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AAO-HNS Intl Tinnitus Miniseminar Summary 2014

Modalities Tinnitus Treatment - Neuromodulation, Instrumentation, Pharmacology, Electric stimulation, Surgery, and Neurofeedback - 2014

INTRODUCTION

The theme of the AAO-HNS Martha Entenmann Abraham Shulman, M.D., Barbara Goldstein, PhD International Tinnitus Miniseminar, 09/23/2014, was Modalities Tinnitus Treatment - Neuromodulation, Instrumentation, Pharmacology, Electric stimulation; Surgery, and Neurofeedback - 2014.

The goal was: 1) to provide to the otolaryngologist and all tinnitus professionals information of clinically applicable new and established methods of tinnitus treatment for all clinical types of tinnitus, individual for each tinnitus patient; and 2) to provide a rationale for the selection of modality(ies) of treatment based upon objective identification with electrophysiology functional brain imaging, i.e. quantitative electroencephalography (QEEG) and Low Resolution Brain Electromagnetic Tomography (LORETA), reflective of multiple brain functions in the presence of the tinnitus signal.

The focus was on the clinical translation for the biophysiological processes of neuroplasticity (NPL), neuromodulation (NM), and neuroprotection (NPT), which are hypothesized to be linked together at a synaptic level to maintain a homeostasis of brain function at cortex, and clinically are reflected for tinnitus in the degree of efficacy of any/all modalities of tinnitus treatment.

The program chairman and moderator was:

Michael E. Hoffer, M.D., F.A.C.S., Professor of Otolaryngology University of Miami.

The invited speakers included:

- Abraham Shulman, M.D., F.A.C.S. Prof. Emeritus Clinical Otolaryngology, Department Otolaryngology, State University of New York, Downstate Medical Center.
- Guest of Honor: Berthold Lannguth, PD Dr. med, Assistant Professor, Head of Out- patient Department, Universität Regensburg- Department of Psychiatry and Psychotherapy; Chairman of Tinnitus Research Initiative (TRI) Executive Committee and member of TRI Scientific Committee.
- Tobias Kleinjung, M.D., PhD: Department Otolaryngology, University of Zurich, Switzerland, ENT Clinic, U. Zurich, Switzerland.
- Richard S. Tyler, PhD: - Professor of Otolaryngology and Communication Sciences, Univ. Iowa.
- Michael D. Seidman, M.D., F.A.C.S. Clinical Professor Otolaryngology-Head and Neck Surgery Wayne State University; Director Division Otologic/Neurotolgic Surgery Henry Ford Hospital.

Michael E. Hoffer, M.D. introduced the program to an overflow audience. The program in 2014, “Modalities Tinnitus Treatment”, was presented as the fifth of a series of AAO-HNS Miniseminars, which over the past 4 years has had as its goal the providing to the AAO HNS membership and guests, state of the art tinnitus information, both clinical and basic science, for clinical translation to the patient for an objectivity and an increased accuracy for the tinnitus diagnosis for all clinical types of tinnitus and its translation for treatment. The themes of the past Tinnitus Miniseminars and the rationale for the order in the selection of past themes since 2010 and selection of the theme for 2014 were reviewed.

The Miniseminar 2014 provided: 1) an introduction to the evolving neurobiology for all clinical types of tinnitus in the context of modalities of treatment, existing and planned for the future focusing on biophysiological processes of neuroplasticity (NPL), neuromodulation (NM), and neuroprotection (NPT); 2) the availability of objective electrophysiological recording of treatment responses with functional brain imaging, i.e. quanti- tative electroencephalography (QEEG) and Low Resolution Brain Electromagnetic Tomography(LORETA) reflective of multiple brain functions in the presence of the tinnitus signal; 3) translation tinnitus theory for treatment with EEG based neurofeedback, transcranial magnetic stimulation, medication, instrumentation and 4) future treatments including vagal nerve stimulation attempting tinnitus relief.

The take home message and goal for the attendee of each Miniseminar since 2010 has been the presentation and clinical translation of advances in neuroscience, sensory physiology, and auditory science to provide an objectivity and an increase both in the accuracy for the diagnosis of all clinical types of subjective tinnitus and efficacy of treatment for the ultimate benefit of the tinnitus patient.

In 2014 the take home message and goal for the attendee of each Miniseminar since 2010 was reaffirmed by introduction to the attendees of the availability of application for all tinnitus patients of the technology of objective electrophysiology quantitative

electroencephalography (QEEG) and low frequency resolution electromagnetic tomography analysis (LORETA). The data, reflective of multiple brain functions in the presence of the tinnitus signal, was demonstrated. Both Qeeg and LORETA were presented in the context of functional brain imaging, which also includes demonstration of alterations in metabolism with nuclear medicine, eg SPECT and PET.

The clinical application of the QEEG LORETA data is not to diagnose tinnitus but to 1) provide an increase in both the accuracy for the tinnitus diagnosis by its integration and correlation with the clinical history and physical examination and 2) to objectively monitor the efficacy of tinnitus treatment modalities.

Attempts for tinnitus relief with instrumentation and future application of surgical vagus nerve stimulation, pharmacology AM-101, and the middle ear implant for moderate severe sensorineural hearing loss were presented.

PRESENTATIONS

In general, the presentations focused on biophysiological processes of neuroplasticity (NPL), neuromodulation (NM) and Neuroprotection (NPT), electrophysiological functional brain imaging QEEG and LORETA, a tinnitus modality of therapy i.e. surgery, pharmacology, transcranial magnetic stimulation, neurofeedback,instrumentation, both existing and planned for the future.

I. Abraham Shulman, M.D., F.A.C.S presentation: Electrophysiology and Tinnitus QEEG/Loreta Update Present/Future; Co-presenter was Barbara Goldstein, PhD, Audiology

The goals of the presentation were:

- To present the biophysiological processes of NPL NM NPT as part of an evolving neurobiology for all clinical types of tinnitus.
- To provide clinical evidence of NPL NM NPT in a cochlear implant soft failure tinnitus patient with functional brain imaging nuclear medicine PET brain and quantitative electroencephalography (QEEG). Functional brain Imaging-Pet brain and quantitative electroencephalogra phy (QEEG) data when correlated with the clinical report of the patient for an efficacy of a particular modality of treatment, provides an objective measure in terms of metabolism and brain function for a subjective response to a particular modality of tinnitus treatment.
- To propose development of an objective measure for tinnitus treatment efficacy based on a correlation of the results of electrophysiology functional brain imaging with the clinical report of a patient.

Definitions of NPL, NM, NPT:

Brain plasticity has been defined by “the father of sensory substitution and brain plasticity” as the adaptive capacities of the central nervous system - its ability to modify its own structural organization and functioning”[1].

