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Transcranial Magnetic Stimulation: Summary of the Proceedings of the Twenty-sixth Annual Meeting of the International Tinnitus Forum

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The theme of the Twenty-sixth Annual Meeting of the International Tinnitus Forum (ITF) that took place in Chicago, Illinois, on September 20, 2008, was "Translational Research in Tinnitus Therapy IV—Transcranial Magnetic Stimulation." For the first time, principal investigators from three of the five major centers in several countries were able, in a roundtable format, to present and discuss among an audience of tinnitus professionals their involvement with transcranial magnetic stimulation (TMS) attempting tinnitus relief. Each speaker who presented at the meeting is a notable leader in the field of TMS and tinnitus, and each presented his individual experiences to date and speculated on his expectations for the future. The presentations, panel discussion, and questions and answers that comprised the meeting are summarized here.

Claus F. Claussen, MD, PhD, affiliated with the University of Wurzburg and the Neurootologisches Forschungsinstitut der 4-G-Forschung e.V., Bad Kissingen, Germany, presented "Tinnitus-Related Changes in Equilibrium Dysregulations Such As Vestibular Recruitment and Decruitment." Prof. dr. Claussen classified tinnitus into two types—endogenous (responding to tinnitus maskers) and exogenous (responding to hearing aids)—for tinnitus relief. He reminded the audience that Hippocrates considered tinnitus to be related to epilepsy and presented the interaction in the brain of auditory and vestibular inputs as a working "human space concept," focusing on the clinical application of the results of vestibular testing for diagnosis and treatment of tinnitus. Professor Claussen described caloric vestibular testing with electronystagmography and simultaneous electrocardiography, recording the nystagmus in a "butterfly" format. Diagnostic differentiation is achieved between a peripheral vestibular lesion and that in the brainstem. Vestibular stimulation with rotary chair testing in patients with endogenous tinnitus has a DC shift pattern. Inhibition of the vestibular response originates in the brainstem and disinhibition in the temporal lobe. Temporal lobe disinhibition was described by Fitzgerald as early as 1941 in patients with a temporal lobe tumor. Responses to caloric testing and rotary chair testing with increase and decrease of acceleration of the chair can differentiate between peripheral vestibular, central vestibular, and combined vestibular disturbances. The results of these three stimuli clinically reflect the threshold, the lower threshold, and the upper threshold for the perception of balance and imbalance. Vestibular testing is recommended to follow techniques used in audiometry (i.e., identification of threshold, superthreshold, and discomfort levels). Such vestibular testing techniques result in the identification of vestibular disinhibition, recruitment, and decruitment. The clinical translation of the vestibular testing results was presented as a basis for attempting tinnitus relief.

Erik Viirre, MD, PhD, presented "Advances in Physiologic Techniques for the Characterization of Tinnitus." Dr. Viirre's talk focused on the electrophysiology of tinnitus, some techniques of measuring electrical changes in the brain, and how recent advances in laboratory technologies can be translated for practical clinical application.

Magnetic resonance imaging (MRI) and functional MRI (fMRI) were reported to be significant advances for identification of neural substrates in tinnitus patients. However, they are some steps removed from the actual physiological mechanisms in the brain that result in tinnitus and audition itself. Electrophysiology is important because it reflects the neurophysiology of hearing and the pathophysiology of tinnitus. Modern technological developments are going to be much easier to use even though the measurements we make are going to be far more complex.

In a review of the central auditory pathways, Dr. Viirre made reference to Prof. Claussen's presentation: that it

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is in the higher auditory circuits where we think that tinnitus of the chronic disabling type becomes active in the brain. He indicated that electroencephalography (EEG) can provide such information. It generally reports only surface electrical potentials (i.e., sources that are really on the surface of the cortex). However, one of the drawbacks of the EEG is that it does not tell us too much about what is going on deeply in the brain; we are not measuring spikes when we measure EEG. The interaction between the thalamus and th auditory cortex and the cortical thalamic feedback loops appear to be critical in the ongoing pathophysiology of chronic tinnitus. We have to keep the activity of these loops and their metrics in mind in terms of what we're going to measure with EEG.

Unfortunately, tinnitus is reflective of very localized changes in the cortex. fMRI has shown that the auditory maps in the primary auditory cortex are very, very small and very, very fine—tonotopic lines from low frequencies to high frequencies at very small steps. Demonstration shows one line to be 4,000 Hz and the next one perhaps 4,012 Hz (i.e., a minute separation). It is at this point that the high-output activity results in the specific tinnitus experience, which is a very, very focal area in the brain. This key point must be borne in mind in terms of tinnitus treatment using TMS and attempts to measure its effect using MRI and EEG.

Electrophysiological measurements can provide very fine maps. TMS can be thus focally located to a specific frequency band that would be the cause of the problem. Hence, some of the important advances in tinnitus have been in the area of qualitative EEG (QEEG). QEEG is an interesting technology: Advances include the method of recording the EEG and the analysis and interpretation of raw EEG data. The old method of gluing electrodes on the scalp is being replaced with better technology and computer-assisted analysis. We start with the general montage (i.e., recording over the entire brain), which QEEG does for us. It is a montage of electrodes all over the brain and interpreting entire brain changes in electrical activity.

Dr. Viirre credited Dr. Shulman with leading the way in our understanding and thinking about how these circuits—the thalamus and the cortex, in particular—have synchrony or dyssynchrony related to the presence or absence of tinnitus. Significant EEG changes all over the brain have been identified in tinnitus patients as compared to patients without tinnitus. They originate in regions that are not even necessarily auditory cortex. The most prominent changes were in frontal cortex, which in TMS conducted by Viirre's group is not even the site of our focal stimulation. Furthermore, all EEG frequency bands showed significant changes related to the presence of tinnitus. These global recordings demonstrated activity all over the brain related to the presence of our pathophysiological condition (i.e., tinnitus).

Other laboratories have shown the same kinds of things. Weisz demonstrated alterations in electrical activity in the right temporal lobe as compared to control subjects and a reduction in power as compared to the control patients. Significant differences were identified in midfrequency bands. The QEEG shows changes over the entire brain. In this particular experiment, they occurred in the gamma range in the temporal lobe. The other important thing about QEEG is seen not only in the measurement of tinnitus but in the related problems associated with tinnitus (e.g., depression). The QEEG and the Loreta mapping technology map significant changes in brain electrical activity. Demonstration showed colored regions in the brain with significant electrical differences in depression patients versus tinnitus patients. Using the same technology and the same recording, Viirre's group could detect a limbic condition, chronic depression, and the presence of tinnitus. Stress was of critical importance in an EEG recording and in the QEEG.

In their experience, Viirre's group has found that many chronic tinnitus patients experience a particular sound or perhaps groups of sounds; therefore, the group has looked at evoked potentials to further refine electrical recordings in the brain as related to the presence of tinnitus. They plan to use sound stimuli as the evoked potential stimulus and then record the related electrical activity that comes from that. Recordings are obtained from regions all over the brain (but typically just at the vertex), and then sound stimuli and the electrical response are looked at. The group has found patients' tinnitus sensation to be the frequency of the tinnitus sensation. The researchers' presumption is that there is a particular tonotopic pathway that is overactive. Stimulation, using a replica of that sensation and comparison to control stimuli, provides data that can be translated for an acoustical signal in attempting tinnitus control.

Viirre and colleagues have identified that the auditory cortex and the input stimuli to that are dramatically overactive, as Dr. Claussen described (i.e., oversensitization). The EEG provides a characterization of the tinnitus. QEEG can show the presence of tinnitus and important associated conditions. Viirre suspects that in the TMS paradigms, it is the presence of associated conditions, such as anxiety or depression, that may predispose to whether the TMS paradigm being used is going to be successful. He believes that the use of evoked potentials can refine tinnitus types by looking at the cortical responses. The trick is going to be in localizing with structural imaging (i.e., MRI or computed tomography [CT] scan) the EEG features that we see with QEEG or evoked potentials to determine where these abnormal activations are occurring.

The theory of tinnitus and the role of the EEG-QEEG have practical application for the clinic. Fortunately, there

are major advances going on in all areas, not only in the hardware but in the software. Analytical systems are going to become much easier to use. The key is going to be in the change in the paradigm of management of tinnitus and other conditions to allow us to be reimbursed for using these new experimental techniques that will become standard clinical technology.

The new EEG systems are dramatically different. Demonstration showed a system that Viirre uses in his laboratory with 128 channels of high-density EEG. In fact, we can now use the same montage on the bottom half of the brain and essentially cover nearly the entire head, obtaining more than 200 channels of recording. The electrodes are now electronically amplified, giving us beautifully recorded signals with very little fuss. Exciting new electrode systems are coming along that require no electrode gel and no preparation of the subject. A fitted cap with these embedded electrodes is essentially just put on the head and produces an EEG equivalent in quality to amplified conductive gel electrodes; within minutes, we will be able to record electrical activity in the brain as these systems come online. Furthermore, advanced mathematical analytical techniques allow us to distinguish all sorts of electrical activity.

Demonstrations showed a montage over the brain localized to show muscle activity dipoles in the brain, the electrical retinal potential. All are distinguished mathematically and analyzed statistically. Ultimately, these mathematical analyses are superimposed on a functional image of the patient's brain that allows us to very accurately locate a dipole. Therefore, in future, we will have essentially turnkey systems instead of requiring a mathematician to be on staff. Practitioners will be able to acquire these analyses automatically and obtain automated analytical support. The big question is how will we get paid; that is an ongoing concern that will require the industry's attention.

