
EDITORIAL

Twenty-Fifth Anniversary Meeting of the International Tinnitus Forum, September 15, 2007, Washington, DC

Attendees to the twenty-fifth anniversary meeting of the International Tinnitus Forum (ITF), September 15, 2007, in Washington, DC, celebrated the occasion by experiencing state-of-the-art presentations and discussion, reflections of the past, plans for the future, and each other's company. Together, attendees were reminded of the initial meeting in Miami, 1982, sponsored by John Shea, Jr., attended by a handful of professionals, and followed by the growth and development in meeting attendance and quality and content of presentations of professionals worldwide.

Recognition was extended to Dr. Barbara Goldstein, AuD, whose expertise in and contributions to planning and organizing ITF functions over the years are reflected in the growth, development, and success of the ITF.

Together, we have witnessed evolution of the new discipline of tinnitus, a multifaceted discipline involving professionals in both the basic sciences—dedicated to understanding how a sensory aberrant auditory stimulus (i.e., tinnitus) becomes transformed into one of affect—and in clinical work—attempting to establish accuracy in tinnitus diagnosis, to identify the medical significance of this entity, and to attempt treatment for all clinical types of tinnitus.

The theme of the twenty-fifth anniversary meeting was Translational Research in Tinnitus Therapy III, with a focus on nuclear medicine imaging. The presentations were selected to highlight the translation from auditory science and neuroscience in basic scientific reports of brain function, biophysiological mechanisms underlying brain function, pharmacotherapeutic targets, and clinical application for treatment. The guest of honor, Arnold M. Strashun, MD, Professor of Radiology and Director of Nuclear Medicine at State University of New York, Downstate Medical Center (SUNY/Downstate), reviewed the contributions to tinnitus diagnosis and treatment of nuclear medicine imaging past, present, and future.

Initial presentations were of neural substrates in the brain as related to tinnitus and a method for its electrophysiological identification.

Martin Lenhardt, AuD, presented an update of the role of the insula and hypothesized its role in a final common pathway for tinnitus. The insula cortex (Brod-

mann's 13–16) has distinct auditory and multisensory areas that have been identified through imaging to be active or hypoactive in cases of severe tinnitus. As such, the insula is a candidate for inclusion in the final common pathway for tinnitus. The insula has connection with the prefrontal and auditory cortices, the amygdala, the thalamus, and the parabrachial nucleus. The parabrachial nucleus is part of the “How do you feel?” circuit that also warrants inclusion in the final common pathway. The hyperactive insula was associated with a reduction in medial temporal lobe activity after high-frequency stimulation. Behaviorally, tinnitus severity declined with high-frequency stimulation, but annoyance remained essentially stable. The insula has a possible role in addiction; after insula stroke, two-thirds of smokers in one study quit smoking without difficulty. This opens the possibility that the insula or the insula circuits may maintain “addiction to tinnitus,” a concept that suggests the application of addiction treatment strategies. Vestibular and multisensory stimulation should also be explored in that these, too, activate the insula.

Claus-Frenz Claussen, MD, presented “The Slow-Brainstem Syndrome: Tinnitus and Dyssynchrony in the Central Nervous System” (which report is published in the current issue of the *International Tinnitus Journal*). Objectively, these patients complain of a “hazy tinnitus in combination with vertigo, giddiness, dizziness” and “a reduced state of alertness.” Objectively, these patients also exhibit an increase in the latencies of experimentally evoked vestibular nystagmus and of acoustically evoked brainstem potentials. Observation of diffuse metabolic changes occurring at the level of the brainstem are considered to be responsible and lead to a functional dyssynchronization within the statoacoustic pathways, appearing also as an age-dependent process. Treatment with “a combination of coccus (picrotoxin), conium (Coniine), amber, and petroleum (Vertigoheel) has a ‘tune-up’ effect on the brainstem in these patients.” Continued use of this preparation is reported to be accompanied by “normalization of the distorted latencies of the statoacoustic pathways, followed by disappearance of the symptoms.” This experience is ongoing and

has been reported since 1985 in a particular cohort of tinnitus patients in whom dyssynchronization within the statoacoustic pathways was implicated.

Erik Viirre presented "High-Density EEG and Tinnitus." The technique was presented in the context of the ability of quantitative electroencephalography to objectify the tinnitus complaint. Research and clinical applications were included, highlighted by the demonstration of dyssynchrony-synchrony of neuronal activity at the cortex in tinnitus patients.