Neuroplasticity (NPL), and neuromodulation (NM), of efficacy of any/all modalities of tinnitus treatment neuroprotection (NPT) are biophysiological processes which maintain a homeostasis of function in the nervous system, hypothesized to be based on maintenance of a balance between inhibition and excitation; a reduction in inhibition resulting in an interference in neural function[2,3].

Neuroplasticity (NPL) is a reorganization in neural circuitries in brain structure, and or function in response to constant, single or repetitive, internal and or external stimulation. e.g. physical, sensory, and/or emotional. Multiple ongoing processes and levels of activity are involved at organ, tissue, cellular, synaptic and molecular genetic locations. The result of the reorganization is a positive or negative alteration in structure and or function from the normal, i.e. “positive plasticity or negative plasticity”. The goal is to attempt to restore and or to maintain a homeostasis of normal neural function in the peripheral and or central nervous system[4].

Neuromodulation (NM) in neuroscience is a modification of neural activity within neural circuits at a synaptic level in brain. It is considered to be a complex biology of physiological process(es) which exert a positive or negative influence on an existing neural signal input or output, but does not eliminate the existing neural signal. It is one of a number of biophysiological processes in which several classes of neurotransmitters in the nervous system regulate diverse populations of neurons, are not absorbed but remain in the CSF and influence/modulate different neurotransmitter activity with resultant brain activity. It is conceptualized to be a process which can alter the circuitry in brain wave activity associated with tinnitus and the responses to modalities of tinnitus treatment[4].

Neuroprotection: refers to processes that protect neuronal function from injury or that improve such function after injury. It is hypothesized that common etiological agents that cause injury to the CNS have similar effects on the inner ear. It is hypothesized that common etiological agents that cause injury to the CNS have similar effects on the inner ear. The chief etiologies to be considered include ischemia, trauma, or hemorrhage, and neurodegenerative disease.

Pharmacological agents that are considered to be neuroprotective have been identified and include calcium channel blockers, free radical scavengers, corticosteroids, antagonists of glutamate at N-methyl-D-aspartate (NMDA) and non-NMDA receptors, the proteolytic enzyme calpain and various thrombolytic

agents. An innovative application of such drug therapy is to provide neuroprotection[5-7].

In general, neuroplasticity (NPL), neuromodulation (NM) and neuroprotection (NPT) are biophysiological processes linked together to maintain a homeostasis of structure and function: a) structural at molecular genetics, synaptic, cellular, tissue, organ, and system levels, and b) functional in the central nervous system as clinically manifest by sensory, behavior, learning, memory and motor activities. It is hypothesized that when the balance between excitatory-inhibitory action is broken in sensory systems, predominantly due to neuromodulatory activity of reduced induced inhibition, excitation predominates, sensory circuits become plastic, and adaptation is established at synaptic levels reflective of environmental inputs. The resulting alterations in synaptic transmission and neuronal network function depend on the extent of calcium signaling and NMDA activation in response to different patterns of stimulation[2,3,8].

The biophysiological processes of NPL, NM, NPT are considered in our experience to provide a "bridge for continuity of function" between both a sensation and its transformation into one of behavior and affective and somatomotor response. The cognitive brain function of "memory" is the predominant brain function that is hypothesized to bind the two together[9].

The biophysiological process(es) of NPL NM and NM were demonstrated with Pet brain and QEEG in a tinnitus patient ear right (rt) in who an initial cochlear implant (CI#1) was inserted with no report of tinnitus relief ear rt, and a mild hearing improvement ear rt. Increased tinnitus intensity was reported with CI#1 On which persisted following CI#1 Off. Integrity of CI#1 confirmed with persistence of increased tinnitus, cochlear implant soft failure. Removal CI#1 and reinsertion CI#2 resulted in hearing improvement and reported tinnitus relief[10].

The clinical significance functional brain imaging is demonstrated by correlation of results of functional brain imaging Pet brain and QEEG (Figure 1, 2, and 3).

Take Home Messages:

A. Tinnitus Miniseminar 2013:

1. The QEEG in 2013 was recommended to be included into the tinnitus evaluation of all tinnitus patients with the diagnosis of subjective idiopathic tinnitus of the severe disabling type. The application of the QEEG for tinnitus is recommended to be called, the Electroencephalotinnitogram (TCG). Clinically, the stage of the QEEG clinical application in 2014 for tinnitus is considered analogous to the EKG for cardiology in the 1930s.

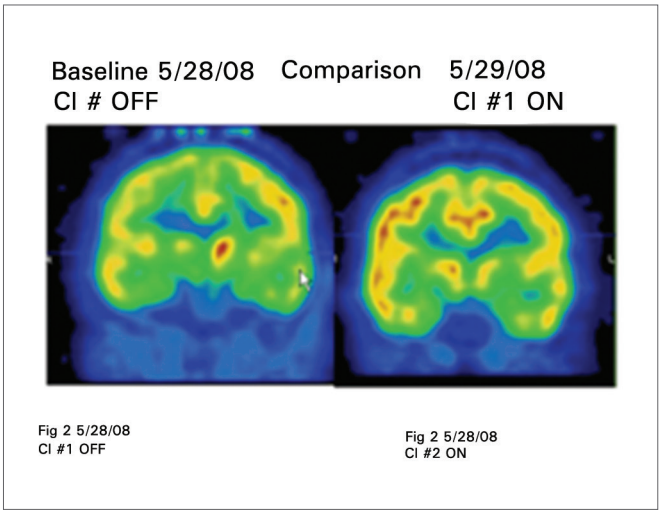

Figure 1. Functional brain Imaging-Pet brain- comparison CI#1 OFF baseline and ON: Demonstration Neuroplasticity. Asymmetry activation thalamus, dorsolateral prefrontal cortex lt > rt CI#1off; CI#1 On asymmetry rt > lt.

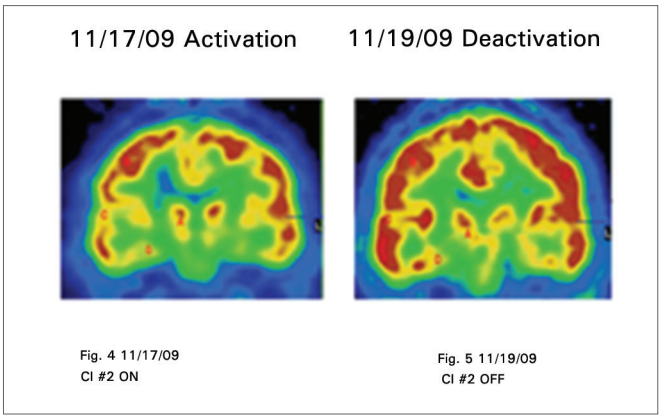

Figure 2. Functional brain Imaging-Pet brain- comparison CI#2 ON and Off: Demonstration Neuroplasticity; NPT. No asymmetry thalamus, dorsolateral prefrontal cortex. Tinnitus relief reported following CI#2 Off consistent with clinical residual inhibition.

