

Third in the International State-of-the-Science Meeting Series



International State-of-the-Science Meeting on **Blast-Induced Tinnitus**



November 15–17, 2011

Westfields Marriott Washington Dulles, Chantilly, Virginia

*DoD Blast Injury Research Program Coordinating Office
U.S. Army Medical Research and Materiel Command*



The opinions, interpretations, conclusions, and recommendations contained herein are those of the authors and are not necessarily endorsed by the U.S. Army.

Preface

It is my pleasure to acknowledge the staff of the Department of Defense (DoD) Blast Injury Research Program Coordinating Office (PCO) for its work in planning and implementing the International State-of-the-Science Meeting on Blast-Induced Tinnitus. They successfully assembled subject matter experts from the science, engineering, and health care disciplines to address the critically important topic of trauma-induced tinnitus in our warfighter and veteran populations. This meeting represents a unique collaboration among the DoD Blast Injury Research PCO, the DoD Hearing Center of Excellence, and the Department of Veterans Affairs.

I wish to commend the meeting planning committee and the meeting presenters, panel members, and attendees for their excellent contributions, both in their presentations and discussions. Without their active participation, it would not have been possible to critically assess the state of scientific knowledge. I thank all investigators who have conducted research that provides vital information on the biological mechanisms of tinnitus, on the scientific and clinical data needed to diagnosis and treat tinnitus, and on the association between tinnitus and both traumatic brain injury and post-traumatic stress disorder. Further, I urge scientists to continue relevant programs of research and implement novel studies that will solve compelling research questions.

This document summarizes the proceedings of the meeting and serves to disseminate information regarding what is known and what still needs to be learned about blast-induced tinnitus to a broad audience, including scientists, engineers, medical researchers, health care professionals, protection system development experts, and military leaders and decision makers at all levels.

Thank you for your contributions to make this meeting a great success.

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Senior Executive Service
Principal Assistant for Research and Technology
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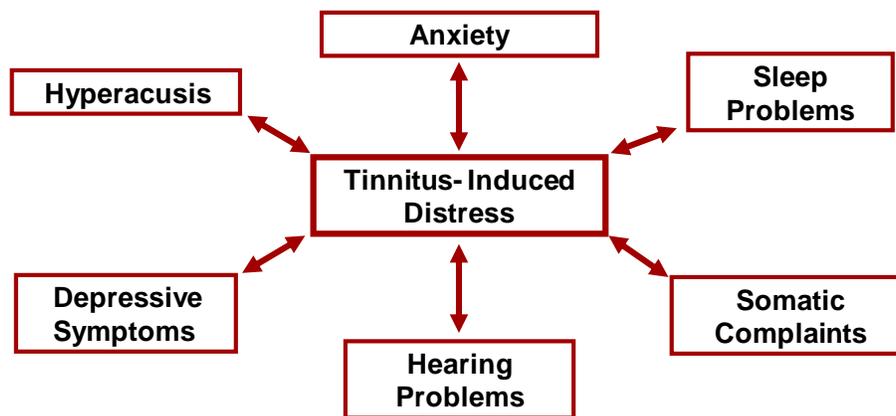
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Executive Summary

Tinnitus is defined as noise or ringing in one or both ears when no external sound is present. It can be a chronic, debilitating condition. Tinnitus most often results from either acoustic trauma or head and neck injury, which are prevalent injuries in current conflicts. Tinnitus and hearing loss are significant medical and cost issues for both the Department of Defense (DoD) and Department of Veterans Affairs (VA). An average of 15,000 new cases of tinnitus was reported each year in active duty service members from 2007 to 2010,¹ and tinnitus and hearing loss were the top service-connected disabilities in veterans receiving compensation in fiscal year 2011.²

The DoD Blast Injury Research Program Coordinating Office (PCO), in collaboration with the DoD Hearing Center of Excellence and the VA, hosted the International State-of-the-Science Meeting on Blast-Induced Tinnitus on November 15–17, 2011 to assess current knowledge regarding the cause, diagnosis, and treatment of tinnitus and to identify research gaps for further investigation. The meeting also served to foster collaboration among researchers and inform DoD research investment strategies.

Factors Contributing to Tinnitus- Related Distress?



From: Presentation by **Dr. Wolfgang Delb**, Heidelberg University

MAJOR FINDINGS

Neurological Basis for Tinnitus – Sufficient understanding of the mechanisms and factors involved in the initial onset of tinnitus and the development of chronic tinnitus, while extensively studied, remains elusive. Changes in auditory brain pathways, auditory input signals, and the interaction with nonauditory brain areas all influence neural processing and can lead to or affect the perception of the tinnitus phenomena. This key knowledge gap impacts the ability to develop effective preventive measures and treatments for tinnitus.

Post-Traumatic Stress Disorder (PTSD) and Tinnitus – The available evidence was insufficient to define a contributory linkage between tinnitus and PTSD in either direction. An indirect relationship may exist through an association of both disorders with brain injury.

Tinnitus Diagnosis and Characterization – The primary means of diagnosing tinnitus relies on subjective patient reports of tinnitus presence, loudness, annoyance, and change over time. A number of techniques are being explored for diagnosing and characterizing tinnitus, including structural and functional imaging, electrophysiological measures, and sound-based testing to identify key markers for tinnitus. Appropriate tinnitus measures are also needed in animals to support preclinical studies. The lack of standardized,

¹ Helfer, Thomas M. Noise-induced Hearing Injuries, Active Component, U.S. Armed Forces, 2007-2010. Medical Surveillance Medical Report (MSMR) 18(6):7-10, June 2011. (http://www.afhsc.mil/viewMSMR?file=2011/v18_n06.pdf#Page=7).

² Veterans Benefits Administration, Department of Veterans Affairs. Annual Benefits Report Fiscal Year 2011. (http://www.vba.va.gov/REPORTS/abr/2011_abr.pdf).

objective diagnostic and characterization tools for tinnitus is a major gap in the ability to conduct clinical evaluations of existing and novel treatment approaches.

Tinnitus Treatment – Treatment of tinnitus is not standardized. Currently, no drugs are U.S Food and Drug Administration (FDA) approved for the treatment of tinnitus. