Eye blinks registered in the concurrently recorded electro-oculogram indicated that subjects remained alert with their eyes open throughout the measurement. The Fourier transform of the MEG signal was averaged across overlapping 8.5 second time windows and across sensors (averaging for magnetometers and gradiometers performed separately) to yield a power spectrum for each subject. The spectra for tinnitus and non-tinnitus subjects clearly differed, specifically at alpha frequencies. Total power in the alpha band (8 - 12 Hz) was significantly reduced in tinnitus subjects ($p < 0.02$). Delta band power, by contrast, showed no significant difference between tinnitus subjects and controls. While advancing the objectification of clinical tinnitus, the results also suggest that the phantom perception of sound can arise from abnormalities outside the classical auditory pathway. The findings support hypothesized links between tinnitus and abnormalities in thalamocortical gating.

Supported by the Tinnitus Research Initiative

DEVELOPMENT AND EVALUATION OF ADVANCED METHODS AND MODELS FOR THE INVESTIGATION OF TINNITUS. PRELIMINARY REPORT

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Tinnitus is a very frequent and sometimes disabling condition: its prevalence in the adult population is over 10%, and approximately 1% of the general population is severely affected with major negative impact on quality of life. No objective method has proven reliable for the assessment of tinnitus.

Among other objective measures, otoacoustic emissions (OAEs) were considered in literature as possible method for tinnitus assessment. However, OAE application shows contradictory results, resulting sometimes in slight significant changes of OAE amplitude that might be attributable to tinnitus¹, and sometimes not². On the other hand, as to existing therapeutic approaches, no treatment has proved real efficacy on the mechanisms at the origin of tinnitus³. As a consequence, the most often used therapies (i.e., TRT and cognitive behavioural therapy) aim at enhancing habituation and at alleviating the impact of tinnitus on life.

The main objective of this study is to contribute to the understanding of tinnitus with the development of original strategies for its assessment, investigation, and therapy. A first phase is focused on the assessment of possible subtle changes in cochlear function attributable to tinnitus by means of two proposed novel techniques for the analysis of OAE signals: i) a high resolution time frequency approach for transient-evoked OAEs (TEOAEs) and ii) an innovative processing technique for distortion product OAEs (DPOAEs) based on modelling the individual hearing systems. An experimental study is being performed, that involves 30 normal-hearing tinnitus subjects and 30 normal-hearing subjects that do not experience tinnitus, in order to measure DPOAEs, TEOAEs and contralateral suppression effects and compare the two groups on the basis of both traditional methods, based on emission amplitude and spectra, and the two proposed analysis approaches. A second objective is to assess if advanced modelling of the eighth nerve is such to provide

¹ Ozimek et al., "Distortion Product Otoacoustic Emission (DPOAE) in tinnitus patients", *JASA* 2006; 119: 527-538.

² Gouveris et al, "DPOAE-grams in patients with acute tonal tinnitus", *Otolaryngol Head Neck Surg* 2005;132: 550-553.

³ Dobie RA, "A review of randomized clinical trials in tinnitus", *Laryngoscope* 1999; 109:1201-11.

some additional information about hearing mechanisms that can be related to tinnitus.

Preliminary analyses and results will be presented and discussed.

Acknowledgements

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TINNITUS TREATMENT AND RESEARCH MEDITERRANEAN INSTITUTE. MULTIDISCIPLINARY MANAGEMENT OF THE TINNITUS

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Our objective was to try to help the tinnitus sufferers as well as possible to leave their insulation, their distress, their feeling of impotence opposite to this disabling symptom. With this ambition we created the IMERTA – Tinnitus Treatment and Research Mediterranean Institute. It is a multidisciplinary institute based on a very powerful technical plate which consists of 3 poles: a pole of reception and evaluation; a pole of decision concerted on the therapeutic strategy and a pole of fundamental and clinical research.

In our institute the patients undergo a meticulous examination to pose, when that is possible, the topographical diagnostic and in the best of the case the etiological diagnostic. The hearing of the patients will be estimated by pure tone and high frequency audiometries. Various assessments are proposed to the patients: an ENT and temporo-mandibular articulations assessments, audio impedancemetry, tinnitometry, otoacoustic emissions and auditory evoked potentials, morphological and functional MRI, biological assessments, cervical rachis radiography, Doppler clinical and instrumental cardiovascular examination, psychological evaluation, as well as a neurological examination when it is necessary.

The results of evaluation are used to define a therapeutic strategy and to adapt to each case a personalized therapeutic sequence. We propose medical treatments, behavioral and cognitive therapy, musicothérapie, alternative medicines (acupuncture, osteopathy), sound and sonic therapies (TRT, TSS), acoustic stimulations, repetitive transcranial magnetic stimulations.

Our institute gathers 18 doctors in 9 specialities, 2 researchers, 2 audioprothesists, 1 technician and 2 secretaries. Since her creation 5 months ago, 300 patients consulted our institute and we answered 1200 e-mails. In addition, 1,5 months ago of time for a first visit and 2 months of time to carry out an investigation program. 50 hearing aids of any type were adapted on the spot and as much in the other large French cities. 5 TMS are carried out each week.

The database which grows rich gradually makes it possible an epidemiological tinnitus study. The technical plate of our institute also makes it possible to develop various clinical and fundamental researches. One of our objectives is to study the short-term and long-term efficiency as well as the neurobiological mechanisms of different therapeutic approaches in chronic and disabling tinnitus treatment. In addition, we consider a tonotopic research on the primary auditory cortex thanks to fMRI and the stimulations reproducing with more closes the tinnitus frequential spectrum. We also consider work on curative sequential acoustic stimulations.

SLEEP SOUND STIMULATION FOR TINNITUS TREATMENT

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The physiological alterations causing subjective tinnitus are found in the central nervous system. It is now evident that most forms of subjective tinnitus appear as a consequence of changes in the function of the central auditory regions while they are not associated with any detectable anatomical lesion. The subjective tinnitus may be the result of the expression of neural plasticity and may develop because of decreased input or lack of sounds or over stimulation or unknown factors. Brain imaging studies support the notion of central activity shifts in tinnitus suffering patients. Since previous research demonstrated the auditory system is working also during sleep, the incoming information is processed and some kind of learning may happen, it is our tenet that the brain could learn during sleep, to mask the tinnitus perception^{1,2,3}.

Different sound stimulation treatments have been used (music, white noise, pure tones) during wakefulness, with no clear results. The sound selected for sleep stimulation had the same tinnitus characteristics in frequency and intensity presented to each patient.

In the present work, four patients with tinnitus were selected while those with psychological and/or sleep disorders, evaluated clinically and with polysomnography (PSG), were rejected. Each patient was initially studied with PSG to assess the personal sleep characteristics through a hypnogram. Then, the tinnitus was analysed in frequency and intensity and, after 15 days of nightly stimulation adaptation, another PSG was recorded during the sound stimulation by night. The resulting hypnograms were analyzed in comparison with the control ones.

The preliminary results showed that sound stimulation during sleep did not alter sleep while inducing a decrement in tinnitus intensity perception. After a few days of stimulation during sleep, the tinnitus showed a tendency to decrease, although

1. Velluti RA, Pedemonte M. (2002). *In vivo* approach to the cellular mechanisms for sensory processing in sleep and wakefulness. *Cell. Mol. Neurobiology*, 22: 501-515.

2. Pedemonte M, Velluti RA. (2005) What individual neurons tell us about encoding and sensory processing in sleep. In: *The Physiologic Nature of Sleep*. P.L. Parmeggiani, R.A. Velluti (Eds), Imperial College Press (London), pp:489-508.

3. Pedemonte M, Velluti RA. (2005) Sleep hippocampal theta rhythm and sensory processing. En: *Sleep and Sleep Disorders: a Neuropsychopharmacological Approach*. M. Lander, D.P. Cardinali, P. Perumal (Eds). Landes Biosciences (Tx) Springer (NY), USA, pp: 8-12.

with oscillations, with periods of total silence, no tinnitus. This treatment should be advantageous because the stimulation time may be longer than the real possibility to stimulate during daytime. Moreover, the night stimulation may help the patients to stick to the treatment and, provoking a tinnitus masking, may improve sleep quality.

In conclusion, we postulate that sound stimulation during sleep, with the same tinnitus frequency and intensity, could be an excellent tinnitus treatment.

VOLUMETRIC CORRELATES OF TINNITUS IN AUDITORY CORTEX

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Introduction

For a number of conditions (e.g. cluster headaches, cervical dystonia, PTSD, schizophrenia) morphological changes in cortical structures have been observed. Recently, tinnitus sufferers have been reported to show subcortical differences in gray matter density (Mühlau et al., 2006). Here we ask, whether tinnitus is accompanied by structural anomalies in auditory cortex.

Methods

Structural MRI images (T1-weighted, Siemens Trio, 3-T) were obtained from 41 tinnitus patients and 49 controls. 12 of the tinnitus patients and 33 of the controls were professional musicians, including orchestra musicians. Hearing status was determined for all participants. In tinnitus sufferers, subjective ratings of tinnitus severity and audiometric measures of tinnitus frequency and minimal masking level of the tinnitus were obtained. The MR data were processed using the BrainVoyager software (Brain Innovation). Sagittal MRI slices were segmented along the Sylvian fissure to obtain 3D gray matter surface reconstructions of the individual auditory cortices. MR data were also analyzed using voxel based morphometry (SPM2-based VBM).

Results

The gray matter volumes of a medial-to-lateral sequence of cross-sectional slices of Heschl's gyrus were calculated. The mHG volume ipsilateral to the tinnitus ear was considerably smaller than the homologous contralateral volume. The ipsilateral reduction was observed both in musicians and non-musicians. However, mHG volume was about a factor of two larger in musicians. Overall, the gray matter volume asymmetry was largest for the postero-medial third of mHG. The results of individual morphometry analysis were corroborated by VBM-based group analysis. Tinnitus intrusiveness, but not the minimal masking level of the tinnitus, was smaller in affected musicians than in affected non-musicians.

Conclusions

Tinnitus sufferers demonstrated decreased gray matter volume of the primary audi-

tory cortex ipsilateral to the ear affected by tinnitus, in particular of the posteromedial part of mHG which corresponds to the higher-frequency edge of the underlying tonotopic organization. Our data suggest that auditory cortex volume could turn out to act as a moderator variable that affects the translation between damage to the auditory periphery and generation of tinnitus.

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ATTENTION, SCENE ANALYSIS AND TINNITUS.

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Simple perceptual constructs of tinnitus such as pitch and loudness may be insufficient to fully characterize tinnitus. Views of tinnitus as phantom perception of a simple sound need to be extended to incorporate concepts with greater ecological validity such as auditory object-hood and figure ground. We consider that tinnitus is complex auditory activity that disobeys rules that normally apply to auditory object identification. A model of tinnitus perception will be presented which proposes involvement of abnormal attention and auditory scene analysis in tinnitus perception. We hypothesize that abnormal attention and auditory scene analysis contribute to the severity of tinnitus and that the incongruence between tinnitus and normal auditory perception is responsible for its resistance to traditional sound-based habituation therapies. New methods of treatment using auditory and visual attention training are proposed as a means to augment counseling and sound therapies for tinnitus management. Attention training has been demonstrated to improve an individuals' ability to attend to relevant sounds while ignoring distracters. The main aim of the current study was to determine the effectiveness of structured Auditory Object Identification and Localization (AOIL) tasks to train persons to ignore their tinnitus. The study looked at the effects of a 15-day (30 minutes per day) take-home auditory training program on individuals with severe tinnitus. Pitch-matched tinnitus loudness levels (TLLs), tinnitus minimum masking levels (MMLs) and measures of attention were compared before and after the auditory training. The results of this study suggest that short-duration auditory training which actively engages attention, object identification and which requires a response from participants reduces tinnitus. There was a greater effect on tinnitus pitch-matched minimum masking levels than on actual tinnitus loudness levels. The reason(s) for this are unclear, although a correlation found between changes in MMLs and improvements in the ability to shift attention may be one underlying reason.

NEURAL MECHANISMS UNDERLYING SOMATIC TINNITUS

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Somatic tinnitus patients can modulate both the intensity and pitch of their tinnitus by manipulating facial regions including their jaws and teeth, areas innervated by the trigeminal nerve. Over the past several years, we have demonstrated functional connections between the trigeminal system and the auditory brainstem and mid-brain. Stimulation of trigeminal neurons can produce changes in the spontaneous and sound driven firing *rates* of cochlear nucleus (CN) and inferior colliculus (IC) neurons. These changes in firing rate could account for the *intensity* changes in their tinnitus perceived by patients. New data indicate that trigeminal neurons can also modify the *temporal* patterns of spontaneous and sound driven responses of both CN and IC neurons, making the firing patterns more regular. Regular firing of neurons in the CN has been proposed as a model for pitch perception. Thus, if trigeminal neurons can change the *regularity* of auditory neurons' firing patterns, they could alter the perceived pitch generated by those firing patterns.

In the initial period of the grant we have begun to examine the changes in temporal responses of CN neurons after stimulating the somatosensory regions in the brainstem that receive inputs from specific regions of the face. We determine this specificity by obtaining receptive fields from the stimulating electrode while manipulating different regions of the face. We have shown that stimulating the spinal trigeminal nucleus and brainstem reticular formation produces changes in the temporal firing properties of neurons' responses. The most frequently observed change is an increase in the regularity of firing. We have also begun the second part of the study to examine the hypothesis that, after sound over-exposure, there will be compensatory increases in trigeminal innervation of the CN. Our studies so far indicate that following deafness, these compensatory changes result in *enhanced* effects of trigeminal stimulation on the firing patterns in CN, as exhibited by lower thresholds and latencies in response to this stimulation. In the third part of the study we begin to assess for the presence of tinnitus following noise exposure by behaviourally assessing the animals with a novel gap-detection startle technique. We have begun adapting this technique for guinea pigs and should have some positive results to present in July.

Understanding how somatic tinnitus occurs will help us to understand how tinnitus itself is generated. Only then can we hope to develop methods to alleviate this distressing condition.

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EXTINCTION TRAINING FOR TINNITUS: FIRST RESULTS

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Tinnitus is associated with hyperactivity in the afferent auditory pathway, the auditory cortex, and limbic structures. Residual inhibition (RI) is a phenomenon of transient tinnitus reduction or even cessation after presentation of a masking sound. We use training of RI in an effort to extinguish excessive hyperactivity of auditory and limbic structures related to tinnitus. In our ongoing study, 28 patients with chronic constant tinnitus are assigned to two age- and gender-matched treatment groups on a randomized double-blind basis, one group receiving residual inhibition training combined with pregabalin, and the other group receiving residual inhibition training combined with a placebo. A multiple baseline design is used in which small groups of patients successively enter treatment 2, 4, 6, or 8 weeks after initial assessment thus providing variable waiting periods. During baseline, tinnitus questionnaires, a clinical psychological interview and a tinnitus diary are presented. Towards the end of the baseline and before the beginning of the training procedure, as well as after 8 weeks of treatment, audiometric tests including hearing thresholds, tinnitus frequency, minimal masking level of the tinnitus, masker threshold as well as residual inhibition are presented and electroencephalographic recordings of the acoustic N100 and electrodermal activity in response to a standard 1000 Hz tone and a tone at the individual tinnitus frequency are obtained. Three months later, psychometric questionnaires are sent to the participants for a follow-up assessment. For residual inhibition training, patients are provided with bandpass noises reliably generating residual inhibition. They are instructed to train to prolong and deepen the effects of residual inhibition by individual imagery techniques in response to the masker. Each daily training session lasts 30 minutes, tinnitus sufferers train at least once a week at the laboratory to assess training effects directly. Patients are also instructed to use their diary to complete a protocol about their training times, RI duration, tinnitus loudness and interference before and after each training session, and substance intake that accompanies the 8 weeks of residual inhibition training.

Initial data from this study show that tinnitus patients show a deficit of short-term habituation of the N100 component of the auditory evoked potential both for the tinnitus frequency and a 1000 Hz standard frequency. Age-matched controls, even if they do not present with presbycusis, show preserved habituation for the standard frequency, but not necessarily for higher tonal frequencies corresponding to the patients' tinnitus frequencies. Younger controls show habituation for all tonal

frequencies. These data suggest that reduced short-term N100 habituation is not only present in tinnitus sufferers, most of whom are older than 40, but also to a lesser extent, in age-matched controls. This habituation deficit may indicate a vulnerability for the development of chronic tinnitus after the occurrence of cochlear trauma. Initial training results show that tinnitus patients can successfully extend residual inhibition in a training procedure and thus influence tinnitus. At the meeting we will present sample data from the training that is still ongoing.

Supported by the Tinnitus Research Initiative.

PIRACETAM EFFECTIVENESS IN TINNITUS OF PRESBYCUSIS PATIENTS

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Background: Presbycusis associates frequently with tinnitus. Tinnitus may be due to the same pathology which leads to the sensorineural hearing loss. The presbycusis classified upon the basis of the Schuknecht's category's may also permit an insight into the pathogenesis of the development of tinnitus in these cases.

Methods: Fifty presbycusis patients (age >50 yrs) with tinnitus were treated by piracetam (3 g) i.v. . Before the treatment and after treatment pure tone thresholds were measured as well as intensity and pitch of tinnitus.

Results: In 28 cases the tinnitus was improved or disappeared simultaneously with improvement in hearing. The responsive tinnitus did not show any characteristic association to pitch as to low (<1000 Hz) or high (>1000 Hz). Interestingly, those patients were better responding to piracetam therapy who developed sensorineural hearing loss of stria vascularis origin associated with tinnitus (8 improvements out of 12 cases)

Conclusion: Tinnitus associated to sensorineural hearing loss of presbycusis patients classified to stria vascularis origin are better responding to piracetam therapy than those of receptor cell or ganglion cell damage of origin.

IDENTIFYING SUBGROUPS OF TINNITUS PATIENTS

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Tinnitus is a symptom, and it is likely that many subgroups exist. Clinical trials are more likely to be successful if appropriate subgroups can be identified. We propose different subgroups based on likely etiology, tinnitus characteristics, tinnitus psychoacoustics and cluster analysis. Etiological subgroups include noise exposure, aging, head injury, neck injury, Meniere's disease, and drug specific ototoxicity. Tinnitus characteristics include its description, location and duration. Tinnitus psychoacoustics includes post-masking effects, ipsilateral and contralateral masking, and frequency-specific tonal masking. Preliminary results using cluster analysis suggests that the presence of hyperacusis and tinnitus handicap severity might also represent subgroups.

PERSPECTIVES ON TINNITUS FROM CLINICAL EXPERIENCE AND RESEARCH

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And Tinnitus Otosound Products. LLC.*

Major advances are occurring in basic and clinical research in the mechanisms and treatment of tinnitus. At UCSD we have carried out a variety of research in humans on assessment and treatment methods for tinnitus. Further, we have a well established tinnitus treatment program that incorporates modern assessment and treatment methods. This report will describe some of the issues facing the tinnitus research community that we feel are compelling.

From our double-blind control study on the use of Paroxetine (a selective serotonin reuptake inhibitor) in the treatment of tinnitus we found that there was no significant difference between placebo and the active medication at the highest doses when measuring with the Tinnitus Handicap questionnaire (THQ). However, we found that if the subjects were asked directly regarding how annoying their tinnitus was, we found that paroxetine at 40 or 50 mg doses per day did have a significant effect. Was this a multiple statistical test effect (i.e. by asking enough questions, we found a significant effect?) or a true phenomenon? Our observation is that the THQ with its wide ranging variety of questions regarding life circumstances and tinnitus may be too confounded with variables that are variably affected by tinnitus treatment. The THQ may obscure any real changes in tinnitus that may be discovered by directly asking about it.

Further, an issues regarding stratification and population selection for tinnitus studies became apparent with the recruitment for the paroxetine study. We found that a newspaper advertisement in one day would result in numerous inquiries by the public for participation. However, our admission criteria required no concurrent administration of medications. Numerous potential subjects were refused because they were already on medication. Importantly, our initial plan to stratify the subject analysis to those meeting criteria for anxiety/depression and those who did not, failed because there was only one who met criteria for depression. Presumably, our selection criteria for rejection of people with antidepressant treatment meant that all depressed subjects who called in were already on drug treatment. The huge penetration of antidepressant medication into the general population has large implications for tinnitus management. How should people with tinnitus who

are on medications be managed? Do we stop or change their drug regimen? How?

As an academic center interested in tinnitus, we have numerous patients who have sought multiple medical opinions for tinnitus. What is the selection pressure for our clinical observations and trials because of our research status? Are we missing a large segment of the tinnitus population that would like treatment, but who have had an opinion indicating there is no treatment and hence they give up? How are primary providers to be educated on the current management techniques for tinnitus? What are the implications of information on the Internet?

Finally, our work has included attempts to develop an EEG marker of the presence of chronic tinnitus. Again, important questions develop on the possibility of a reliable marker. What patient population will such markers really identify? How will such markers be used and what are the ethical implications of their use? How will such markers be used in management of patients with tinnitus.

TINNITUS AND NEURONAL SYNCHRONY

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Tinnitus is thought to be a result of an abnormal synchronized activity of neurons in the central auditory system. Animal studies have shown this to be the case for the auditory cortex. Despite the frequently stated importance of synchrony, researchers are only beginning to catch a glimpse of ongoing oscillatory activity generated on a level of cell assemblies or even distributed networks. I will present various evidence from our group showing that ongoing neuronal activity of awake individuals with tinnitus is altered. Generally our results indicate a breakdown of the normal excitatory-inhibitory balance, and the emergence of gamma band synchronization on a local level as well as between distant brain regions.