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Cognitive Neuroscience in Tinnitus Research: A Current Review

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Abstract: Advances in methods of examining the human brain have led to a dramatic increase in specific knowledge about the origins of tinnitus. Neural modeling, behavioral measurements of hearing performance and psychological state, neuro-morphology, metabolic measurements of neural activity, electromagnetic recordings of synaptic potentials, and optical measurements of action potentials are all modalities that have provided insights or the promise of new information about the pathophysiology of tinnitus. This review examines these techniques and their contributions to knowledge about tinnitus.

Key Words: brain structure; cognitive science; electroencephalography

In this review, we examine current approaches to tinnitus research. As of this writing (2007), it is an exciting time in research in neural disorders, as a number of important advances have been made. Current means of examining humans with tinnitus are described. The studies of humans have been greatly served by animal and computational models. Animal models of tinnitus have reached a high level of sophistication wherein animal behavior can be trained to indicate the presence of tinnitus. Further, advanced techniques for examining single units and systems of neurons in the auditory systems of animals now yield complete views of integration of signals related to sound perception. From these animal models, computational models of auditory processing have been developed. Extending beyond previous descriptive models of neural systems of sound perception, these computational models are being used to directly examine pathological changes in the auditory system and means of using neural plasticity to modify the pathology. Understanding from animal and computational models at the molecular, genetic, and neural system levels set the stage for examining the percept of sound in humans and what happens when that percept goes awry: tinnitus.

A wide variety of techniques examine tinnitus in humans. Advanced methods of auditory system screening yield a view not only of the immediate neural processing of sound inputs to the cochlea and brainstem but of how the higher-order circuits in the colliculus, the thalamus, and the cortex process sound in intact and damaged hearing systems. Ultrastructural changes in gray-matter and white-matter structures in humans now are giving evidence of differences in units in the brains of people with tinnitus as opposed to those with normal sound perception. Excitingly, metabolic and electrophysiological recording systems now make possible experiments wherein changes in local neural network can be evaluated in the presence of tinnitus. We can see the differences in primary auditory structures and distant cortical and other neural systems that directly influence auditory perception and tinnitus. Fine detail down to the level of distribution of neurotransmitters and neural signaling units of synaptic potentials and action potentials are available. With this plethora of detail, we are able to examine local structures and systems throughout the brain in people with tinnitus. These examinations will lead first to understanding of a newly recognizable sort of pathophysiology—*neural systems failure*—and then to new means of correcting those failures.

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HISTORY

Though tinnitus has been described for centuries, modern theories of its origin began in the twentieth century. Indeed, as is often the case, experience from failed attempts led to a theory of origin [1]. Attempting to treat tinnitus by severing the auditory nerve resulted in not only loss of hearing on that side but no effect on the tinnitus or, worse, increase in its severity. Thus came the understanding that chronic tinnitus was a phenomenon of the higher-order auditory pathways. Now hearing loss is understood to be most likely the primary cause of much chronic tinnitus. Especially noteworthy is the variety of acute forms of tinnitus, such as salicylate toxicity, responses in minutes or hours to loud sounds, and pathological activation of the cochlea, such as in endolymphatic hydrops. These acute forms of tinnitus are deserving of their own research and description; however, they are distinct from tinnitus of the severe disabling type [2], which is the most common clinically presenting form of this disorder.

How shall we understand what is going on in the higher-order circuits of the human brain? In this review, modern methods of looking at human brain neural activity and the results for tinnitus research are examined. The approach looks at the brain in various ways: models of tinnitus, behavioral measures of tinnitus, structural neural changes related to tinnitus, and technologies for looking at neural activity. Finally, interventions aimed at the human auditory system also provide robust information about tinnitus mechanisms and treatments.

MODELS

Two types of models apply to tinnitus: animal and computational. Animal models are very informative in the study of tinnitus and have been cleverly designed to reveal sophisticated behavioral expressions and relate those behaviors to neural activities. However, a review of animal models is beyond the scope of this report. For details, various authors' writings (Yang [3]; Norena [4]; and Brozoski [5]) are recommended.