Until now, we have been highly restricted in our capabilities of recording activity in the human brain. There have been four limitations: poor spatial resolution (i.e., localizing signal sources); poor temporal resolution (being unable to resolve the immediate actions of signal sources on the millisecond scale); poor signal-to-noise ratio (wherein it has been difficult to distinguish one local source from another); and finally, the limited ability to monitor multiple sources simultaneously to determine how they act together.

In each of these areas, our limitations for human recordings are shrinking: Better spatial localization is now enabling distinction of groups of neurons on the sub-millimeter level, timing of sources on the millisecond level, distinction of sources a millimeter apart, and the ability to monitor simultaneously hundreds of groups of neurons. Recording of single neurons remains the province of heroic procedures (by the patient) conducted during neurosurgery. No one modality of recording now offers all of these capabilities simultaneously. We must do multiple recordings with multiple technologies and integrate them to obtain all these features. There are three fundamental modes of recording: measurement of local blood flow changes of neuronal groups as they change their activity, measurement of emitted electromagnetic fields as neurons are active, and measurement of changes of optical properties of neuronal groups as they are active.

Regional blood flow changes are recorded with positron emission tomography (PET) or functional magnetic resonance imaging. The advantage of these techniques is that brain regions that are active in relation to a given activity can be reliably resolved to sub-millimeter resolution. However, the coding of signals in the active neurons is relatively opaque in recordings of regional blood flow. We do not know whether there is an increase in activity in inhibitory or excitatory neuron firing or the specific coding details of activity of a given neuronal group. Recording of the electroencephalographic or magnetoencephalographic (MEG) signals from the brain has been improved greatly by advanced amplifiers and signal analysis. These signals still tell us of the activity of only a group of neurons and the signals of only postsynaptic potentials, not action potentials. Ac-

tion potential recording is the Holy Grail of neural signals. Interestingly, it appears that there are some changes in the reflectivity of axons taking place when action potentials occur. Thus, the event-related optical signal is an intriguing possibility. In this presentation, these recording methods, the auditory science established with them, and how they will help us with tinnitus were described.

Subsequent presentations at the anniversary meeting introduced an understanding of the medical significance of neurodegeneration (ND) in tinnitus patients for diagnosis and treatment from the perspective of clinical experience, drug development, and nuclear medicine imaging.

Abraham Shulman, MD, presented a review of clinical experience of ND and tinnitus since 1979 (reported in this issue of the *International Tinnitus Journal*). To highlight this experience, data from consecutive tinnitus patients who were seen in neurotological consultation from November 1, 2005, to June 30, 2007, (N = 96; ages 22–90 years) and were recommended for nuclear medicine imaging were reviewed. Patients selected for nuclear medicine imaging (n = 18 of 96; ages 39–75 years) fulfilled the criteria of a medical-audiological ND tinnitus profile, which has evolved since 1979 (i.e., completion of a medical-audiological tinnitus patient protocol that diagnosed a predominantly central-type, severe, disabling, subjective, idiopathic tinnitus lasting in excess of 1 year and failure of existing modalities attempting tinnitus relief).

Objective evidence of ND (n = 16 of 18) was reported in multiple neural substrates of brain obtained via nuclear medicine imaging (single-photon emission computed tomography [SPECT] or fluorodeoxyglucose positron emission tomography). Classification of central nervous system (CNS) ND and tinnitus differentiated between (1) ND, nonspecific and of unknown etiology; (2) ND manifested by perfusion asymmetries in brain associated with ischemia (n = 11 of 18); and (3) ND CNS disease consistent with nuclear medicine criteria for senile-dementia Alzheimer's-type disease (n = 5 of 18). The etiology identified has been associated with cerebrovascular disease in 16 of 18 patients. The identification of ND CNS disease in a selected cohort of subjective idiopathic tinnitus patients as a "soft sign" of ND CNS disease has implications for diagnosis and treatment.

Alfred Stracher, PhD, presented "Calpain Inhibitors as Magic Bullets for Treatment of Neurodegenerative Disease and Tinnitus." An intracellular Ca^{++} -activated protease known as calpain has been implicated in a diverse group of neuromuscular and ND diseases. For the last 25 years, Dr. Stracher's laboratory has studied the therapeutic potential of calpain inhibitors in several animal models of denervation atrophy, muscular dystrophy, multiple sclerosis, Huntington's disease, and hearing

loss. In each instance, therapeutic efficacy was demonstrated using our targeted calpain inhibitors that direct the agent to muscle tissue or the CNS (or both) selectively. The results suggest a common pathway for all forms of tissue degeneration. Examples were presented to substantiate this hypothesis, highlighted by the neuroprotection effect for noise-induced hearing loss in the animal model.