2. NPL NM NPT:

The degree of success of modalities of tinnitus treatment reflect the attempt of the biophysiological processes of NPL NM NPT to establish and maintain a homeostasis of function between excitation and inhibition at brain cortex clinically manifest by the patient report of control of the sensory and affect behavioral components of the tinnitus.

3. QEEG:

The data both metabolic with PET and electrophysiologic with QEEG in the case of the cochlear implant soft failure with ES when correlated with the subjective report of the patient provides: 1) an objectivity for a reported subjective report of tinnitus relief. 2) The role of NPL NM NPT in an evolving neurobiology for a predominant central type severe disabling tinnitus.

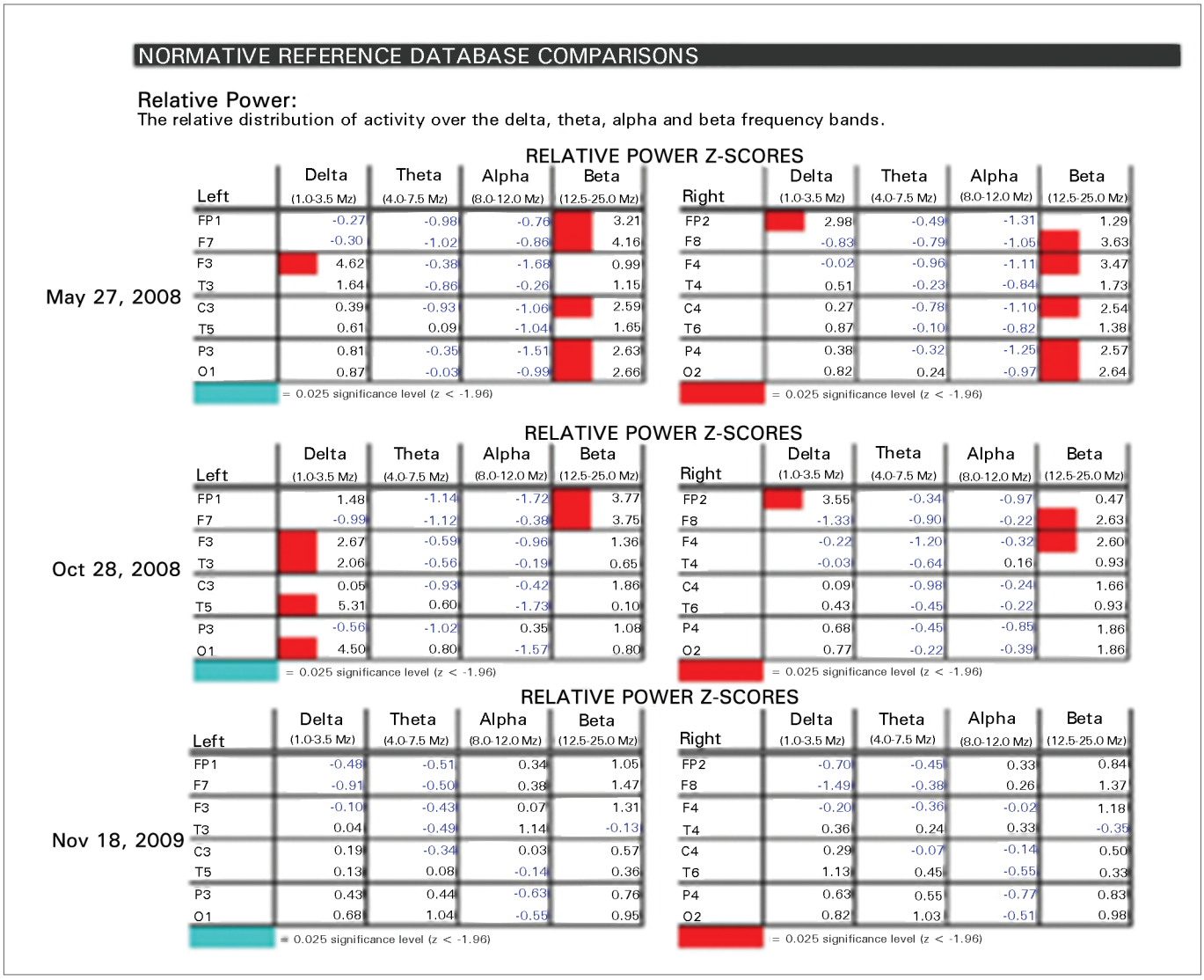

Figure 3. Quantitative electroencephalography (QEEG) - relative power. a) 5/27/08: CI #1 Off - baseline: delta, beta increased bilateral. b) 10/28/08: CI#1 Off - no electrical stimulation; medical treatment factors influencing the clinical course of the patient. Reduction beta bilateral, increase delta bilateral. Demonstration NPL, NM, NPT. Correlation with reported tinnitus relief "10-20%". c) 11/18/09 CI#2 On Absent increased electrical activity. Demonstration NPT. Tinnitus relief reported with CI#2 ON.

The QEEG data to be considered to reflect not tinnitus but multiple brain functions in the presence of the tinnitus signal. The clinical application of the data is not to diagnose tinnitus but to provide an increase in both the accuracy for the tinnitus diagnosis by its integration and correlation with the clinical history and physical examination and to objectively monitor the efficacy of tinnitus treatment modalities.

Terminology for the QEEG analysis when applied for tinnitus is recommended, i.e. Electroencephalotinni tography (ETG).

B. Miniseminar 2014:

1. Neuroplasticity,(NPL), neuromodulation (NM) and neuroprotection (NPT) are biophysiological processes which maintain a homeostasis of function in the nervous system, hypothesized to be based on maintenance of a balance be tween inhibition and excitation; a reduction in inhibition resulting in an interference in neural function.
2. The Qeeg in 2014 is a tool which demonstrates electrophysiologic data of brain wave activity i.e. oscillation, in multiple regions of interest, reflective of multiple brain functions in the presence of the tinnitus signal.
3. The clinical application of the QEEG data is not to diagnose tinnitus but by its integration and correlation with the clinical history and physical examination, to 1) provide an increase in both the accuracy for the tinnitus diagnosis;

and 2) to objectively monitor the efficacy of tinnitus treatment modalities.

4. Clinical correlation of the QEEG data is recommended to determine its medical significance, individual for each tinnitus patient. The deviation from the normal electrical patterns in these structures likely is reflected in suboptimal functioning.
5. The QEEG Is not an instrument/test to prove causality. The abnormal Qeeg provides objective evidence of brain wave oscillations to support the clinical recommendation of innovative pharmacologic therapy attempting tinnitus relief, e.g. antiepileptics, and neurofeedback for patients with the clinical diagnosis of subjective idiopathic tinnitus of the severe disabling type.
6. The sLORETA analysis provides source localization in brain, in the narrow band frequency range, which is the mathematically most probable source of the electrical potential (EEG) recorded from the surface scalp electrode[11].

Summary: The Qeeg is a spectral analysis of the raw EEG data, i.e. analysis of brain oscillations in the "EEG space"; sLORETA is a 3D analysis of brain oscillations in the Qeeg space with source localization.

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II. Tobias Kleinjung, M.D. Department of Otorhinolaryngology University of Zurich, Switzerland. "Neurofeedback (NFB) for tinnitus Treatment"

The "dialectics" of the brain were presented as brain wave activities of different frequencies, recorded from external scalp placed electrodes.

NFB, also known as EEG biofeedback, is a computerized learning strategy that enables people voluntarily to alter their own brain activity[1].

The presentation, EEG based NFB, was introduced by a brief review of brain wave activities.

- Delta Waves (up to 4 Hz, deep sleep stages).
- Theta Waves (4-7 Hz, sleep stages).
- Alpha Waves (8-12 Hz, quiet waking).
- Beta Waves (13-30 Hz, activated cortex).
- Gamma Waves (30-100+ Hz, «cognitive» frequency band).

Relevant information of brain wave activities applicable for tinnitus and NFB attempting tinnitus treatment included the following:

1. Tinnitus patients demonstrate less Alpha and more Delta power in temporal cortex areas as compared to normal controls[2].

Tinnitus patients show significant differences in the analysis of the contralateral temporal cortex (the louder the tinnitus is perceived, the higher the gamma power)[3].

2. Tinnitus patients demonstrated after NFB -power for delta and theta bands was reduced; however, an increase of power was noted for the alpha bands[1].
3. The basic principles of Neurofeedback include:

Changes in activity are related to certain symptoms, e.g.in cases of tinnitus reduced alpha power in the auditory cortex.

- The goal of EEG NFB is to Increase alpha power in the auditory cortex.

METHOD

Voluntary control of activity in certain parts of the brain is not possible. Subjects learn how to influence brain activity by presentation to the patient of a visible activity and subsequent changes in activity. Brain wave recordings are obtained initially and during presentation of subsequent alterations in activity.

Feedback to the patient establishes a desired level of brain activity resulting in tinnitus relief.

Operant conditioning of EEG characteristics: Training to decrease slow activity and to increase fast, desynchronized EEG activity. The desired activity

changes followed by positive feedback or rewards result in the learning of self-regulation by the tinnitus patient.

A review of the NFB literature with tinnitus outcomes of 5 investigators for tinnitus was reported:

- Alpha increase 8-12 Hz/delta decrease 3-4 Hz - alpha/delta ratio increased over time; significant reduction Tinnitus handicap inventory (THI) and visual analog scales (VAS).

- Alpha increase 8-12 Hz/delta decrease 0.5-4 Hz-alpha/delta ratio increased over time. Decrease in tinnitus loudness; tinnitus distress.

- Alpha increase 8-13Hz, beta reduction 14-30 Hz. In 24/40 tinnitus patients there was an increase in alpha, no beta change; 16/40 tinnitus patients demonstrate beta decrease but no alpha increase- both report reduction in tinnitus distress.

- Alpha increase (8-13 Hz)-increase in alpha demonstrated in rt auditory regions. Significant reduction in tinnitus symptoms reported with tinnitus questionnaire.

- Alpha increase (8-13 Hz), decrease beta 14-30 Hz- increase in alpha demonstrated; reported reduction tinnitus distress.

Open issues for discussion included the following:

- Previous Neurofeedback studies have recorded activity from surface electrodes. Unclear to what extent the recorded activity reflects the activity of the auditory cortex -OR-nonspecific effects e.g. overall relaxation[4].

- Location of the auditory cortex- Not on brain surface but in the medial 2/3 of Heschel's gyrus adjacent to the retro insular strip of the Sylvian fissure[5].

- sLORETA presented as best source estimation, i.e. localization, in brain of electrical potential recorded from surface electrode on scalp[6].

- Combination results of sLORETA based neurofeedback has not been reported for tinnitus. It has been reported for attention deficit disorder (ADHD)[7,8].

Standardized low resolution brain electromagnetic tomography (sLORETA[6]).

- sLORETA is the most frequently used reconstruction technique of EEG data.

- Each voxel is seen as a possible location of a current source. Voxels are seen as dipoles of which degree of activation needs to be estimated.

- Assumption, that neighboring neurons are simultaneously and synchronously active.

- sLORETA computes the electrical source activity in each voxel of the grey matter.

- Wide acceptance and validation for source localization of EEG activity with sLORETA.

The problem is that EEG measures activity at the surface of the brain. The sLORETA provides a reconstruction technique in the narrow band frequency which is mathematically most probable to be the source localization as an estimate inside the brain of the electrical potential recorded from surface electrode at the scalp.

NFB- The Zurich Approach:

Hypothesis: Significant reductions of trained delta and gamma frequency range in combination with an increase in alpha frequency power in the auditory cortex results in improvement in subjective tinnitus measurements.

- Method: Application LORETA analysis for source estimation for identification of the oscillatory activity in the primary auditory cortex.

- Focal alteration of the neuronal activity is identified with sLORETA.

Zurich Pilot study:

Results of 6 subjects were presented, mean age 42 years, 4 male and 2 female.

The protocol included:

a. Baseline recording:

- Duration October/November 2013.
- Site U. Zurich.
- Baseline resting state EEG recorded.
- Questionnaires - tinnitus/psychological.
- Baseline Audiometry performed.

b. NFB training sessions:

- Duration October/November 2013.
- Site- NFB center.
- Training sessions 15, duration 30-45 minutes.
- QEEG session number 1 and 15 (i.e. first and last).

c. Post test:

- Site U. Zurich March/April 2014.
- Resting state EEG recorded.
- Questionnaires - tinnitus/psychological.

d. NFB technique:

- Region of interest (ROI) analysis-averaging and summarizing the activity from 4 voxels representing the rt and lt primary auditory cortex.

- Reward is 8-12 Hz (Alpha).

- Inhibit 1-6 Hz (delta/theta and 20-35 Hz high beta gamma).

- Threshold choice based on individual neural signature.

- Feedback from a computer game eg. "Navigation of a space ship through a narrow tunnel and collecting power-ups".

- Alpha increase results in space ship going faster (reward).