Neural computational models of tinnitus are becoming more prevalent and will be extremely useful in the study of signal processing in the brain and how to modify it. The development of a modern hearing assessment technology—distortion product otoacoustic emissions—was the result of careful study and review of the biophysics of the ear and the neural circuitry of hearing [6]. Initial models of tinnitus in humans were descriptive, including important details of the widespread distribution of neural changes in the brains of people with tinnitus [7]. Development of neural models of tinnitus is now reaching the level of computational description. For example, Parra and Pearlmutter [8] demonstrated the presence of information transmission efficiencies in the organization of auditory signal transmission in the normal auditory pathways. However, with hearing loss, these signal efficiencies are lost, and compensatory gain changes in the circuits result in high signal levels that may result in tinnitus. Konig et al. [9] produced similar findings by which the compensatory gain changes modeled by traditional neural network gain adaptation show sharp signal peaks that appear in the auditory system and might well be perceived as tinnitus. In a more elaborate model, Dominguez et al. [10] have examined the importance of lateral inhibition in the compensatory network changes that occur in the auditory cortex in response to hearing loss.

BEHAVIORAL TECHNIQUES

Measurements of hearing ability and cognitive behavior are advancing and can be used for research on tinnitus. Perhaps one of the most important questions in current tinnitus research is the observation of many people with tinnitus who present with normal audiogram results. If deafferentation is the primary cause of tinnitus, what is going on in these people? Advanced hearing testing techniques are providing important information. The threshold equalizing noise (TEN) hearing test [11] is providing some of that information. By systematically presenting masking noise bands along with pure tones for threshold testing, the TEN test can demonstrate that off-frequency listening may be happening in many people. They can detect a tone only through off-frequency pathways and, when these pathways are masked, their ability to hear a given frequency disappears. Weisz et al. [12] have carefully examined a large number of tinnitus patients using the TEN test and found most of them have hearing deficits, even if they have a normal audiogram reading.

Advanced tinnitus-matching techniques and thorough audiometric measurements show the link between altered hearing and tinnitus. As described earlier, Konig et al. [9] showed sharp discontinuities in the hearing thresholds of people with tinnitus. The discontinuities were close to the tinnitus match frequencies.

Residual inhibition is a phenomenon reported by many people with tinnitus, wherein their internal sensation is reduced or temporarily eliminated by listening to sounds. Roberts et al. [13] demonstrated an increased residual inhibition when noise bands centered on the tinnitus match frequency were presented to subjects.

The work on hearing, tinnitus matching, and sound presentations suggests that further work on responses to sound in people with tinnitus can be more closely

examined with fruitful results, particularly in the high-frequency range (>8 kHz) and ultra-high-frequency ranges (20–26 kHz), both in hearing thresholds and effects on residual inhibition [14].

Questionnaires

A variety of efforts are ongoing to better define through questionnaires the effects that tinnitus is having on subjects and to predict their response to treatment. For example, Kaldo et al. [15] have examined the mental state of subjects and their willingness to accept the possibility of change in their tinnitus. This Stages-of-Change Questionnaire demonstrated some ability to predict treatment success. This finding indicates the commonly held belief that cognitive and emotional conditions influence how well tinnitus patients manage. Further extensive work is ongoing in refining tinnitus and mental status questionnaires in multiple laboratories. Better characterization of different forms of tinnitus and concomitant conditions will result from this work, and efficient procedures for using such instruments clinically will be an important advance.

HUMAN NEURAL STRUCTURAL CHANGES

Though the number of neurons active in auditory pathways during tinnitus are few, functional imaging techniques (see later) are able to resolve changes in activity that occur with changes in tinnitus. Can we detect structural differences in brains with chronic tinnitus of the chronic disabling type? The basis of a structural difference in a brain with chronic tinnitus versus that without could be either causative or reactive. If causative, some sort of structural anomaly could be the predisposition for a brain to develop tinnitus. Thus, excitatory structures might be overly active and, consequently, perhaps enlarged and inhibitory structures could correspondingly be small and hypoactive. Such structural differences would predate the tinnitus. In contrast, one could imagine structural changes that are reactive to ongoing neural activity in continuing tinnitus. Interestingly, it may not be possible a priori to determine whether neural structural differences in brains with and without tinnitus are on a causative or a reactive basis. Detecting volumetric changes in neural structures related to tinnitus will be difficult, as the number of neurons is very small. Thus, we have techniques wherein averages of structural sizes over large numbers of the active and control populations are called for.

In voxel-based morphometry, such averaging techniques have been successfully deployed. Muhlau et al. [16] demonstrated potentially important differences in the brains of people with tinnitus. In particular, these researchers found in the posterior thalamus, in the medial geniculate nucleus, an increase in neural volume relative to controls. The medial geniculate nucleus is the major way-station of signals from the brainstem and inferior colliculus to the auditory cortex. As Muhlau et al. [16] suggested, the increase in volume may well be related to an increase in activity in this region. However, until we can obtain volumetric data from people before and after they develop tinnitus, it is not possible to ascertain whether this larger volume is causative or reactive. Importantly, Muhlau et al. [16] also found that limbic system structures in the sub-callosal region were smaller in tinnitus subjects. They postulate that such a small volume might be unable to inhibit activity in the auditory pathways and can result in the passing through of signals above the perceptual threshold. Again, we cannot determine for certain whether such changes are causative or reactive.

Diffusion tensor imaging is a dramatic new technique that uses magnetic resonance imaging signals to investigate the integrity of white-matter pathways. Lee et al. [17] were able to employ the technique to compare tinnitus subjects with control populations. In tinnitus subjects, the fractional anisotropy was found to be lower than in controls throughout prefrontal, frontal, and limbic cortical regions. Further, the arcuate fasciculus connecting auditory to frontal regions is also putatively damaged. These statistics suggest a deterioration of white-matter fibers in people with tinnitus and that the cortical interconnectivity is an important component of the phenomenon. Fractional anisotropy increases dramatically in brain regions with stroke or demyelination, wherein decrements in cortical function are clearly causative to neurological deficits. What is the connection between loss of white-matter tract integrity in the cortex and tinnitus? These fiber tract changes are an interesting complement to the volumetric changes seen in the voxel-based morphometry study described earlier.

METABOLIC STUDIES

The ability to study changes in neural activity noninvasively in the human brain is extremely important in understanding such phenomena as tinnitus. Though animal models guide us, the ability to interact with conscious humans while their brain is being measured is an incredible feat of technology. Various means of measuring neural changes exist, but they come in two basic groups: metabolic and electrophysiological. In metabolic studies, changes in the energy consumption of a local region of the brain are measured. The entire brain can be examined simultaneously with the metabolic techniques having a resolution capability on the order of a

cubic millimeter. The ability to examine widely disparate regions of the brain gives us a view of the interconnectedness of neural regions in relation to a neural phenomenon. There are several means of examining metabolic changes in brain regions.

In positron emission tomography (PET), chemicals that are used in natural-energy metabolism pathways are radiolabeled: they have an attached radionuclide that emits a specific type of radiation at a well-characterized half-life. The labeled metabolite is injected into a subject, and a task requiring neural activity, such as listening, is carried out by the subject. Regions that have a relative increase in energy consumption will accumulate the labeled metabolite. The radiation emitted from the metabolite can be measured and localized to a specific brain region with a tomographic radiation detector. Figure 1 shows the localization that can be achieved with PET scanning.

Cognitive neuroscience has a dramatic tool for studying the neural basis of behavior: functional magnetic resonance imaging (fMRI). In contrast to PET scanning, fMRI does not require radiolabeled moieties for identification of localized increases in metabolic activity. Further, it can act on a time scale lasting seconds. A number of studies of fMRI have been carried out [18–20]. These studies have revealed fascinating detail on changes in human neural activity in relation to tinnitus, from brainstem to auditory and higher cortices demonstrating differing lateralization of neural activity in people with tinnitus as compared to controls and even possible changes in tonotopic maps.

However, the use of fMRI has limitations. A most important limitation in studies of audition and tinnitus is the fact that the scanner mechanism is extremely noisy and usually requires subjects to wear earplugs. Clever protocols wherein periods of silence are interspersed with signal acquisition intervals make the interpretation of fMRI with tinnitus easier. The limitation of metabolic markers in determining the meaning of the increase in metabolism is as important in fMRI as it is in PET (described earlier). Alternative interpretations of data sets from fMRI studies make this limitation apparent [21,22]. Though a presumption that an increase in signal from metabolic markers means an increase in neural activity and thus that the signal increase is related to an increase in the relevant variable (e.g., increased firing means increased perceived sound), this may not always be the case. A large proportion of neurons are inhibitory; thus, an increase in metabolic signal may mean an increase in inhibition. Attempts to refine interpretation of metabolic studies will improve as this important tool is further used.