Viirre summarized his presentation by stating that tinnitus of the chronic disabling type shows dramatic EEG changes, and QEEG demonstrates the presence of tinnitus and of associated conditions. He and his colleagues believe that sound stimuli might add further refinement to the characterization of tinnitus. Advanced hardware and software should lead to clinically realizable systems.

Abraham Shulman, MD, and Barbara Goldstein, PhD, presented a single case report of a 56-year-old man with a predominantly central-type severe, disabling tinnitus, in whom TMS was attempted to achieve tinnitus relief. The tinnitus was located in the right head and extended to the left side, with increased tinnitus intensity in the right ear. The patient described the tinnitus as a "siren," and the masking curve was a type four. The presenters reviewed the background and theory of TMS. Their patient selection criteria for TMS included a medical audiological tinnitus patient protocol that identified a predominantly central-type severe, disabling tinnitus and tinnitus that existed in excess of 1 year and was refractive to treatment. Factors known to influence the clinical course of the tinnitus were identified and treated. Attempts for tinnitus relief with instrumentation and medication failed. The research team recorded brain electrical activity before and after TMS with QEEG and performed TMS using a Bistim module connected to two Magstim 200 stimulators (Magstim Co., Whiteland, Dyfed, UK). The TMS stimulator was applied to the left temporoparietal area of the scalp at 90% of the thenar motor threshold, using 1, 5, 10, and 20 Hz at the time of a stimulation session consisting of 200 pulses. Results were classified as either no effect (0–19% improvement), partial effect (20–79% improvement), or good effect (80–100% suppression). The QEEG was performed at the Brain Research Laboratory at New York University.

The statistical analysis was a neurometric analysis of the raw EEG data as published in 1987 by E. Roy John. This method of QEEG provides a precise reproducible estimate of the deviation of an individual record from the normal and makes possible the detection and quantification of abnormal brain organization. This is done by providing a quantitative definition of the severity of brain disease and the identification of subgroups of pathophysiological abnormalities in groups of patients with similar clinical symptoms. It is a statistical analysis. One must differentiate between statistical significance and clinical significance.

TMS resulted in no tinnitus relief. The QEEG data before and after TMS was interpreted as not statistically significant. The tinnitus dyssynchrony-synchrony theory, a tinnitus theory integrated with brain functions, provides a basis for clinical translation of the QEEG data for diagnosis and treatment and suggests a positive clinical significance and influence of TMS for the patient and a potential for tinnitus relief. Specifically, the persistence of a focus of theta activity in the right temporal area T4, considered to reflect a paradoxical auditory memory, and persistence of the beta activity in T4, considered to reflect a focus of epileptic activity, were clinically significant. Alterations in electrical activity identified in the delta, theta, and beta bands were considered clinically but not statistically significant. Alterations in parameters of TMS were suggested (e.g., increase in the duration and frequency of stimulation or a possible change in the position of the magnet for stimulation). The post-TMS QEEG may indicate an influence of the TMS in the brain that precedes the accurate subjective report of the patient of no alteration of tinnitus.

In conclusion, Drs. Shulman and Goldstein suggested that TMS attempting tinnitus relief is individual for each

patient, including duration and frequency of stimulation. Significant factors are hypothesized to influence the efficacy of TMS for different clinical types of tinnitus, highlighted by the existing sensorineural hearing loss and degree of plasticity of the brain to reestablish a homeostasis of brain function. The research team considers QEEG to be a sensible tool for tinnitus diagnosis and treatment. TMS is recommended at this time as a research tool for tinnitus theory, diagnosis, and treatment.

Tobias Kleinjung, MD, presented "Transcranial Magnetic Stimulation for Treatment of Tinnitus: The Regensburg Experience." The author, acting as course director and moderator, introduced the presentation and alerted the audience to the significant basic science and clinical efforts of the tinnitus team at Regensburg University (i.e., the Tinnitus Initiative Research Group, who attempt tinnitus relief with instrumentation and medication, headed by Berthold Langguth, MD). The group's contributions to the new discipline of tinnitology for the theory, diagnosis, and treatment of tinnitus are considered internationally acclaimed at this time. Dr. Kleinjung's overview of the approximately 6-year experience with TMS at Regensburg for nearly 300 patients focused on their results. The Regensburg approach for attempting TMS tinnitus relief was begun in 2003 and was influenced by reports of positron emission tomography (PET) brain nuclear medicine imaging data in the primary auditory cortex and of functional imaging data together with what has been identified in animal experimentation in the motor cortex with TMS. Specifically, tinnitus is associated with increased metabolic activity in the auditory cortex, and TMS influences and modifies cortical activity. Dr. Kleinjung offered an interesting report of imaging laterality in the primary auditory cortex of tinnitus patients, showing in an asymmetry index (e.g., left side) that it was independent from the laterality of the tinnitus perception (i.e., whether it was a bilateral or right-sided or left-sided tinnitus). Reference was made to a model to explain different clinical types of tinnitus and the TMS effects for tinnitus control—the thalamocortical dysrhythmia translated for the clinical explanation of the reported imaging result. The theory of TMS for attempting tinnitus relief provides the possibility to modify cortical neurons in superficial brain areas. TMS parameters of stimulation include both single and repetitive TMS (RTMS). Multiple single pulses do not have longer-lasting effects, but RTMS effects can outlast the stimulation period. Additional parameters are the intensity and the frequency of the TMS. Low-frequency RTMS induces long-term depression-like changes of synaptic activity. The effects are most prominent when areas of increased activity are stimulated. In depression patients, an increase in low-frequency RTMS of the left prefrontal cortex results in reduced cortical excitability. RTMS reduces alterations of synaptic activity in both the stimulated area and in functionally connected remote areas.

Dr. Kleinjung's review of the Regensburg group's clinical experiences since 2003 highlighted the following theories:

1. The longer the tinnitus persists, the less the TMS effect for tinnitus relief. Tinnitus duration between 1 and 4 years relates to a high incidence of tinnitus control. A very negative treatment response accrues after 10 years.
2. As regards hearing loss, better hearing was associated with better TMS tinnitus relief outcome. No other parameter had an impact.
3. A high metabolic activity in the PET scan was correlated with poor TMS response.
4. Review of reports of TMS efficacy for tinnitus relief show approximately 40% with high interindividual variability areas. RTMS results in increased cortical activity and gamma-band activity based on thalamic differentiation. Tinnitus is associated with hyperactivity in the central auditory system, probably owing to increased high-frequency gamma oscillations. RTMS can modulate thalamocortical dysrhythmia, which leads to an increased inhibitory function of the thalamus and resultant reduced cortical activity and subjective reduction in tinnitus.
5. Anatomical structures significant for tinnitus and future sites of TMS are the dorsolateral prefrontal cortex contralateral to the hyperactive primary auditory cortex, the anterior cingulate, the hippocampus, and the amygdala. Yet to be considered are anatomical structures involved in cognitive reward and emotion.
6. TMS of the auditory cortex has shown some evidence that it can reduce tinnitus and has shown promise as a new treatment tool. However, the treatment effects are characterized by interindividual variability and only moderate effect sizes. In Dr. Kleinjung's words, "I think we should be careful; we are far away from a routine procedure."

There was a call for a large multicenter clinical trial of RTMS just to evaluate the real evidence of this procedure, to enhance our understanding of the neuronal correlates of different forms of tinnitus; to help us achieve a better understanding of the neurobiology of tinnitus; to explore a combined stimulation of auditory and nonauditory cortical structures; to test whether therapeutic combination of TMS and pharmacology (e.g., dopamine agonists) enhances TMS treatment effects; and to elucidate both the effects of RTMS and the pathological processes underlying the conditions for which it is used. All

these advances will reveal whether RTMS really does offer therapeutic potential.

In Dr. Kleinjung's words, "TMS is far away from a routine procedure, but TMS has shown some evidence that it has positive effects in tinnitus patients." He invited the audience to attend the Third Tinnitus Research Initiative in Italy in June 2009.

John Dornhoffer, MD, presented "Transcranial Magnetic Stimulation for Tinnitus—Prolonging the Response." Dr. Dornhoffer extended recognition to two grants (from the Tinnitus Research Consortium and from an NIH Cobra grant) and to Mark Mennemeier, director of the TMS laboratory at the University of Arkansas. He considered that the model of thalamocortical dysrhythmia "fit nicely" with the theory of his group (i.e., hyperexcitability at the level of the brain initiated perhaps by an injury to the cochlea). Specifically, he hypothesized that "a loss in the normal depolarizing input from the cochlear hair cells leads to hyperpolarization at the level of the thalamic nuclei and spontaneous firing; it could also be related to the loss of inhibition and the edge effect."

The initial research effort of Dr. Dornhoffer's group was to try to understand the pathophysiological response of tinnitus and to develop perhaps from measures of tinnitus a future objective outcome to serve as an objective protocol for tinnitus therapy. The group initially focused on attentional mechanisms based on reports in the literature of neuropsychological testing performed in tinnitus patients, positing that an attention deficit is a significant part of the clinical pathophysiological response of tinnitus patients.

The researchers investigated major neuraxes for attentional mechanisms in the brain, starting with the P50 response, considered to be a measure of the attentional mechanism and mediated by the brainstem or the brainstem thalamic pathway. They investigated the cortical thalamic pathway by applying the psychomotor vigilance task—mainly a reaction time test, sensitive for cortically mediated attentional mechanisms.

This research revealed that the brainstem thalamic pathway was satisfactory, demonstrating no evidence of any problem with attentional mechanisms based on the P50. However, the team pointed out that tinnitus patients demonstrated a deficit in cortically mediated attention. Their impression was that perhaps this would be an objective outcome measure. The main hypothesis was that perhaps asymmetrical activation, as reported by Dr. Kleinjung, creates a neural noise with resultant constant attention, similar to how a stroke patient will have attentional deficits. If this constant attention is related to asymmetrical activation, the reestablishment of a symmetry in the brain could be achieved by decreasing areas of hyperexcitation. The training of tinnitus patients to habituate to the internally generated sound with the tinnitus could result in symmetry and resultant tinnitus relief.

The application of TMS was introduced to achieve this symmetry in the brain. TMS can modulate the frequency. Low frequency as treatment is considered to be inhibitory and to reduce cortical activity. High frequency conversely is believed to potentiate cortical activity. The intensity of the low frequency can be varied. The intensity is usually the motor threshold. How many pulses are necessary with repetitive TMS?

Dr. Dornhoffer acknowledged Dr. de Ridder's statement that TMS can be applied as single pulses to determine, as a predictive value, whether brain stimulation or implantation may be appropriate. However, when it is used in a repetitive fashion, TMS is a treatment. The coil can influence penetration. The depth of penetration with TMS at the scalp is approximately 2 cm. However, even though we can stimulate only a small area, we can have a widespread influence in the brain through the descending pathways. Kleinjung's group was one of the first to investigate TMS for tinnitus control in a repetitive fashion. The Regensburg TMS protocol was applied with 1,800 pulses at 110% motor threshold for 5 consecutive days. PET-guided CT scans with radioactive glucose were used. Outcome measures included the P50, visual analog rating, and posttreatment PET scans. Significantly, asymmetry in the primary auditory cortex was identified only about half the time. Activation of the PET scan tended to correlate with the loudest contralateral ear. Dr. Dornhoffer referred back to the question of what significance the PET scan provides for the identification of TMS site of stimulation, as raised by Dr. Kleinjung in his presentation. Improvement of the PET scans, when identified, did not always correlate with tinnitus perception. In other words, does the PET scan really predict anything? The P50 results were nonspecific and, according to the presenter, appear "not to be a great objective measure of tinnitus."

In summarizing, the group's experience included 10 bilateral tinnitus patients who were stimulated with TMS in a sham study. Six of the 10 said noise in one ear was louder. The TMS target was the ear with the louder intensity. No placebo effect was noted. About one-half of the subjects reported a positive response, and one-half did not. No placebo effect was reported. Of the responders, about two of three reported the tinnitus in both ears was reduced dramatically; two got responses in the contralateral ear and did not get a response in the ear opposite the stimulation. Significantly, Dr. Kleinjung, in his presentation, reported that there was no specific conclusion at this time with the prognostic indicators for TMS efficacy for tinnitus control (i.e., sensorineural hearing loss and duration of the tinnitus).

Dr. Dornhoffer concluded that first-time responders appear to respond the second time. Approximately 25% may have some lasting effect with maintenance TMS therapy. The new sham study in 10 patients reported preliminary results of TMS efficacy for tinnitus control of approximately 50%. The questions remaining to be answered included value of the PET scan, reproducibility of results with repeated TMS, maintenance therapy for responders, and target selection for TMS.

The forum allowed sufficient time for questions and answers during the discussion period. The main questions and answers are summarized here.

Question 1: What changes in the personality of the patient have been observed after magnetic stimulation (e.g., sense of humor, worsening of the depression)?

Answer [Dr. Shulman]: No investigations of personality have been reported to date. Anecdotal reports of improvement in affect have been observed in patients reporting tinnitus relief with TMS.

Question 2: What is the EEG experience of transnasal recordings from the nasopharynx?

Answer [Dr. Viirre]: The point was made that, by placing electrodes in the nasopharynx, we get very close to the brainstem and the cochlear nucleus. In fact, the distance from generator to recording source is a critical factor in high-resolution metrics. What is exciting is that new electrode technologies will make it far simpler to capture these recordings quickly so that we will be able to put electrodes into the nasopharynx without a lot of electrode preparation and get very high resolution activity. In essence, instead of having to put electrodes at the base of your face, placement in the nasopharynx will be right at the base of the brain. I think that will be a dramatic way to improve the recording quality and get to the brainstem sources as you describe and suggest. I totally agree with you.

Question 3: If you are looking just at chronic disabling tinnitus, it seems to me that what makes tinnitus disabling is the patient's response to the tinnitus as opposed to any particular character or quality of the tinnitus. So, if you're just looking at chronic disabling tinnitus and stimulate the brain, how are you teasing out which QEEG changes are due to the tinnitus itself and what QEEG changes are just due to the reaction to the tinnitus?

Answer [Dr. Viirre]: An excellent point. As I mentioned in the talk, it looks like some of these EEG recording techniques can actually look at the brain responses. If we look at anxiety patients versus the depression patients versus people with normal psychometrics, we can see that in the EEG. My point is exactly as is yours (i.e., we have to do subtypes of the tinnitus sensation itself and the emotional reactivity). It looks like these kinds of stimuli or these kinds of recording technologies can do that. Interestingly, in evoked potentials, what we perform is the use of stress-evoking stimuli and look at the brain reactivity. Of course, in the tinnitus patient, the tinnitus itself is stress-evoking. Your point is well taken. We want to see the emotional reactivity to tinnitus. That means looking beyond the auditory cortex and limbic systems and to other reactive areas as well.

Answer [Dr. Shulman]: The question highlights the need and recommendation for the translation of basic sensory physiology for tinnitus—that is, for every sensation, there are different components: the sensory, the affect, and the psychomotor. The clinical translation for tinnitus diagnosis of advances in sensory anatomy and physiology for each of these components allows one to differentiate different neural substrates for the different components of the tinnitus. The question asked focused on the sensory component in tinnitus patients experiencing severe disabling-type tinnitus, and the presentations that follow will address the other components and issues presented by the question. The question was very well placed.

Question 4: What is the source of the equipment used for the QEEG recording? Who performs the test? What is the duration of the test?

Answer [Dr. Shulman]: The QEEG equipment is called the Neurosearch 24, (Lexicor Company, Boulder, CO). The equipment is relatively inexpensive. The data are sent by e-mail for analysis using a normative database. Dr. Barbara Goldstein, audiologist, performs the test. The QEEG has been incorporated into her medical audiological testing expertise. The QEEG report is clinically interpreted for the tinnitus patient.

Answer [Dr. Goldstein]: The test involves the placement of 19 electrodes on the patient's scalp (i.e., the EEG cap) using the international 10/20 EEG montage. Impedance is measured at each electrode site with respect to a reference, followed by the running of the test. The test takes 45 minutes to a maximum of 1 hour to complete. The data are sent by e-mail for analysis.

Question 5: In your experience, what is the difference between electrical and transcranial magnetic stimulation in the brain in TMS tinnitus relief responders and nonresponders ?

Answer [Dr. de Ridder]: Actually, all our patients are implanted only if they have a placebo-controlled tinnitus suppression (even if temporary) with TMS. Basically, the nonresponders with electrical stimulations are responders to TMS. The reason is not known. TMS most likely has a working mechanism different from electrical cortical stimulation. First of all, you're hitting a very big area with TMS. Probably the activation patterns with TMS are different

from those with local electrical stimulation. For TMS pain control, it's actually better to stimulate next to the area of where the pain is being generated in the brain. So, if something similar might be occurring in the auditory system, then the targets that we have to look for with TMS and electrical stimulation might also not be exactly the same.

Question 6: Given that, how focused do you think electrical stimulation needs to be? I mean, what is an appropriate-size electrode?

Answer [Dr. de Ridder]: Well, the electrodes we use require improvement. If you stimulate constantly, you expect habituation to the stimulation. We actually use multiple programs to target one negative pole. We have multiple positive poles. Ideally, you would have electrodes with multiple rows next to each other and target the middle one to the fMRI bold spot. In this way, you can use multiple stimulation designs at the same time to achieve constant suppression. If this is not done, habituation develops, and the tinnitus is suppressed for a very short time. If you can stimulate not only different geographical anatomical sites with different patterns of activation and with different frequencies, you can attempt to prevent habituation to the stimulation. So, the more chaotic the stimulation, actually, the better the result.

Question 7: Do you think you can do that with surface TMS, or do you think ultimately that you're going to have to go deep?

Answer [Dr. de Ridder]: When we look at our initial extramural results, which included two patients who were nonresponders, we thought that if we stimulated the primary auditory cortex, they would respond. Stimulation of the primary auditory cortex resulted in no response. Actually, when they did not respond to secondary auditory cortex stimulation, they did not respond to primary auditory cortex stimulation. This may be explained by a long-standing duration of the tinnitus and that we were just targeting the wrong spots. In the case of responders to stimulation on the secondary auditory cortex, we could not control the habituation. For both of these patients, the implantation of electrodes on the primary auditory cortex resulted in a sustained suppression, probably owing to habituation in the primary auditory cortex being less than in the secondary or association cortices to constant stimuli. There may be prevention of habituation by stimulation onto or into the auditory cortex with a technique of stimulation in the somatosensory area, as recommended by Michael Seidman.

Question 8: With respect to the thalamus, does the ventral intermediate nucleus of the thalamus play a role in your concept or not?

Answer [Dr. de Ridder]: No, not really. At least not for tinnitus. Probably the extralemniscal system information from the brainstem is received into the intralaminar posterior thalamus. The laminar nuclei are like a network surrounding specific nuclei. The activity in the thalamus, which is controlled by the brainstem, will result in a change in arousal, predominantly based on intralaminar nuclei activity. This activity will then basically be directed to the specific nuclei that, for the intensity component of the tinnitus, is most likely related to the medial geniculate body, as suggested by our fMRI studies. The emotional component, of course, has to come either from the medial dorsal or the anterior nuclei. That is a separate issue that we have not yet addressed.

The International Tinnitus Forum was pleased to have as its guest of honor Professor Dirk de Ridder, from the University of Antwerp, whom the author was fortunate to meet at the time of his visit to the Brain Research Laboratory at New York University, directed by Drs. Roy John and Leslie Prichep. That visit included attempts for achieving tinnitus relief with TMS in two patients from the Martha Entenmann Tinnitus Research Center with a predominantly central tinnitus of the severe disabling type. Dr. de Ridder's background in medicine, basic sciences, neuroscience, and neurosurgery have provided him with a basis for the clinical application for investigation of brain function, identification of neurocircuitries in the brain, development and clinical application of objective outcome measures of EEG for tinnitus diagnosis and treatment, and the development and clinical application of neurosurgical approaches for attempting tinnitus relief. This author considers Dr. de Ridder's contributions to date for the diagnosis and treatment of the tinnitus patient to be of a significance equal to that of Bill House for the cochlear implant and treatment of severe profound sensory hearing loss.

Dr. de Ridder's presentation, "Tinnitus: From Basic Science via Noninvasive Magnetic Stimulation to Brain Surgery," focused on how the technology of EEG, QEEG, and the Loreta mapping technology can better delineate and improve brain stimulation with TMS or electrical stimulation via implanted electrodes to achieve tinnitus control. In addition, attempting to answer the most difficult question of why not all tinnitus patients respond to TMS with tinnitus control, Dr. de Ridder hypothesized that altered activity in the auditory cortex is going to be part of the final common pathway of the generation of tinnitus.

The introduction to Dr. de Ridder's talk proposed a theory for the generation of tinnitus (i.e., "the auditory part"). The second part of his presentation focused on the distress that accompanies the tinnitus percept. The speaker reviewed the tonotopic organization of the auditory system within the cochlea and its projection in the ascending auditory pathways to the auditory cortex and

presented it as one of development dependent on the input that one experiences in utero and predominantly post utero. This infers that the tonotopic organization of the auditory system can also be altered in response to any change in input.

Dr. de Ridder presented this dynamic activity as having an application for tinnitus treatment. Alteration in the tonotopicity of auditory cortex has been reported in the sense that areas that were previously processing high-frequency input were now processing middle-frequency input. Hence, the working hypothesis is that tinnitus is actually a phantom perception similar to phantom pain related to a deafferentation reflecting a lack of auditory input. The lack of input induces changes at the level of the thalamus and cortex, called a *thalamocortical dysrhythmia*. At the cortex, this is reflected in an increased synchrony that induces Hebbian plasticity. This Hebbian plasticity says that "cells that fire together will wire together"—which might then induce cortical reorganization. Treatment would then have as its goal a reafferentation by presenting missing information either directly or indirectly to the cortex. Multiple methods can be attempted to bring new auditory inputs to the cortex (e.g., cochlear implants in unilaterally deaf patients, hearing aids in patients with residual hearing, direct stimulation of the auditory nerve, brainstem, thalamus, cortex). Multiple locations on the trajectory of the auditory input to the cortex can be targeted to modulate the abnormal activity associated with the tinnitus.

However, the question posed was, "Is it just the auditory cortex or are there additional structures involved in the generation of the tinnitus?" Normally to be considered is that the auditory input is received at the primary auditory cortex and goes to the secondary auditory cortex, where it is integrated with visual information (i.e., sensory information) in multimodal areas (i.e., cross-modal cortical stimulation). This information is received and compared to already stored information, and a decision is required as to whether one must respond. Furthermore, this new information will be evaluated both emotionally and cognitively and then undergoes an integration in relation to the input.

Multiple pathways have been described in the brain for such integration. The predominant emotional activity has been hypothesized in the past to start in the amygdala. From there, the information goes to the anterior cingulate and from there to the orbitofrontal cortex (actually, the ventral medial prefrontal cortex) just anterior to the amygdala. The cognitive pathway is hypothesized to start at the level of the hippocampus, posterior to the amygdala. From the hippocampus, the information is transmitted to the posterior part of the cingulate gyrus and from there to the parietal, superior temporal, and frontal areas. This cognitive and emotional input has to come together somewhere. Recent information suggests that the dorsolateral prefrontal cortex (DLPC) might be the area wherein an integration of emotional and cognitive inputs occurs.

Dr. de Ridder made reference to two pathways that have been reported to induce an emotional response. An emotional stimulus will go to the thalamus and from there in a direct pathway to the amygdala, which will allow an immediate response. The information is also transmitted to the auditory cortex and from there to the prefrontal cortex and from there to the hippocampus, which will then influence the amygdala. Translation of these emotion reports to tinnitus suggests that an auditory stimulus, whether internally or externally generated, will activate both the lemniscal and extralemniscal pathways and directly or indirectly influence the amygdala. The primary and secondary cortices connect to multisensory association areas and to the prefrontal cortex. From another part of the anterior cingulate, there are direct connections to the anterior insula, which is most likely involved in the autonomic response to the internally or externally generated auditory information. From the amygdala, the reward pathways are stimulated, with resultant activation of the orbitofrontal cortex or update of the received input (or both). The end result is integration of cognition and emotion in the DLPC. From the DLPC, direct pathways extend basically to every single structure mentioned and also to the A1 primary cortex, with a probable modulation of the gain of activity in A1.

Dr. de Ridder hypothesized that if the complexity of the processes increases by the combination of multiple pathways, a point of impracticability is reached, with a resultant failure of brain function. In other words, if you are going to stimulate one of the brain areas with TMS, it is very easy to get activity changes in areas of the brain other than that of the primary site of stimulation. So how and why is TMS of the auditory cortex useful?

The basic hypothesis proposed is that tinnitus is related to reorganization and hyperactivity of the auditory cortex. If one can demonstrate this hyperactivity in a noninvasive way, using whatever functional imaging tool is available (e.g., EEG, magnetic encephalography, fMRI, or PET) and if one can demonstrate activity in a particular region, one can target it in with neuronavigation and deliver a noninvasive TMS. If TMS is beneficial, with neuronavigation you can basically implant an electrode onto the same area for delivery of electrical stimulation with resultant continuous tinnitus suppression.

Dr. de Ridder posed basic questions: Is tinnitus related to hyperactivity of the auditory cortex? Would stimulation or neuromodulation of the auditory cortex area result in tinnitus suppression and tinnitus relief? It must be considered that the brain is an information-processing machine with a huge amount of cells connected to a

huge amount of cells—that is, the brain is a complicated structure. Conversely, the information theory, which is a mathematical framework to quantify information transmission, has actually shown that the firing rate of the brain is related to the amount of information that is being transmitted—a very logical deduction. The speaker pointed out that the quicker one talks, the more information can be conveyed up to a certain level, at which point nobody will understand what is being said because the speaking rate is too fast. Theoretically, he hypothesized this as taking place in the brain. However, the higher the firing rate and the higher the oscillation rate, the more information can be transmitted.

This activity can be recorded with EEG. In general, what you see is low-frequency activity that has been correlated with deep sleep, anesthesia, and coma (i.e., delta). A somewhat higher frequency of activity occurs with light sleep (i.e., theta activity). Basically, the normal firing rate, and the normal oscillation rate of the sensory cortex, is the alpha frequency. Everybody has an individual alpha rate, between 8 and 12 Hz.

When gamma activity is approached (30 Hz and higher), the speaker suggested, this frequency of brain activity is necessary for conscious awareness of any percept. This was first studied in the visual system, wherein visual awareness requires gamma-band activity. In the auditory system and for any stimulus to be perceived, Dr. de Ridder suggested that this gamma-band activity is actually required. As tinnitus is a conscious auditory percept, it would be logical to identify this gamma-band activity. Gamma-band activity has been confirmed with magnetoencephalography (MEG) in tinnitus patients. In addition, it has been hypothesized and reported that gamma-band activity is predominant on the side contralateral to where the tinnitus is perceived (i.e., left-sided tinnitus correlates very nicely with gamma-band activity increase in the contralateral right auditory cortex).

The replication of this result with EEG is desirable because MEG is a high-tech, expensive examination. According to the presenter, Loreta analysis of EEGs in tinnitus patients with a unilateral right-sided narrowband tinnitus has revealed activity in the contralateral auditory cortex with a little spread. A reported increase in gamma-band activity has been correlated to the intensity of the tinnitus. Therefore, the louder the tinnitus is being perceived on a visual analog scale, the more gamma-band activity seems to occur. The tinnitus intensity not only correlates with the gamma-band activity in the auditory cortex; it correlates with the decrease in theta activity at the edge of the occipital, temporal, and parietal lobes, a cross-modal association area, and a decrease in theta activity in the DLPC. If one applies a masking stimulus for tinnitus, one can expect—if tinnitus relief is experienced—that the gamma-band activity in the contralateral auditory cortex should disappear.

Tinnitus patients in whom the tinnitus intensity is reduced should then demonstrate asymmetry in the current density, and the amount of gamma-band activity should decrease in the contralateral auditory cortex, suggesting a causal relationship and not just a correlation. To Dr. de Ridder, reporting of the gamma-band activity in the visual system has actually demonstrated that, in a comparison of visually perceived stimuli with visually non-perceived stimuli, the amount of gamma-band activity is more or less equal, which is the opposite of what he had been talking about until now. What is different is that there is a lot more synchronous gamma-band activity in the perceived than in the non-perceived stimuli, basically suggesting to the speaker that gamma-band activity is a prerequisite but does not equal conscious perception.

For Dr. de Ridder, gamma-band activity data from the olfactory system suggest that the gamma-band activity is nothing more than a carrier wave, similar to a carrier wave used in radio transmission (i.e., a particular frequency is superimposed on this carrier wave). The speaker suggested that the information of the gamma-band activity actually is reflected in the amplitude modulation of the carrier wave of the gamma-band activity. The gamma-band activity has been investigated from another point of view (i.e., independent component analysis). Independent component analysis is a statistical technique that looks at the EEG activity and then separates statistically independent components that are found within this activity. One can perform a spectral analysis of the data, identify the gamma-band activity, and complete an independent component analysis.

Dr. de Ridder compared the independent component analysis to a mixed salad of potatoes and tomatoes. First, one separates all the potatoes from all the tomatoes in the mixed salad, thus obtaining separate components that are then analyzed. Clinically, a practical example can be a patient with right-sided pure-tone tinnitus. The Loreta QEEG displays 40-Hz activity in the contralateral auditory cortex. Loreta analysis of the independent components looks at each location, where each of these components is being generated. This is followed by identification of a specific component that is co-localized with the gamma-band activity, suggesting that this component is actually information within this gamma-band activity that contains the content of the tinnitus. Is this just speculation or could this be true?

The speaker suggested one way of validating this theory: simultaneously recording a complete EEG from each of the electrodes in the EEG cap, visually inspecting for a component localized in the contralateral auditory cortex, and then actually comparing the independent

component localized in the auditory cortex with a spectral analysis (i.e., fast Fourier transformation) of the recorded activity in the auditory cortex. If a correlation analysis reveals that the independent component recorded with EEG is correlated to the activity directly recorded from the electrodes, this then suggests that independent component analysis may be another worthwhile approach to examine information in the brain that might code for tinnitus.

Dr. de Ridder's summary stated that decrease in auditory input results in a reduction in brain activity of the higher frequencies and higher oscillation rates, which is a reflection of less processing within a specific thalamocortical column within this specific receptive field. The brain automatically oscillates at a lower rate (i.e., theta activity). At the level of the thalamus, the decreased activity is relayed to the cortex and results in an initial area of lower-frequency activity in the auditory cortex. As a result, there will be less lateral inhibition, with a resultant induction of a halo of hyperactivity within the gamma-band range, called the *edge effect*. The edge effect for tinnitus is suggested as correlated to pain (i.e., a coupling of pathologies). In the brain, deafferentation slows down activity and then increases activity in a surrounding area of the cortex. This view of thalamocortical activity at a microscopic level has also been replicated at the cellular level. The significance is that using a power-to-frequency analysis of brain electrical activity, normally an alpha activity is present in the sensory cortex. When a thalamocortical dysrhythmia occurs, more theta-like activity and more gamma-band activity ensue.

As Dr. de Ridder pointed out, the persistent question is whether the auditory cortex by itself is sufficient for conscious awareness. Patients in a persistent vegetative state (PVS) provide some insights to answering this question. In a vegetative state, the patient appears awake but demonstrates no awareness of input. The amount of awareness in PVS is correlated with a decreased metabolism and decreased connectivity in the brain. The decreased metabolism is not recorded only in the auditory cortex but in the prefrontal and the medial and lateral side of the parietal lobe. These areas are multiple, always the same, and demonstrate a decreased metabolism. There is also a decrease in connectivity between the thalamus and the prefrontal cortex and between the prefrontal cortex and the parietal cortex. There is the combination of less activity and, especially, a decrease in connectivity. Awakening from a PVS triggers a restoration of the connectivity between anterior cingulate, the frontal cortex, and the intralaminar nuclei of the thalamus. Not only is there an increase in activity but, more important, the connectivity between the different parts of the brain returns to normal.

Auditory processing in a PVS is decreased. A person in a PVS still exhibits recorded auditory activity, indicating that the auditory cortex is activated by auditory stimuli. The problem is that this activation is disconnected from all the other areas with which it is normally connected. Even though the auditory cortex is activated, it does not seem to be correlated to auditory awareness. Most likely, the auditory cortex itself is not sufficient for conscious perception. If taken one step farther, perhaps tinnitus is not related just to auditory cortex activity. Studies of different levels of consciousness suggest that there is global workspace (i.e., there is activity going on in the brain at multiple areas). Stimuli can be supraliminal and attended. For example, in the visual system, activity is possible at the primary visual cortex, at the secondary visual cortex, and in the frontal cortex. This combination of activity is needed for a supraliminal stimulus to become attended to with attention. One can have an unattended supraliminal stimulus, in which case basically the connectivity between the frontal cortex and the sensory cortex is absent. One is still aware of the stimulus but not attending to it. A subliminal activity is basically just some activity in the primary sensory cortex as seen in PVS patients. If one has activity just in the sensory cortex but not connected to anything else, basically one is not perceiving anything consciously: When the gamma band of activity is not localized, there is no awareness. This suggests that there is actually more connectivity going on in this gamma-band activity than just the perceived stimulus. For a visual stimulus to be perceived, enhanced data oscillations of the frontal region are needed, which is interesting because examination of EEG tinnitus data reveals activity in the DLPC and an alteration in the theta activity associated with the intensity of the tinnitus. Our tinnitus data relate very well to what has been reported in the visual system.

A third important differentiation, according to Dr. de Ridder, between consciously perceived and nonconsciously perceived data is a P300 component in the event-related potentials. The P300 was present when the stimulus was perceived. Does this P300 represent the activation of the global workspace? He posits that this may be true because examination of the neural generators of the auditory P300 shows that the same areas are activated (i.e., auditory cortex with the prefrontal cortex, the anterior cingulate, the posterior cingulate, and parietal areas). These areas are exactly the same areas as in PVS patients disconnected from the auditory cortex. The P300 may just be a sign of activation of the global workspace. Practically, the gamma-band activity is probably a requirement for conscious perception of tinnitus, but this gamma-band activity is not restricted to the auditory cortex and needs to be connected to the global workspace and other areas in the brain. The bold effect obtained with fMRI, which provides high spatial resolution, is related to gamma event–related synchronization, at least in the visual system.

Dr. de Ridder cited a report that suggested that it is also likely in the auditory cortex. The bold effect in the auditory cortex relates to a local field potential. Recordings with EEG provide a correlation between the gamma-band activity and what is seen on fMRI, suggesting that fMRI may serve as an indicator of gamma-band activity as related to tinnitus perception. fMRI studies in tinnitus patients have identified a change in bold activity related to the unilateral tinnitus in the contralateral auditory cortex and, in bilateral tinnitus, no significant difference between auditory cortices. Not only is there a difference in the contralateral auditory cortex in gamma-band activity, but there is a difference in the inferior colliculus and in the medial geniculate body. The change in gamma-band activity is not only at the cortex but basically in the entire auditory pathway. If this is correct, fMRI may be a technique to identify in the tinnitus patient this abnormal gamma-band activity, which is a prerequisite for conscious perception.

If one has achieved temporary tinnitus suppression with external TMS, the next step would be fMRI to target the area with an electrode, using neuronavigation to produce a temporary suppression of the activity at the cortex associated with the tinnitus. If that is successful, the tinnitus patient and physician are satisfied. However, the speaker pointed out that a couple of things might go wrong. First, the electrode might not be on the right location. He described the process and technique for site localization for TMS and electrode placement with neuronavigation. Then he presented the case of a 30-year-old man who had a pure-tone, 3,000-Hz tinnitus in the left ear greater than the right, related to a dip on the audiometric test and suggesting deafferentation. The tinnitus was a grade 4 on the tinnitus questionnaire (i.e., a psychologically decompensated severe tinnitus). The visual analog scale of intensity was 8 of 10. The patient was selected for implantation. Empirically, the best stimulation design that can maximally suppress the tinnitus was selected. Over one pole of the electrode, the response was positive, one pole was negative, and all the others were neutral. Dr. de Ridder made a comparison of the EEG activity and co-registered with the fMRI. His team recorded from the electrodes and performed a power-to-frequency analysis. Translation of the thalamocortical dysrhythmia concept is considered a plausible model for tinnitus. A normal alpha activity was identified at the posterior electrodes. The first pole demonstrated an abnormal recording. The bold effect was actually an alpha peak next to which was a theta peak, which was exactly what has been predicted for the edge effect. Electrical stimulation suppressed the tinnitus. In a period of residual inhibition, when the patient did not perceive tinnitus, the recording was repeated, and the theta peak disappeared. The concept of thalamocortical dysrhythmia might actually be correct.

Dr. de Ridder reported next on an analysis of similar data in progress for 10 patients. However, his team wondered why, if the theory of thalamocortical dysrhythmia is correct, some people did not improve with electrical cortical stimulation? First, their theoretical model might have been wrong. Second, they might have been using the wrong stimulation design or might just be looking at the wrong target based on the wrong model. There is probably some truth in the thalamocortical dysrhythmia model.

Regarding hyperactivity in the auditory system, two auditory pathways bring information to the cortex, and two auditory pathways bring information back to the periphery and to the cochlea. The extralemniscal system is phylogenetically much older and is not tonotopic or, at least, the tonotopic structure is very poor. The lemniscal system is tonotopically structured and phylogenetically more recent. Some have suggested that when something is changing in the auditory environment, this extralemniscal system becomes active. It recognizes that something is changing. The change itself, the content of the change, is transmitted in the lemniscal system. The lemniscal system fires in a regular mode, and the extralemniscal system fires in a burst mode, at the level of the thalamus. This is clinically interesting because one can hypothesize that white noise or noise like tinnitus might be generated by hyperactivity in the extralemniscal system, which is non-tonotopic, and that pure-tone tinnitus might actually be generated in the lemniscal system. Furthermore, narrow-band tinnitus might be a co-activation of both. If this is correct then basically the burst firing has to be a more potent activator of the auditory cortex than the tonic firing. This has indeed been reported (i.e., a burst is perceived at cortex as a wake-up call from the thalamus).

Actually, if the hypothesis is correct—that the extralemniscal system that fires in burst mode generates a narrow-band tinnitus and that burst is a more powerful activator of the cortex than a tonic stimulus—then researchers would predict that basically narrow-band tinnitus does not respond as well to tonic stimulation because it is generated in a neural substrate (i.e., the extralemniscal system, which fires in a burst mode and cannot be suppressed by tonic stimulation).

The speaker also reported results of an analysis of 46 placebo-negative patients with unilateral narrow-band tinnitus. Burst TMS was a lot more effective than tonic TMS for the suppression of that tinnitus. Results from another group of patients were investigated to determine whether burst TMS would alter pure-tone tinnitus and reported no difference with a burst or tonic stimulation for such tinnitus. Pure-tone tinnitus seems to respond equally well to burst or tonic stimulation, but noise-like tinnitus did not. Dr. de Ridder concluded that they might

have been using a wrong stimulation design. Metaphorically speaking, he suggested that the TMS machine was talking to the brain in a way that the brain did not understand or perhaps the researchers were just targeting the wrong spot in the brain.

What Tobias Kleinjung has reported and what John Dornhoffer and his colleagues have also demonstrated is that basically, in time, the TMS effect for the amount of positive tinnitus suppression decreases. The longer the duration of the tinnitus, the worse has been the incidence of occurrence of tinnitus suppression with TMS. That (1) there is a network stabilization going on and that network (the global workspace model) is too strong for TMS machine influence, (2) the auditory cortex is not involved or has become less involved, and (3) the network might be changing were concepts all open to consideration. Dr. de Ridder cited chronic and acute tinnitus, the demarcation empirically set at 4 years' duration, which suggested that the network does indeed change for both alpha and gamma frequencies. The connectivity between the gamma-band activity changes in time. Examination of the EEG data, which includes a current density trend analysis (i.e., a mathematical way of identifying changes of activity in the brain related to the tinnitus duration) has revealed over time significantly less gamma-band activity in the contralateral auditory cortex, which is statistically significant. In addition, the researchers reported a theta increase in the bilateral auditory cortices. In time, not only did the gamma-band activity decrease in the auditory cortex, but the theta activity tended to increase and become bilateral. If the auditory cortex is the generator, then in time, because it becomes bilateral, unilateral TMS may not be successful. Additional observations for the factor of tinnitus duration and its reflection in TMS efficacy for tinnitus suppression revealed that the change in time was accompanied with less gamma-band activity in the auditory cortex but an increase in gamma-band activity in the anterior cingulate. The anterior cingulate might be taking over part of the activity of the auditory cortex.

Interestingly, an increase in beta activity was reported in the hippocampal-parahippocampal area (i.e., the hippocampus-parahippocampus became more involved). A report from the Regensburg group, using voxel-based morphometry, demonstrated a decrease in gray matter concentration in the same area. The hippocampus in chronic tinnitus patients may become more important in time. If that is correct, this might be helpful for tinnitus research from a clinical point of view (i.e., the clinical application of the EEG with Loreta source analysis and brain PET to possibly predict responders and nonresponders to TMS and electrical stimulation for tinnitus relief). Furthermore, the results from an approach with EEG Loreta analysis of responders with electrical stimulation would serve as a source of comparison to that of the Regensburg group performed with PET.

The report from the visual system provides information of why the hippocampal area and the DLPC data activity are important. In the visual system, the presentation of a visual stimulus results in activity in the thalamus, the visual cortex, and the parietal and bifrontal cortices (i.e., the global network and the visual cortex are activated). With sustained perception—such that the perceptual awareness of the stimulus outlasts the stimulus itself—one has a prolonged conscious perception of a stimulus no longer present. Neuroimaging has identified differences in activation in the DLPC. The voxel-based morphometry studies of the hippocampus and the left hippocampus are similar to what has been identified with EEG Loreta source analysis. This was suggested to reflect an increase in the generation of the tinnitus percept by the hippocampus and the DLPC, just like a sustained perception of an external stimulus. The auditory cortex might not be needed any more.

The clinical relevance of this finding is further supported by an experiment with selective Amytal injections into the anterior choroidal artery. The anterior choroidal artery supplies blood to the hippocampus and the amygdala. Amytal is a barbiturate that can be injected intra-arterially. Basically, the amygdala and hippocampus are put to sleep for 10 minutes after Amytal injection. In tinnitus patients, if the patient has a tinnitus of long duration, the tinnitus was suppressed, but only the pure-tone component of the tinnitus. This suggests that indeed the hippocampus might actually be involved at least in the network generating the tinnitus percept. The hippocampus can, therefore, be considered to be a new target for electrical stimulation. Still unclear is whether the hippocampus can be reached by TMS with insertion of an electrode behind the ear and traveling on a trajectory through the hippocampus all the way into the amygdala, on the spot activated on fMRI over a particular tinnitus frequency. The speaker presented an fMRI demonstration of response to the tinnitus frequency and another frequency as a potential technique for the visual display of the location of site for stimulation. If the amygdala hippocampus was activated, it could be targeted for electrical stimulation. This has already been started in Antwerp.

The second part of Dr. de Ridder's talk was a focus on the distress that accompanies the tinnitus percept. Most patients are seen for the distress and not the tinnitus intensity. Dr. de Ridder suggested that the tinnitus intensity, at least in the acute stage, correlated with an increase in the gamma-band activity in the contralateral auditory cortex that changes in time.

The results of EEG and Loreta source analysis were reported for the evaluation and comparison of distress in

two groups of tinnitus patients (i.e., grade 1 and grade 4 tinnitus). Differences reported between the two groups were considered to be a reflection of a distressed neural network. The network started from the amygdala and extended to the anterior cingulate and from the anterior cingulate to the anterior insula and BA 10. This network seemingly was reported to correlate with an increase in distress. The tinnitus distress might actually be a phase synchronization of neuronal activity at brain cortex between the distress network and the thalamocortical oscillation on a level of gamma-band activity. If they are in phase synchronization, everything occurring at the same time in the brain is considered by the brain as one unified percept. Assuming that this is correct, it might be useful in the near future to actually stimulate in tinnitus distress patients the prefrontal cortex at BA 10 or at the level of the insula and the auditory cortex, out of phase, to break this phase synchronization to treat the tinnitus. Two magnets would need to be applied at the same time.

Dr. de Ridder summarized by saying that tinnitus intensity might be related to a gamma-band activity in the auditory cortex distress network of the right DLPC, the right amygdala, the anterior cingulate, the anterior insula, and the BA 10. This was explained to coincide with the exact same network as is activated in pain distress except that, in pain distress, instead of auditory co-activation, a different somatosensory co-activation is seen. Tinnitus distress would then be affecting the phase synchronization between these two networks in the acute stage. The hypothesis for the chronic stage was that the tinnitus intensity was related less to the auditory cortex activity and more to hippocampal and anterior cingulate activity.

Dr. de Ridder concluded his presentation by acknowledging appreciation for his coworkers at the University of Antwerp and in the Regensburg group and for the invitation from the Martha Entenmann Tinnitus Research Center (METRC). The forum's director, speaking on behalf of the METRC, congratulated Dr. de Ridder on an outstanding presentation and thanked him for providing basic science pathophysiology support for the original hypothesis of a final common pathway for tinnitus and the association of tinnitus chronicity with hippocampal-parahippocampal activation.

A panel discussion entitled "Transcranial Magnetic Stimulation/Cortical Brain Stimulation/Tinnitus Diagnosis and Treatment" attempted to provide to the attendees basic take-home information of the clinical application of TMS for tinnitus diagnosis and treatment. The panel members included Drs. de Deridder, Dornhoffer, Kleinjung, and Shulman.

The clinical TMS experience of Drs. de Ridder (since 2003), Dornhoffer (since 2005), Kleinjung (since 2003), and Shulman (since 2007) is limited to a trial of TMS for attempting tinnitus relief in two patients. Moderator Dr. Michael Seidman introduced the panelists to the issues for discussion: (1) patient selection, (2) categorization of tinnitus patients, (3) duration of tinnitus, and (4) the types of magnet. A meeting of the American Academy of Otolaryngology–Head and Neck Surgery Board of Governors, to which Dr. Seidman had recently been appointed, necessitated his early departure from the forum and assignment of his moderating role to Dr. Shulman. An edited version of the panel discussion follows.

Question 1: What are the specific criteria for selection of patients for attempting tinnitus relief with TMS?

Answer [Dr. de Ridder]: Basically, we don't have any specific criteria. Everybody who does not respond to a pharmacological treatment or to an audiological treatment has the opportunity to undergo TMS to find out which tinnitus patients benefit from it. We perform about 500 TMS sessions a year but not as a treatment. Basically, we want to know whether the cortex can be modulated in any other way. We don't have specific criteria yet because we don't know who will be responders and who will be nonresponders.