- Activity threshold in the inhibited frequency when surpassed results in decrease in visibility and decrease in size of the power-ups (i.e. penalty).

e. Results:

- High variance between individuals.

- No statistical significant results in analysis of subjective tinnitus data, but mean decrease in the tinnitus handicap inventory of 8 points.

- Significant decrease in activity of trained gamma in the rt auditory cortex.

- NO effect trained alpha lt, medium effect rt side.

f. Conclusions:

- sLORETA performance is feasible in the NFB of tinnitus patients.

- No definite conclusions sLORETA NFB (small group, high interindividual variability).

- Some evidence of change in brain of participants.

November 2014- start larger study with controls.

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III. Berthold Langguth, M.D. Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany; Interdisciplinary Tinnitus Center, University of Regensburg, Regensburg, Germany; Tinnitus Research Initiative, Regensburg, Germany; Guest of Honor "Neuroplastic changes in tinnitus learned from brain stimulation and pharmacotherapy"

The presentation focused on two main issues-brain stimulation, tinnitus and trans cranial magnetic stimulation (TMS); and pharmacological methods of tinnitus treatment:

a. Brain Stimulation:

The presentation started with a series of questions:

Q1. What is the location of tinnitus in the brain and what are its neuronal correlates?

A diagram of the central auditory system was presented. The structures involved in tinnitus were highlighted in the ascending auditory pathways.

Neuroimaging fMRI studies of tinnitus patient were presented[1,2]. The regions included the cochlea, cochlea nucleus, caudal midbrain, inferior colliculus, medial geniculate body, and primary auditory cortex. Although the localization of the tinnitus with brain neuroimaging results are inconsistent in the literature, regions of interest demonstrating brain activation, in general, involve auditory and non-auditory regions. Included are activation in the anterior cingulate cortex, the prefrontal cortex, the amygdala, and hippocampus.

Q2. Are the alterations in the auditory system causing tinnitus?

Does noise trauma result in a primarily neuronal change which clinically is expressed as tinnitus or is the noise trauma producing both neuronal change and tinnitus?

Translation of the basic findings of tinnitus localization were applied for clinical research with transcranial magnetic stimulation (TMS) in an attempt to provide tinnitus relief to the patient. An initial method for focal noninvasive and painless stimulation of brain activity in these areas was demonstrated. Initially, a magnet was placed on the scalp at a level above the external ear, towards the midline of the scalp i.e. temporoparietal. It was hypothesized that neuronal changes would take place in the underlying neural substrate. The results for tinnitus relief were inconsistent, i.e. both reduction as well as increase of tinnitus in some patients. About half of the patients treated with TMS demonstrated some relief. Overall, about half of the patients treated with TMS demonstrated some benefit. However the degree of the improvement and the number of patients involved was small. There was, however, high interindividual variability in the treatment outcome[3].

Repeated TMS applications were reported to result in a lasting tinnitus reduction[4,5].

b. Transcranial magnetic stimulation:

It was questioned what the interaction was between different brain regions when a magnet is placed in this location?[6]. Activated ROIs included the amygdala, hippocampus, parahippocampus, posterior and anterior cingulate cortex and precuneus. Were these areas of activation acting alone or represented interconnections between different brain systems of activity, highlighted by activity between the prefrontal, parietal cortices, and the anterior insula. It was hypothesized that the activated ROIs reflected different dynamic overlapping brain networks and should be considered as targets for the treatment of tinnitus with TMS.

This approach of TMS stimulation at multiple ROIs was based upon the hypothesis that brain networks are

involved in phantom perception which includes tinnitus. The hypothesis of a perceptual network was presented. Initially, sensory deafferentation causes neuroplastic change which in the case of phantom pain results in an increased activation of the somatosensory cortex (SSC), and in the case of tinnitus, activation of the primary auditory cortex (PAC). The awareness of the stimulus arises when the activity is connected to a larger co-activated awareness or perceptual network.The perceptual network involved the anterior cingulate cortex (ACC), dorsal cingulate cortex (dACC), and posterior cingulate cortex (PCC), precuneus, parietal, and frontal cortices. A salience exists to the phantom percept reflected by activation of dACC by the anterior insula. There is a constant learning process in which the phantom percept becomes associated with chronicity and reflected in distress of the patient reflected in a nonspecific distress network i.e. ACC and dACC, anterior insula, and amygdala. The phantom percept persists due to memory mechanisms involving the parahippocampus, hippocampus, and amygdala.

The results of a randomized double-blind parallel group study were presented of patients who received rTMS treatment on 10 consecutive working days using either multi-site rTMS protocol (left dorsolateral prefrontal, 1000 stimuli, 20 Hz; left temporoparietal, 1000 stimuli, 1 Hz; right temporoparietal stimulation, 1000 stimuli, 1 Hz) or a single site protocol (unilateral stimulation of the temporoparietal cortex, 3000 stimuli, 1 Hz). The patients were of age 18-70, chronic tinnitus greater than six months' duration and a Tinnitus Handicap Inventory score greater than 38 were recruited for this study. A total of 50 patients were needed to detect the clinical relevant change of tinnitus severity. Changes in brain structure and activity were evaluated using functional magnetic resonance image and EEG in the resting state. Twenty five (25) healthy controls were also tested. The neurobiological model used for this study was that described by Schlee and Collins which involve several brain regions all of which can be stimulated with different frequencies in a different order and with a varying number of stimuli[7]. It was hypothesized that rTMS treatment protocols on brain structure and function should provide a basis for neural correlates of tinnitus[8]. Tinnitus patients identified combined treatment of left frontal and temporal rTMS compared to left temporal rTMS for the efficacy of tinnitus relief than single site stimulation.

The results of triple TMS stimulation was reported with electrode placement on the right frontal, right temporal and parietal area, and left temporoparietal area[9], comparing single site with multi-site rTMS for triggering of chronic tinnitus. This one was a randomized double line parallel group study. The patients received rTMS treatment on 10 consecutive days using either multi-site rTMS protocol. Fifty (50) patients were included in this study. Twenty five (25) control subjects without tinnitus were matched for age, gender, and hearing function, and were examined once using EEG, MRI, functional MRI, and questionnaires. Both groups improved from baseline to day 12. However, there was a difference on day 90, i.e. the multi-site stimulation group showed an overall improvement, whereas the patients receiving temporal stimulation returned to their baseline level of tinnitus severity. These data suggests that multi-site rTMS is superior to temporal rTMS. It represents a promising strategy to enhance treatment effects of rTMS and tinnitus with multisite.

c. Pharmacotherapy:

Pharmacotherapy recommendations attempting tinnitus were recommended to differentiate between acute and chronic tinnitus.