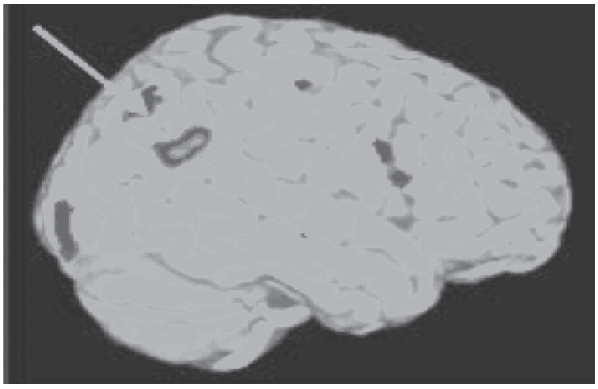

Figure 1. Area of increased activity in patient with tinnitus, demonstrated with positron emission tomography. Regional transcranial magnetic stimulation was directed to the region indicated by the arrow and was found to reduce the perceived intensity of the tinnitus sensation in the subject. (Reproduced with permission from Plewnia et al. [37].)

Single-photon emission computed tomography (SPECT) is an important modality for examination of tinnitus, as it enables definition of active regions in the brain. Initially it was used to detect regional changes in blood flow that are related to changes in tinnitus activity. Shulman [23] made the important demonstration that there were changes in cortical and limbic medial temporal lobe regions in tinnitus subjects as compared to controls, and he hypothesized a final common pathway for tinnitus. Fascinatingly, amobarbital (Amytal) injection into the anterior choroidal artery contralateral to the tinnitus percept in unilateral tinnitus results in maximal tinnitus suppression [24]. This suppression could correspond to the suppression of the medial temporal limbic regions by the Amytal and changes in the same limbic region observed in the SPECT scans. The initial SPECT technology used radiolabeled moieties to detect regional changes in blood flow in the brain. Going beyond markers, the concentration of which represents regional blood flow, we will be able to detect changes in neurotransmitter receptor numbers with SPECT and MRI spectroscopy [25]. Indeed, Daftary et al. [26] showed the distribution of biochemical receptors in tinnitus. Thus, as behavioral interventions, neural stimulation, or pharmaceuticals are used to treat tinnitus, we will be able to detect long-term changes in receptor concentration for such entities as glutamate, GABA, and glycine.

ELECTROPHYSIOLOGY

The sine qua non of brain research is the detection and interpretation of the neural code that relates to a behavior. Such a quest is difficult, even in situations calling for some ability to be invasive, such as using microelectrodes in an animal or awake human neurosurgical preparation. In a human, we really have no way of approaching

the coding of signals in neural structures. However, we can monitor emitted electric and magnetic fields and have some indication of mass signaling in outer layers of the brain. Particularly in the field of electroencephalography (EEG), two important technological developments have emerged: improved recording systems with large numbers of electrodes (>100) and superb signal-to-noise ratios and greatly improved algorithms for managing and interpreting data from large data sets of EEG recordings. In addition, technological advances have been made in recording the concomitant magnetic fields of the brain emitted during electrophysiological activity. The magnetoencephalogram (MEG) has similarly been improved with better signals and analytical algorithms. These technological advances will enable more research on electrophysiological markers of tinnitus.

Weiler et al. [27] were the first to demonstrate the presence of cortical changes in the EEG signature of tinnitus. With a large EEG montage, these researchers were able to examine the spectral changes across the cortex, not only in auditory cortex but in connections to frontal and other regions. They demonstrated in the tinnitus population substantial spectral changes, particularly in frontal regions relative to a normative database of EEG recordings, especially in alpha and theta frequency ranges. From these findings, Shulman and Goldstein [28] extrapolated the presence of changes in the congruence or dyssynchrony in cortical regions in the auditory and frontal cortices in people with tinnitus. As important, Weisz et al. [12] were able to extend and quantify these concepts. These researchers found in resting MEG recordings of people with tinnitus an increased gamma band activity, particularly at 55 Hz. Weisz et al. proposed a cortical reorganization after deafferentation that results in their observed spectral changes in electrophysiological signals. Changes in cortical activity with thalamus and limbic systems are the possible neural basis of the sensation of tinnitus and the signals related to it.