The guest of honor, Arnold M. Strashun, MD, reviewed the contributions to tinnitus diagnosis and treatment of nuclear medicine imaging past (since 1989), present, and future in his presentation "Tinnitus: Scintigraphy to Molecular Imaging." Tinnitus of the central and disabling type was inadequately characterized physiologically and its etiology was a mystery when our SUNY/Downstate working group initiated cerebral perfusion SPECT scintigraphy of these patients more than 20 years ago. SPECT data demonstrated reproducible perfusion abnormalities in most afflicted patients. Complex SPECT patterns of perfusion disturbance were the first objective sign of abnormality in tinnitus. Though the medial temporal lobes demonstrate the most frequent perfusion abnormality in tinnitus, other cerebral cortical, pontine, and basal ganglia sites are involved. More elaborate PET imaging of cerebral glucose use confirms the SPECT data. More specific molecular tracer imaging suggests a GABA neurotransmitter disturbance in tinnitus. These data are intrinsically quantitative and thereby allow customization of future therapy by providing a noninvasive monitor of response.

These molecular imaging data are the key to understanding the molecular abnormalities that form the basis of this disease as a new twenty-first-century imaging paradigm that will include multiple image-capture techniques beyond radiolabeled molecules, including maps of sound, electrical brain transmission, magnetism, and light. Image fusion across modalities will transform diagnosis and therapy by providing unique quantitation of regional cerebral activity before, during, and after therapy as the study of biochemical markers of tinnitus advances.

The concluding presentations focused on treatment modalities of medication and surgery for tinnitus relief clinically applicable at present and for the future.

Barbara Goldstein, PhD, AuD, presented a prospective clinical trial of a homeopathic preparation—Clear Tinnitus—in 15 tinnitus patients (14 male, 1 female; mean age, 47.6 years); she attempted to identify its clinical efficacy for establishing tinnitus relief for a 3-month period. Tinnitus relief with Clear Tinnitus was hypothesized to reflect improvement in the sensory component of the tinnitus complaint by control of the factor of aeration of the middle ears and improvement in eustachian tube function. The study was completed by 11 of

the 15 patients; four subjects did not complete the study. Seven responders reported tinnitus relief, and four did not respond. All 11 patients who completed the study demonstrated with tympanometry either a statistical and clinical significance in middle-ear pressure (MEP) improvement ($n = 8$) or maintenance of MEP ($n = 3$) or both.

Patients with tinnitus of the severe disabling type responding to Clear Tinnitus ($n = 7$ of 11) reported tinnitus relief: as an accompaniment of improvement in 5 or as maintenance of MEP in 2. The statistical and clinical significance of Clear Tinnitus for establishing tinnitus relief remains to be established with a larger cohort of tinnitus patients.

Michael L. Hoffer, MD, CMDR USN, and Benjamin Balough, MD, Capt. USN, presented "Blast Injury and Head Trauma and Tinnitus." The data reflected evaluation of cochleovestibular complaints in military personnel in Iraq after blast injury or head trauma (or both). Tinnitus was evaluated in this group of patients with traumatic brain injury for the parameters of origin (i.e., blunt head injury or blast exposure or both); postinjury symptom complex; and the level of hearing. Approximately 30% reported hearing loss. Tinnitus was a delayed complaint.

John L. Dornhoffer, MD, presented the results of "Repetitive Transcranial Magnetic Stimulation as a Treatment for Tinnitus: A Pilot Study." Explanations of tinnitus are changing. Whereas early theories focused on peripheral mechanisms, tinnitus is now thought to involve central mechanisms: thalamocortical dysrhythmia and cortical reorganization. This change in understanding has led to the search for treatment modalities that target the central mechanism. Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been shown to alleviate tinnitus perception, at least temporarily, presumably by inhibiting cortical activity associated with tinnitus. The study design included four patients with chronic tinnitus who were enrolled in a randomized, crossover-designed pilot study to assess the effectiveness of neuronavigated rTMS on tinnitus. Each of these patients underwent 5 consecutive days of active, low-frequency rTMS and 5 consecutive days of sham treatment using a 45-degree coil tilt method. Tinnitus was assessed at baseline and at the end of each week using a tinnitus-related disability questionnaire, analog scales, and a rating of the best tinnitus perceived in each ear during treatment. Integrated PET and computed tomography (CT) scans were obtained (1) at baseline to target rTMS to areas of increased cortical activity in the auditory cortex and (2) immediately after active treatment to examine change in cortical activity associated with rTMS. As attentional vigilance is impaired in patients with tinnitus, simple reaction time was