Acute tinnitus:

Recommendations included systemic/Intratympanic steroids, vasodilators, and antiviral agents. Good evidence is only available for steroids particularly intra- tympanic steroids. Noise-induced hearing loss also is a form of acute tinnitus by exposure to loud noise 85 db and higher. Acute tinnitus may also be a side effect of pharmacological treatment. Investigation was recom- mended to identify the mechanisms such drug(s) have in common resulting in the clinical manifestation of tinnitus.

The chief limitation of drug development for tinnitus is an incomplete understanding of the pathophysio- logical mechanisms involved.

Chronic Tinnitus:

There is no specific pharmacological compound approved for treatment of chronic tinnitus. A variety of drugs approved for other indications are used for the treatment of tinnitus in clinical practice. The most relevant drugs can be differentiated by the type of drug tested. Off-label drug use in the treatment of tinnitus includes antiarrhythmic, anticonvulsants, angiolytics, glutamate receptor antagonist, antidepressants, and muscle relaxants. Other drugs have been reported with either limited efficacy and to need further controlled trials. This includes a HMG-CoA reductase, atorvastatin, the vasodilators cyclandelate, furosemide, herbal products, Ginkgo biloba, melatonin, Prostaglandin E1, misoprostol, L type calcium blocker amlodipine, phosphodiesterase type 5 inhibitor, Vardenafil, and minerals including zinc[10].

Antidepressants are frequently proposed for management of chronic tinnitus In particular, tricyclic antidepressants have been recommended mostly because of the beneficial effects on chronic pain syndromes. In the interpretation of the effective antidepressants for tinnitus, it must be considered that the scales used for

tinnitus measurement correlate highly with depression scales[11]. Therefore, the reduction of tinnitus severity with antidepressants may at least partially be a pure coincidence of antidepressant effect of the investigated drugs. There has been report of some improvement in tinnitus associated with improvement of depression and anxiety. One cannot, however, say that one antidepressant is superior to others. Positive effects were reported for Xanax and Klonopin.

No report was mentioned of positive effect with Ginkgo biloba 40 mg once a day.

A Cochrane meta-analysis of the use of anticonvulsants for tinnitus treatment concluded that studies so far show small effects of doubtful clinical significance and no evidence for large positive effect of anticonvulsants in treatment of tinnitus.

A slide was presented grouping different drugs by the underlying mechanism of action and trying to correlate them with the underlying tinnitus mechanism for its production.

A network pharmacology side-effect analysis searched for genes that are involved in tinnitus generation. A network of 1,313 drug-target pairs, based on 275 compounds that elicit tinnitus as side effect and their targets reported in databases were analyzed. A quantitative score was used to identify emergent significant targets that were more common than expected at random. Cyclooxygenase 1 and 2 were significant[11].

Baclofen, a GABA-B antagonist with muscle relaxant effects also reduces tone exposure-induced hyperexcitability in the inferior colliculus of rats. L-baclofen up to 60 mg per day has been reported with improvement of tinnitus, however, frequent side effects.

The challenge for future tinnitus research is to consider differentiation of pathophysiological distinct subtypes of tinnitus.

Future drug development was recommended to focus on identification of specific clinical and chemical entities that interact with discrete molecular targets.

Tinnitus is considered as a complex network pathology similar to other complex CNS pathologies for which a combination of different drugs will be more effective than a single drug alone. Such a combination of treatment could consist of different drugs even if one in isolation has shown only some limited benefit for tinnitus suppression. For example, antidepressant melitracen and antipsychotic lupentoxil which is shown to be superior as an add-on medication to Klonopin.

Summary:

1. Alterations in auditory and in non-auditory brain areas are involved in tinnitus pathophysiology.
2. Tinnitus can be best influenced by modulation of auditory and non-auditory brain areas.
3. Neither TMS nor medication alone have a role for routine treatment but provide important information for better understanding of the pathophysiology of tinnitus.

Drug development should be directed to the areas identified with fMRI and neuroimaging techniques which have identified an under- lying matrix for tinnitus as well as non-auditory responses of brain function as reflected in the areas of the somatosensory cortex or in auditory cortex, perception network, salience network, distress network, and memory areas. In other words, tinnitus is best influenced by modulation of auditory and non-auditory brain areas with medication.

There is currently not a single FDA or EMA-ap- proved drug in the market. A variety of drugs with different therapeutic uses have been used off-label with some effect in a limited subset of patients. Pharmacological approaches are limited to treatment of comorbidities such as depression, anxiety, or insomnia. The future is development of a drug or combination of drugs for tinnitus relief.

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IV. Richard S. Tyler, PhD; Otolaryngology The University of Iowa "Instrumentation - New Techniques"

The presentation focused on instrumentation to be considered for tinnitus relief: 1) Hearing aids for tinnitus. 2) Sound therapy and 3) Sound therapy devices.

Hearing aids for tinnitus:

Hearing aids were recommended even with mild hearing loss since it often helps tinnitus. Support for this opinion was supported by a study in which the effectiveness of hearing aids was established in mitigating the effects of tinnitus in 1314 patients. The results were: 4.2% were made worse, 13.7% showed a significant reduction, 14.1% had moderate reduction, 15.7% had a mild reduction, and 52.4% showed no effect[1].

Sound Therapy:

Wearable sound therapy devices for tinnitus include small portable computers, cellphones and watches, which can produce a wide variety of sounds. Some of them download directly to hearing aids. Sound therapy should be combined with counseling for best results. Tinnitus treatments activities were recommended and have been ongoing since 1990s. It combines cognitive behavioral therapy, existentialism, acceptance, and relaxation. Improvement can be seen in sleep, hearing, emotion, and concentration[2].

Sound therapies:

Low-level noise makes tinnitus more difficult to detect. Differences among sound therapies are reflected in the sound quality and the level at which the therapy is provided.

Masking refers to the substitution of one sound by another. The level of the background sound provides total or partial masking. Total masking covers the tinnitus completely. The patient hears a "masker" instead of the tinnitus. The masker is an effective therapy for some tinni- tus patients. In partial masking, the tinnitus and acoustic sound both can be heard. The prominence or loudness of the tinnitus is reduced. "Both the noise and tinnitus are heard, but the tinnitus is reduced in loudness." The patient should "use the lowest-level masker that provides adequate relief"[3,4] "urged the patient to use the lowest level of masker level that provides adequate relief." Some patients prefer total masking. With complete total masking, the intensity level of the masker is just above the intensity level of the tinnitus. With partial masking, the intensity of the masker is not sufficient to cover the intensity level of the tinnitus.