Beyond the recording of spontaneous neural activity, responses of the brain to presented stimuli are important means of probing what is happening in a neurophysiological system. In our own laboratory, we examined the response of the primary auditory cortex to stimuli that replicated a tinnitus subject's tinnitus experience or to stimuli that were off tinnitus frequency [29]. Our findings suggest that the on-frequency response is exaggerated as the sound stimulus amplitude is increased and that the off-frequency response is suppressed. Further work is necessary to delineate the cortical responses to sound stimuli.

Weinbruch et al. [30] used MEG to examine evoked responses to tones modulated at 40 Hz in tinnitus subjects versus controls. As important, these authors were able to demonstrate that the tonotopic maps of the primary auditory cortex were modified in people with tinnitus and the presence of a greater signal strength in the evoked responses. As with the spontaneous EEG and MEG recordings described earlier, apparently the loss of signal in the lower auditory system results in reorganization of the primary auditory cortex and above; such reorganization may result in tinnitus. Figure 2 shows the fine localization of electrophysiological activity that can be achieved with MEG.

Optical Techniques

Beyond the classic methods of recording the electrophysiological signals related to neural firing, new methods are using optical techniques that are tantalizing. The coin of the realm of neural signals is axon potentials. However, axon potentials in the higher centers of the brain have relatively low signal strengths and so are not recordable. The event-related optical signal is a method using light reflected through the brain from external light sources. This may represent a probe that can give indications of changes in action potential firing rates. Sable et al. [31] show the changes in localization of auditory cortical optical activity that occur in sound stimuli with odd-ball timing. Though this technique has technological and interpretation difficulties, it potentially represents a new means of examining the cortex.

INVASIVE INTERVENTION

Reduction of tinnitus after cochlear implantation for deafness has been observed since the early days of implant technology development [32]. Indeed, now cochlear implants are being studied for primary relief of tinnitus secondary to unilateral hearing loss [33]. Reduction of tinnitus through stimulation of the auditory nerve is expected on the basis of the idea that tinnitus is triggered by hearing loss. Implants are now being attempted at higher centers of the auditory system and represent an opportunity to examine how the higher auditory system is involved in tinnitus. Further, an early report on auditory brainstem implants [34] showed that six of seven patients with usable implants experienced a reduction of tinnitus.

Implants of stimulating electrodes into the cortex have been successfully tested for treating tinnitus [35]. This is a fascinating means of dealing with tinnitus and is associated with an array of important issues, including localization of the offending cortex and determination of its type (primary or secondary auditory cortex). Indeed, understanding the functional reorganization of