Moderator comment [Dr. Shulman]: I think what we're hearing, and correct me if I'm wrong, is that we're looking into the effect of a modality of treatment for the problem of tinnitus, for the phenomenon of an aberrant auditory sensation. That's quite different from a clinical approach attempting to diagnose a particular entity and to provide a specific treatment modality.

Answer [Dr. Dornhoffer]: I agree pretty much with Dr. de Ridder. We have a predominantly research protocol. Our main objective is to look specifically at the tinnitus percept and not necessarily at TMS as a treatment modality. Tinnitus patients with depression and other problems are excluded simply because we want to have a clear subset of tinnitus patients for investigation. Right now we don't know who will respond and who won't respond. So, I pretty much take any tinnitus patient who has failed pharmacological intervention attempting tinnitus relief or who may be interested in the research protocol. I was a subject, for example, for my tinnitus.

Answer [Dr. Kleinjung]: In Regensburg, we have a similar problem. It is known that TMS investigation is an ongoing investigation attempting tinnitus relief at the University of Regensburg. Tinnitus patients who attend our clinics request TMS. We have an open approach, whereby we include everybody, without any specific criteria, and a controlled group for investigative studies. The inclusion and exclusion criteria were mentioned in my talk. Significant are considered to be (1) duration of the tinnitus (i.e., an important predictor for achieving tinnitus relief with TMS) and (2) severity of the hearing loss (i.e., we have the impression that patients with bad hearing do

not improve very much with TMS). PET of brain activity might be another indicator for TMS and resultant positive tinnitus relief.

Answer [Dr. Shulman]: First, our team recommends that tinnitus patient selection for TMS treatment protocols be restricted to patients with tinnitus of a severe disabling type of at least a year or more. Second, tinnitus patients require identification and treatment of preexistent conditions in the ear (e.g., fluctuation in aeration of the middle ear and secondary endolymphatic hydrops) and in the brain (e.g., central nervous system disease). If not identified and treated, whatever the modality or treatment attempting tinnitus relief, whether it's medication or devices, such preexistent conditions will seriously influence the result of the treatment modality under investigation. A bias will be introduced into the result. Third, the degree of nerve loss of hearing is important in tinnitus patients. The greater the nerve loss of hearing, the less may be the result for tinnitus relief with TMS. The clinical translation of the tinnitus dyssynchrony-synchrony for tinnitus diagnosis and treatment finds support for these recommendations. Last, to be excluded are tinnitus patients with epilepsy or on medication resulting in a hyperactivity in brain cortex and resultant seizure activities.

Answer [Dr. de Ridder]: Metallic implants are also in the excluded criteria.

Moderator Summary, Question 1—Take-Home Message: For the issue of tinnitus patient selection for TMS attempting tinnitus relief, one needs to differentiate between TMS research protocols and those that are for clinical applications. The take-home message at the present time is that TMS is primarily a research approach with no specific criteria for patient selection for attempting tinnitus relief.

Question 2: What is the significance in patient selection for TMS attempting tinnitus relief of the identification of the clinical type of tinnitus and the duration of the tinnitus?

Answer [Dr. de Ridder]: Multiple studies have suggested that the longer the tinnitus lasts, the less is the auditory cortex a good target for suppressing tinnitus. The duration of tinnitus is definitely of importance. Clinically, on the basis of available knowledge and our preliminary data with functional neural imaging in time, maybe targets other than the primary auditory cortex, such as the DLPC, which has also been suggested by Dr. Kleinjung, may be a more interesting point of stimulation. There may be a need to utilize specific coils, which have a deeper penetration, to reach the anterior cingulate, which seems to be more involved in tinnitus generation over time. We will have to stimulate at multiple cortical areas, including nonauditory cortex areas. Maybe that's in the future, because the bilaterality of the tinnitus and the network involved may require the application of two magnets at the same time at different targets.

Answer [Dr. Dornhoffer]: I pretty much agree. In our protocol, the duration of tinnitus has to be chronic, and we define that the tinnitus is a duration of at least 1 year. However, we're taking everybody beyond that time and still trying to determine whether the duration of tinnitus is going to have an impact. It probably will, but we need more studies.

Answer [Dr. Kleinjung]: In our most recent controlled trial, which just started a year ago, we treat tinnitus patients after half a year of tinnitus. We like most of them to have tinnitus up to 4 years. That's not part of the protocol. The tinnitus has to be at least half a year before we start TMS attempting tinnitus relief.

Answer [Dr. Shulman]: Tinnitus is not a unitary symptom. Clinical types of tinnitus can be identified with a neurotological protocol. TMS attempting tinnitus relief is recommended for tinnitus patients with the clinical diagnosis of a predominantly central-type tinnitus of the severe disabling type of at least 1 year's duration and resistant to treatment by instrumentation or medication or both.

Moderator Summary, Question 2—Take-Home Message: Tinnitus patient selection attempting TMS tinnitus relief recommends patient selection for a tinnitus duration of at least 1 year.

Question 3: Which theory of tinnitus explains tinnitus control with TMS?

Answer [Dr. de Ridder]: With regard to the tinnitus sound percept, it may be related to the theory of a thalamocortical dysrhythmia. At least that's what our preliminary data suggest. In tinnitus of recent onset, where you have hyperactivity in the gamma range, we think it has to be in the contralateral auditory cortex. In tinnitus of chronic duration, we might have to look at other areas that might become more involved, especially the parahippocampus, the hippocampus, and the DLPC. If you look at tinnitus distress, you probably have to address other networks, all of which are actually limbic structures going from the amygdala to the anterior cingulate, the anterior insula, and the BA 10. This is probably a network completely different from that for the tinnitus intensity.

Answer [Dr. Dornhoffer]: I think what's happening here is we're getting a thalamocortical dysrhythmia, a constant loop between the thalamus and the cortex. I think there is pretty good proof that you get sensory reorganization. Larger areas and areas adjacent to the auditory cortex are drawn into this, and it makes the tinnitus perception louder. I think what we are probably doing is perhaps reversing some of that sensory disorganization that's happening; the tinnitus is still there, and I think the generator is still in the cochlea. Ultimately, the tinnitus is going to come

back, unless you do something more permanent, as Dr. de Ridder is doing. I think what is happening with TMS is affecting the sensory reorganization in the adjacent areas of the cortex, but the generator is still there. How long we can maintain suppression of the tinnitus signal I don't know.

Answer [Dr. Kleinjung]: I mentioned the model of thalamocortical dysrhythmia. I agree with Drs. de Ridder and Dornhoffer. I think we have to differentiate between low- and high-frequency stimulation. Low-frequency stimulation probably induces long-term depression. Although I don't have very much experience with high-frequency stimulation, I suggest that high-frequency stimulation probably creates a temporal disturbance of tinnitus-related activity. The TMS more or less addresses the neuronal axis more than the cell bodies.

Answer [Dr, Shulman]: My input to this question is based on the work that we've done with the short-latency recording of the auditory brainstem response in tinnitus patients back in the '70s—specifically, the identification of dysrhythmia in the short-latency auditory brainstem response to broad-band acoustical stimulation in tinnitus patients. I ask the panel and the audience to consider the following: that in every patient, whether they are now clinically manifest or not with tinnitus, that tinnitus exists, not as a phantom symptom but rather as a manifestation of a dyssynchrony of neuronal activity reflecting an ongoing nerve loss of hearing. The development of the ongoing sensorineural hearing loss is individual for each patient; that is, it's different in different patients.

Two factors that are involved in the clinical manifestation of the tinnitus are (1) the area where the nerve loss of hearing develops, which can be the cochlea or any place along the ascending or descending auditory pathway, and (2) the brain cortex itself (i.e., brain plasticity) and the multiple brain functions associated with the clinical manifestation of the percept of the tinnitus signal and the affect or behavioral response to the aberrant auditory signal (i.e., tinnitus). These two factors are most significant in whether the tinnitus becomes clinically manifest to the patient and its clinical course.

The model of thalamocortical dysrhythmia is a definite positive explanation of what we're seeing with EEG and nuclear medicine imaging and its clinical manifestation. The dyssynchronous auditory signal, when it reaches the thalamus, is converted at cortex into various degrees of synchrony manifested as different brain rhythms. The thalamocortical dysrhythmia is suggested to be not a theory for the production of the tinnitus but a physiological process that results in an area of hyperactivity at brain cortex. The clinical manifestation of a particular symptom is at the edge of the hyperactivity and is called the *edge effect*. The localization of the "edge" at the cortex can stimulate different neural substrates, with resultant different neurological complaints reflecting the stimulated underlying neural substrate (e.g., pain, Parkinson's disease, and tinnitus). In the case of acute tinnitus, the neural substrate is reported to be the primary auditory cortex.

The clinical manifestation of the tinnitus signal as an audible percept ultimately depends on the plasticity of the brain, individual for each patient. The edge effect is probably an ongoing one and is activating areas that Dr. de Ridder has described. The integrated tinnitus dyssynchrony-synchrony theory reflects what clinicians are hearing from their tinnitus patients, what has been reported at this meeting, and what one is observing objectively with EEG recordings and nuclear medicine imaging. I think that any modality used to attempt tinnitus relief—for example, a magnet on the patient's head—is not really stimulating only one area of brain. Basic sensory physiology teaches that every sensation has three parts: One is the sensation itself, the sensory stimulus; the second is the affect-behavioral response; and the third is the psychomotor response. The beautiful diagram that you, Dr. de Ridder, have of your model of the involved substrates fits that of basic sensory physiology and of the hypothesis of a final common pathway for tinnitus.