The Tinnitus Retraining Therapy (TRT) was introduced by Jastreboff in 1995[5]. The patient was recommended to use the device not as a masker, but to use the stimulus from the device to achieve a "mixing point". The "mixing point" was defined by Jastreboff as "where the patient perceives that the tinnitus sound and the external sound start to mix or blend together. Hatanaka et al.[6] concluded that the mixing point could be too loud. Tyler[1-7] recommended that the mixing point should not be the goal in partial masking. It is recommended that one should use the lowest level that is effective.

Comparison of the effectiveness of TRT and "mixing point masking" compared to "total masking therapy" compared to "counseling alone" was presented[7]. Traditional TRT recommends mixing point (i.e., partial masking) masking, as total masking previously was considered to not allow the brain to habituate to the tinnitus and therefore not perceive the tinnitus. Disagreement was expressed to "historically" accepted ideas and protocols that all tinnitus patients should avoid silence or that silence may be bad for tinnitus patients. It was recommended that "hearing aid use without providing background sound" is not beneficial. It was stated that hearing aid use offers great potential for tinnitus management. Support is recommended for the beneficial effects of group therapy. In conclusion, Tyler stated "we believe that for some patients of tinnitus all forms of masking therapy, including those that use total masking and low--level partial masking might provide relief." Mixing point and total masking are equally effective[7].

Sound therapy stimulus options include broadband noise, noise-modifying spectrum, noise-modifying envelope, combined tones and modulated tones, music which is processed and the sounds of the music are spectrally adjusted to the audiogram -i.e. SPA tones, Zen tones and notched noise or music around the pitch match, which is the Neuromonics stimulus. With Neuromonics,the patient is exposed to various stages of processed music. In stage 1, the processed music is inversely matched to the audiogram plus noise. In stage 2, the processed music is inversely matched to the audiogram. In theory a neural stimulus, i.e. relaxing customized music, in a two phase protocol program, interacts with the tinnitus perception to result in plastic changes in the central auditory pathway. The desired result is reduction in tinnitus perception, and long term tinnitus relief. (Davis 2007)[8].

Tailor-made notched music reduces tinnitus loudness and tinnitus-related auditory cortex activity (Okamoto, H. et al. 2010)[9]. The patient chooses enjoyable music which is modified, i.e. "notched", to contain no energy in the frequency range surrounding the individual tinnitus frequency. In other words, the frequency of the tinnitus is removed from the music that is being used as

the stimulus. The music is "notched". Significantly, after 12 months of regular listening, a target patient group of eight patients reported a significant reduction in the loudness of their subjective tinnitus. In addition, they demonstrated reduced evoked activity in areas of the auditory cortex corresponding to the tinnitus frequency compared to patients who received an analogous placebo notched music treatment. This report suggests that tinnitus loudness can be significantly diminished by an enjoyable, low-cost, custom-tailored notched music treatment. Okamoto et al.[9] has stated: "potentially the mechanism is a reversal of the maladaptive auditory cortex reorganization".

To date, tinnitus treatment strategies, for example TRT, are symptom-management approaches. Spectrally, "notched" music and reduced cortical activity corresponding to the notch center frequency, possibly occur due to lateral inhibition.

Tyler et al.[10] investigated patient preferences for multiple tinnitus treatment options from wearable to implantable devices. and willingness to pay for tinnitus treatment. The report was based on a 197 attendees from a tinnitus self-help group. The attendees rated acceptance from 0, not acceptable, to 100, fully acceptable. A statistically significant relationship was identified between perceived tinnitus loudness and annoyance. Most patients are most prepared to use medications for tinnitus treatment. It was stressed that no widespread evidence-based pharmaceutical agent is available that "cures" tinnitus at this time. Most patients were reported to seek, accept, and pay for treatment; however, they preferred less-invasive (i.e., external) devices if they can completely eliminate tinnitus. There was only a "little relationship between tinnitus loudness and annoyance and the amount of money". Tinnitus patients are willing to pay for relief. Many patients reported that they would pursue surgical options and many would pay $10,000 for treatment to reduce their tinnitus.

In conclusion, a wide variety of sound therapies were presented in an attempt to provide tinnitus relief. Any and all sound therapy should be combined with counseling, for example tinnitus activities treatments. Low levels of partial masking are best for most patients. Preference for quality of sound varies widely across patients. It was stressed that any and all options should be provided to patients.

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V. Michael D. Seidman, MD., FACS., Director Otologic/Neurotologic Surgery Henry Ford Health System and Wayne State University. Co-presenters: Susan Bowyer, PhD, Jinsheng Zhang, PhD, Anthony Ca- cace, PhD. "Paired Vagus Nerve Stimulation for the Management of Tinnitus; Diffusion tensor imaging; Magnetoencephalography (MEG); AN-101; The Esteem System Implant"

The presentation was a glimpse into the future for tinnitus, diagnosis and treatment. Specifically the clinical experiences of Dr. Seidman with: Paired Vagus Nerve Stimulation for the Management of Tinnitus; Diffusion tensor imaging (DTI), Magnetoencephalography (MEG); AN-101; and The Esteem System Implant attempting hearing improvement for sensorineural hearing loss.

The introduction was a brief review of what is an evolving pathophysiology for tinnitus. Hearing loss or noise exposure results in a pathological alteration in plasticity at brain cortex resulting in tinnitus. A reorganization in the frequency map occurs. Hearing loss has been associated with identification of an increased spontaneous firing in specific regions of the ascending central auditory system. The association of hearing loss and tinnitus has been identified clinically; however, there is no correlation between hearing loss and the severity of the loss. The increase in spontaneous firing is converted, translated, transformed at the thalamocortical level resulting in a synchronization of multiple brain wave oscillations of different frequencies, which in primary and secondary auditory cortices is perceived by the patient as tinnitus.

Vagus nerve stimulation (VNS)

Vagus nerve stimulation (VNS) releases the neurotransmitters, acetylcholine and norepinephrine from the locus coeruleus and the Nucleus basalis. The result is hypothesized to produce neuroplasticity at brain cortex. The tonotopic map at auditory cortex was demonstrated when normal, distorted as with tinnitus and following VNS with Tones Pairing. Following VNS in combination with Tones Pairing the initial distortion accompanied by increased excitability and spontaneous firing and synchrony at cortex was seen on the tonotopic map to be restored to normal as demonstrated with decreased excitability, reduced synchrony and spontaneous activity. A tone was paired with vagus nerve stimulation 300 times per day for 20 days. After 20 days, there was a massive expansion of the auditory cortex map specific to the paired tone. It is concluded that VNS paired with a tone generates massive plasticity in the auditory cortex specific to the paired tone[1].

Blast injury and Distortion tensor imaging (DTI)

Blast-induced tinnitus and hearing loss was demonstrated in rats with diffusion tensor imaging (DTI). Specifically, the DTI suggests fiber distortion to and from AC and MGB[2].