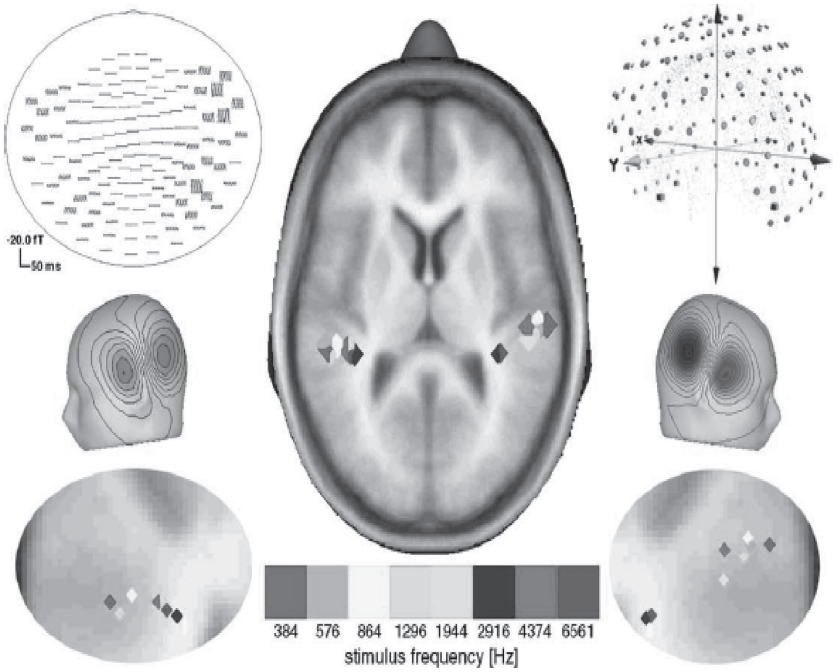

Figure 2. Magnetoencephalographic image of tonotopic representation of sounds. Source modeling in a representative normal hearing subject. Axial view of the tonotopic representation is shown in the center panel. Regional sources determined for each frequency are superimposed on the average brain of the brain-source localization software. Source locations in the right hemisphere are anterior and medial to those of the left hemisphere, in agreement with the group data. An expanded frequency representation is shown for each hemisphere in the lower left and right panels. The distance between the endpoints in the frequency representation for this subject is 13.9 mm in the left hemisphere and 23.8 mm in the right hemisphere. The upper left and right panels show the time domain steady-state response at 1,296 Hz and the sensor array with the coordinate system, respectively. The middle left and right panels show the pattern of magnetic flux at 1,296 Hz at their amplitude maxima in the left and right hemispheres. (Reproduced with permission from Weinbruch et al. [30].)

auditory cortex with chronic stimulation will be critical. Though it is difficult, chronic long-term electrical stimulation of the sensory cortex has been shown to result in neural kindling with development of seizures [36]. The dramatic reorganization of the sensory cortex that results in seizures after chronic electrical stimulation suggests that lower-level—but still behaviorally significant—reorganization might occur in the paradigms now being used. Concomitant examination of cortical morphology, metabolic parameters, and electrophysiology with long-term cortical stimulation are called for.

The advent of transcutaneous magnetic stimulation (TMS) is presenting an interesting direct means of manipulating the auditory cortex. Crucial to appropriate study and implementation of this technology is focal stimulation of the cortex and use of appropriate neuronavigation to identify potential stimulation sites. Plewnia et al. [37] have been working with stimulation using TMS and have been guided to stimulation sites by using PET scan identification of hyperactive cortical regions. They have found that some subjects do experience a reduction in tinnitus intensity for up to 2 weeks after stimulation sessions. Interestingly, high activity in the anterior cingulate cortex appears to correlate with success of the stimulation technique. The finding of cortical activity in a region distant to primary auditory cortex suggests the importance of detailed functional information about the human nervous system for maximizing understanding of tinnitus and the efficacy of treatment for it.

THE FUTURE

With the two parallel advances in tinnitus research—more fundamental knowledge and more precise techniques—it appears that convergence of understanding with intervention is nearly upon us. Tinnitus may well be a combination of a system predisposed to higher-order gain changes and the onset of pathology. One can envision a future convergence of the various methods available to examine the human nervous system to provide a full appreciation of an individual's tinnitus problem and a specifically designed approach for it.

Thus, as was outlined in this article, full assessment of tinnitus could conceivably include a behavioral review of a tinnitus patient's hearing, including advanced threshold assessments at high frequencies with appropriate masking to uncover off-frequency listening. Also possible would be a psychological review to determine the presence of psychopathological conditions, such as clinical depression interacting with the tinnitus.

An ultrastructural review of local neural structures and fiber tracts known to be relevant to tinnitus would be an important aspect of the modality. Metabolic studies could be used to examine regional blood flow, oxygen uptake, and energy consumption in the primary and secondary auditory cortices and other regions affecting tinnitus.

Radiolabeled markers of neurotransmitters may someday determine local hypo- or hyper-concentrations, along

with electrophysiological metrics of local processing of auditory signals in auditory and distant neural structures. Further methods would include optical metrics of action potentials in the local auditory cortex and studies of noninvasive and invasive stimulation techniques to determine how the measured anatomy and physiological indicators in the measurements change as treatment occurs.

Ultimately, measurements of all the foregoing parameters may not be necessary for managing any individual case of tinnitus. However, because of the varied nature of the condition and the different presentations of patients, some or all of these metrics may be useful in some cases. Of particular note is the realization that a relatively disconnected auditory cortex may be responsible for much tinnitus. If the findings using TEN hearing tests are confirmed, dramatic losses of hearing may occur, especially in the higher frequency ranges, wherein most people match their tinnitus frequency. Intervention at the cortical and perceptual level of the auditory system may thus be the most important means of treating tinnitus. Further, advanced knowledge of the formal signal-firing organization of primary, secondary, and higher-order cortices related to hearing combined with sophisticated models of induction of plasticity should lead to advanced interventions.

Finally, of interest is the concept of feedback-driven intervention, wherein near-real-time, invasive techniques, such as TMS, are matched to neural metrics, such as electrophysiological markers (e.g., evoked cortical potentials). Hartman [38] proposed such a technology. We live in an era wherein advanced knowledge of activity in the brain is leading to specific understandings of tinnitus and its management.

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