I think we need to translate advances in basic sensory anatomy and physiology for the position selected for magnetic stimulation. The results for tinnitus relief will vary in every tinnitus patient because every tinnitus patient is different, as reflected in the degree of sensorineural hearing less and the integrity of their brain (i.e., degree of brain plasticity—the ability for change in the brain cortex). Specifically, the goal of brain function is to reestablish and maintain what Roy John and his group and Hughes have identified to be a homeostasis of brain function, as reflected in the alpha rhythm. I think that fits what Dr. de Ridder has described and the experiences he has reported.

Moderator Summary, Question 3—Take-Home Message: The panel members are in agreement that thalamocortical dysrhythmia can explain the onset of the percept of tinnitus and its clinical course, particularly for acute tinnitus. A difference was presented to consider the thalamocortical dysrhythmia to be not a theory for tinnitus but a process-mechanism associated with the tinnitus percept.

Question 4: What do you think is the depth of penetration of the TMS magnet?

Answer [Dr. de Ridder]: I personally don't think that we actually modulate the primary auditory cortex directly, but rather indirectly. Functional connections have been described between the superior and posterior parts of the temporal lobe (i.e., association

auditory cortices to the primary auditory cortex). fMRI study with stimulation and without electrical stimulation reveals changes on the primary auditory cortex even though the electrodes are overlying the secondary auditory cortex. I think that TMS may actually be doing the same thing: That is, we are not really hitting the primary auditory cortex directly because the penetration depth is about 2 to 3 cm, depending on the amplitude and the coil configuration. There are coils with a deeper penetration, but the effect is probably indirect via the secondary or association auditory cortex.

Answer [Dr. Dornhoffer]: I think the depth is probably 2 cm. That's what we're told, and the target is the primary auditory cortex. However, I think some of the resultant TMS effect is related to or connected to some of the descending pathways. The problem is that with the functional scan, the high level of activity of the thalamus makes this determination difficult to evaluate. I think studies with your QEEG and MEGs will provide answers to this question. I think we're probably targeting the primary auditory cortex. However, I think the determination of the effects of TMS would improve with more sensitive measurement measures. The effects of TMS are probably much more widespread in the brain than what we are reporting at this time.

Answer [Dr. Kleinjung]: I think that the depth of penetration of the TMS with a "figure-of-8 coil," and that's what is usually applied, is about 1 to 2 cm. I agree with the views expressed that the TMS effects we report reflect the influence of the TMS on the secondary auditory cortex, not the primary auditory cortex, because the primary auditory cortex is too deep in the Sylvan fissure.

Moderator Summary, Question 4—Take-Home Message: The application of the usual figure-of-8 coil has a penetration of 2–3 cm. The brain area of stimulation is targeted to the primary auditory cortex, but the panelists agree that the TMS effects we report probably reflect the influence of the TMS on the secondary auditory cortex, not the primary auditory cortex, and other functional connections in the brain (i.e., "some of the descending pathways").

Question 5: What is the advice to the audience for the selection of a particular coil?

Answer [Dr. de Ridder]: Well, it depends on the aim of the TMS. We always use a figure-of-8 coil because it has a larger penetration depth. We would be very interested in also looking at the H coils, which have an increased depth of penetration. This would make possible the stimulation structures not reached with figure-of-8 coils. I think most routinely used TMS coil types are figure-of-8 coils. I don't think there is a lot of difference between the TMS machines. Significant are the parameters of stimulus intensity, frequency rate of stimulation, and whether you need a cooling system.

Answer [Dr. Dornhoffer]: Our experience has only been with the figure-of-8 coil.

Answer [Dr. Kleinjung]: We also use the figure-of-8 coil. As far as I know, it's the most focal way for stimulation of very specific areas. We started with the Magstim device for the first 30 patients and switched to the Medtronic device, which has been taken over by a Danish company. We have the impression that the cooling system of the Medtronic device works better than the Magstim device, when the goal of the TMS is clinical and therapeutic, because the sessions are longer.

Answer [Dr. Shulman]: As far as our team is concerned, we're just starting and we are open to various systems of TMS. Our protocol for TMS is planned for collaboration with the Brain Research Laboratory at New York University, which has used the figure-of-8 coil.

Moderator Summary, Question 5—Take-Home Message: The figure-of-8 coil is being used by all panel participants.

Question 6: What are the parameters of TMS for attempting tinnitus relief (i.e., intensity, frequency rate, and duration of stimulation); what is the opinion of the panel of single versus repetitive TMS; and what has been their experience with the efficacy of TMS for tinnitus relief for the factors of the frequency of clinical application of TMS and duration of the tinnitus prior to stimulation?

Answer [Dr. de Ridder]: With regard to single therapy versus repetitive as a treatment, single therapy is definitely not sufficient. One also has to consider that the clinical efficacy of TMS for achieving tinnitus suppression and sound suppression itself is in general of very short duration. Review of the studies from the Regensburg group all look at changes in the answers to questions of how the tinnitus is being perceived, and not changes in the tinnitus quality (or qualities). Therefore, in most studies, tinnitus perception is actually what is being analyzed. For the higher frequencies, because the tinnitus disappears for maybe 1 or 2 seconds, it can be evaluated only by using a visual analog scale.

As for treatment, I agree with Dr. Dornhoffer that one single treatment won't be sufficient. As long as the generator is there, it will come back. With regard to the frequency (or frequencies) selected for TMS, the tinnitus duration is important. Tinnitus of recent onset actually seems to respond better to high-frequency TMS than does chronic tinnitus of long duration. The longer the tinnitus duration, the better are results obtained with lower-frequency TMS.

In addition, significantly, a burst stimulus might be better for tinnitus with a noise-like character—but

I'm not sure. With regard to the selection of TMS stimulus intensity, it depends on the definition of the intensity. If you define the intensity based on the TMS motor threshold, the intensity level can be observed by visual inspection or recorded with an electromyograph. A major problem with the parameter of intensity is that the motor threshold is not the same as the auditory cortex threshold. Investigations of the visual system report that the use of the motor threshold for the selection of the stimulus intensity is probably not the best.

Ideally, one could theoretically establish a threshold for TMS stimulus intensity by examining alterations in the otoacoustic emission resulting from auditory cortex stimulation. At this time, the motor threshold is theoretically not a good way of looking at the intensity of TMS needed to activate or inactivate the auditory cortex.

Answer [Dr. Dornhoffer]: We use repetitive TMS via the Regensburg protocol (i.e., generally only low-frequency stimulation for 30 minutes each day for 5 days). Low frequency is the only TMS frequency approved by our institutional review board (IRB) at this point for safety reasons. We are recently investigating the concept of maintenance (i.e., the application of repeated TMS in patients reporting tinnitus relief). We look forward to investigating the use of pharmacological promoters or perhaps even high-frequency TMS as discussed by Dr. Kleinjung. We have not done that yet owing to our IRB constraints.

Answer [Dr. Kleinjung]: Single therapy is used only for diagnostic purposes in our lab. We usually use repetitive stimulation for attempting tinnitus relief. The frequency is 1 Hz for the DLPC stimulation. We also use 20 Hz, which is similar to the approach attempting control of depression. Concerning determination of threshold of intensity for TMS, Dr. de Ridder has said everything about our approach. Historically, one uses 110% of the motor threshold. Duration of stimulation should consider the overall time frame planned for stimulation (i.e., 1 week, 2 weeks, or 3 weeks). We have the impression that the longer the duration of stimulation, the better is the result. This observation appears to extend to the issue of maintenance therapy. I think a TMS duration of 3 weeks might be even better than one of 2 weeks. Three weeks is the standard for depression relief at the moment.

Moderator Summary, Question 6—Take-Home Message: Single therapy is used for diagnostic purposes and repetitive stimulation for attempting tinnitus relief. The frequency is 1–20 Hz. With regard to the frequency (or frequencies) selected for TMS, the tinnitus duration is important. Tinnitus of recent onset actually seems to respond better to high-frequency TMS than does chronic tinnitus of long duration. For tinnitus of longer duration, better results were obtained with lower-frequency TMS. Recommendations for maintenance therapy have not been established at this time. Reference was made to TMS results for depression relief to be 3 weeks.

Question 7: What is your opinion of the results reported of efficacy of the TMS for tinnitus relief when interpreted in regard to the placebo effect for tinnitus?

Answer [Dr. de Ridder]: Indeed, the significance of the placebo effect was demonstrated initially by the tinnitus patients selected for TMS attempting tinnitus relief. Specifically, in tinnitus patients in the placebo group who knew a positive response to TMS would render them eligible for implantation, the placebo rate was more than 60%. Now, the routine introduction into the protocol of, for example, audiometry prior to TMS has reduced the placebo rate back to the normal 32–33%. The placebo rate is, like you said, very important in evaluating the efficacy of TMS attempting tinnitus relief.

Answers [Drs. Dornhoffer, Kleinjung, and Shulman]: From our clinical perspective, it is important to keep in mind the placebo effect, for the interpretation of the efficacy of any modality of therapy attempting tinnitus relief. The placebo effect for tinnitus, particularly of the severe disabling type, has been reported in the literature to be as high as 40%.

Moderator Summary, Question 7—Take-Home Message: There is agreement that the placebo effect must be considered in the evaluation of efficacy for tinnitus relief for any and all protocols including TMS.

The forum concluded after the panel discussion. The focus of the ITF on transcranial magnetic stimulation at this meeting will be followed by updates at future meetings of the ITF.

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