Magnetoencephalography (MEG)[3]

The detection of tinnitus by MEG using coherence imaging was demonstrated. The MEG is a technique to localize sources of electrical activity within the human brain by noninvasively measuring the magnetic fields arising from such activity. It is also called magnetic source imaging (MSI). MEG coherence analysis or spontaneous activity can be seen in a tinnitus patient. A patient with a unilateral tinnitus in the left ear demonstrated localization of high coherence in the right auditory cortex (AC), Brodmann area, BA 42. The maximal frequency was determined from a graph that displayed the coherence level for all the frequencies in this particular region of interest. Coherence imaging in a controlled subject with no tinnitus and no neurological disorder exhibited patterns of low coherence and no areas of high coherence as seen in the tinnitus patient, specifically in the AC.

The VNS with Tones Pairing Serenity System

The VNS with tones pairing Serenity system was demonstrated in a patient. A Vagus Nerve Stimulator (VNS) is implanted in the OR during a 60 minute outpatient procedure. VNS devices have been used to treat epilepsy safely for 15 years. Over 60,000 patients have been implanted.

The components of the Serenity System include: 1) the clinical headphones positioned on the ear rt and lt of the patient; 2) implantable VNS device; 3) wireless transmitter; and 4) laptop with therapy software.

Steps in the delivery of the VNS with Tones Pairing Serenity System to the patient include the following:

1. The patient listens to tones while receiving stimulation (2.5 hour session, 5 days a week, 4 weeks) - initially in clinic, then at home.
2. A physician given laptop with software is loaded for the paired stimulation/tone therapy.
3. The patient, sitting in a chair with clinical headphones with the implantable VNS device in the neck area, is connected by a wireless transmission to the laptop loaded with therapy software.

The VNS - Tone Pairing Therapy includes the following:

- Stimulus: 0.5 sec auditory (500 ms tone and vagus stimulation 0.8 mA, 30 Hz,100 microsec pulse width VNS).
- 30 seconds between VNS-Tone pairings;
- 300 VNS-Tone pairings per day.
- 2.5 hours per day.
- 20 days of therapy.

The results of a clinical trial on 10 patients in Belgium which were presented at the Tinnitus Research Initiative Meeting in June 2012 were presented again. The assessment of results utilized the tinnitus handicap inventory (THI), tinnitus handicap questionnaire (THQ) and Minimal masking level (MML).

Safety summary issues reported with VNS - Tone Pairing Therapy included the following:

Adverse events were minimal as expected based on VNS for epilepsy/depression.

- The first patient demonstrated redness at the abdominal site and vocal cord hypomobility (mild). Surgery was more difficult due to previous neck surgery. Both issues resolved within two weeks of the surgery.

- The fourth patient demonstrated an increase in tinnitus and depression during the first week after implant. This resolved with therapy modification during week 2. The patient also had mild hoarseness during stimulation for the first two weeks, namely unable to tolerate standard settings.

At long-term follow-up return, the patient also had worsened depression (two-day stimulation, four days no stimulation, then suicide attempt) no further VNS was applied.

- Patient JK-003-a lead extender was removed during a long-term follow-up due to infection.

Improvement was reported in 7/10 on THQ, 6/10 on MML, and 4/10 on THI. Improvement in depression scores were > 5 points in 4/10 patients and all others had less than five-point alteration Patients appeared to maintain improvement for 3-4 months.

An ongoing Blinded Randomized Pilot NIH Study Assessing Vagus Nerve Stimulation (VNS) paired

with Tones for Tinnitus *vs.* VNS with Unpaired Tones with MIcroTransponder's Serenity System was presented. The primary objective is to provide additional and better controlled evidence that VNS coupled with precisely timed tones in subject suffering from moderate--to-severe subjective tinnitus is an effective treatment for tinnitus. The study is a four-site 30-patient study. All patients to be implanted were divided into two groups; half to VNS plus tones and the remainder half to sham VNS plus tones. Following implant there was six weeks of acute treatment. Then, long-term where all patients received paired VNS treatment. Nine patients were reported im- planted to date. If the pilot is successful, a 150-patient study at 15 sites will follow.

Inclusion criteria included ages 22 to 65. Tinnitus diagnosis - subjective tinnitus due to hearing loss with some tonal quality of the tinnitus. Tinnitus location -unilateral or bilateral. Tinnitus duration for at least one year. The MML greater than or equal to 7.

The THQ score > 40. No tinnitus treatment for at least four weeks prior to entry into the study. Willing to comply with all study-related procedures during the course of the study.

Exclusion criteria included acute or intermittent tinnitus. Hearing loss greater than 80 dB HL, Meniere's disease, ear tumors, evidence of active middle ear di- sease, i.e. fluid, infection, tumor, and mass. Any other implant or device such as a pacemaker or neurostimu- lator. Any other investigational device or drug. Pregnant, plan to become pregnant or breast-feeding during the study. Medications that influence neuromodulators. Significant cardiac history. Taking medication known to worsen tinnitus.

AM-101 pharmacological treatment of acute inner ear tinnitus.

It is hypothesized that: 1) activation of NMDA receptors and glutamate excitotoxicity occur with noise, trauma, barotrauma, surgery, and otitis media with production of proinflammatory cytokines and 2) tinnitus is the result of NMDR mediated aberrant excitation of the auditory nerve[4]. The results of AM-101 randomized control trials have reported the drug to be well tolerated, reduction in tinnitus loudness, masking level improvement, and tinnitus attenuation[5].

Plans are in place in North America and Europe for Phase 3.

Esteem System Implant:

The Esteem system implant is a total middle ear implant for a moderate sensorineural hearing loss for patients 18 years and older with a stable moderate severe sensorineural hearing loss and good speech discrimination[6].

The components of the implant are the sensor, sound processor and driver.

Limited data with Esteem was presented of 30 patients of 57 (54.4%) who reported a history of tinnitus at baseline.

Through the 10-month post-implant follow-up, there were 8 reports of tinnitus as an Adverse Device Effect (ADE) - of these 5 had resolved by the 10-month follow-up and 3 were ongoing.

Through the 10-month post-implant follow-up period, there were a total of 9 reports of tinnitus in 8 patients (14% of patients) associated with either the Device and/or Procedure.

The clinical application for severe subjective tinnitus was not reported.

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The attendees to the 5th AAO HNS International Tinnitus Miniseminar 2014 were provided with information of the present, ongoing and future state of the art basic science and clinical medical audiological advances for understanding tinnitus theory, an evolving neurobiology for tinnitus, and its application for diagnosis and treatment for the benefit of the tinnitus patient.

We look forward to meeting in 2015.

Barbara Goldstein, PhD.
Michael E. Hoffer, M.D.
Abraham Shulman, M.D.