measured at baseline and after both active and sham rTMS. All four patients had a response to active (but not to sham) rTMS, as indicated by their best tinnitus ratings during treatment; however, tinnitus returned in all patients the week after active treatment. Three patients had reduced cortical activity visualized on PET immediately after active rTMS. Mean reaction time improved ($p < .05$) after active (but not sham) rTMS. It was concluded that rTMS can have an effect on tinnitus, but further trials are needed to determine the optimal administration techniques required to achieve a lasting response. Reaction times improved after active rTMS, but it is unclear whether this effect is due to tinnitus reduction or a general effect of rTMS. PET and CT scans immediately after active rTMS suggest that improvement may be related to a reduction of cortical activity associated with tinnitus.

Ilaaf Darrat, MD, an otolaryngology resident with Michael D. Seidman, MD, presented "The Effect of Electrical Stimulation of the Auditory Cortex for Tinnitus." The objective was to evaluate the effect of direct electrical stimulation of the auditory cortex on tinnitus. The design of the study was to report the results of four tinnitus patients with severe debilitating tinnitus in whom medical management had failed and who received the implantation of an electrode into Heschl's gyrus for control of tinnitus. The setting was a tertiary referral center.

Four patients were refractory to therapies, including counseling, medications, nutritional supplements, and herbs; trials at masking; and tinnitus retraining. The patients were evaluated with Beck depression indices, tinnitus handicap inventories, tinnitus reaction questionnaires, and the modified somatic perception questionnaire. The frequency and pitch of the patients' tinnitus was determined and reintroduced to the patients while they underwent cortical localization of the corresponding frequency using MEG and functional magnetic resonance imaging techniques. Using MEG-guided neuronavigation, the hyperexcitable area of Heschl's gyrus of patients were implanted with deep brain electrodes (Medtronic Inc, Jacksonville, FL). A pulse generator (Versitrel, Medtronic) was implanted in all patients to deliver long-term electrical stimulation. The main outcome measures included reduction or elimination of tinnitus with improvement in validated handicapping inventories. The results reported that patient RP had near elimination of tinnitus. Patient MV noted 30–35% abatement in her symptomatology, though some of the electrical stimulation paradigms exacerbated her tinnitus. Patient SH has experienced no benefit to date, and patient BF

has a 50–60% improvement. It was concluded that the perception and annoyance of tinnitus can be significantly reduced through electrical stimulation of the auditory cortex.

In summary, the discussions that followed each section of the meeting were clinically significant and provided the attendees with take-home information for tinnitus diagnosis and treatment and an insight into the future. The hypothesis of a final common pathway for tinnitus and the tinnitus dyssynchrony-synchrony theory found support for its diagnostic and treatment applications: for diagnosis, to consider the slow brainstem syndrome and recommendations for its treatment; to consider the ability of quantitative electroencephalography, an office-based procedure, to provide an objective electrophysiological correlate for a predominantly central-type, severe, disabling, subjective, idiopathic tinnitus; to consider the recommendation for nuclear medicine imaging based on the criteria of a medical-audiological profile for patient selection for the presence or absence of ND in a predominantly central-type, severe, disabling, subjective, idiopathic tinnitus patient; to consider ND to have a medical significance for a particular patient a predominantly central-type, severe, disabling, subjective, idiopathic tinnitus, with implications for diagnosis and treatment. Innovative treatment modalities directed to pathophysiological mechanisms underlying ischemia and inflammation provide a basis for attempting tinnitus relief. "The magic bullets" targeting ND CNS disease have already demonstrated neuroprotective effects applicable for hearing loss and tinnitus relief.

For the future, molecular genetic imaging and the efforts and results reported for transcranial magnetic stimulation and electrical cortical stimulation are considered landmark efforts for the understanding of tinnitus and a start for patient selection for tinnitus treatment.

The twenty-sixth meeting of the ITF will be held in Chicago, September 20, 2008. The theme will be Translational Research in Tinnitus Therapy IV: Transcortical Magnetic-Cortical Electrical Stimulation.

The *International Tinnitus Journal*, the official journal of the Neuroequilibriometric Society, and the Martha Entenmann Tinnitus Research Center, Inc., extend to all professionals involved with tinnitus an invitation to attend.

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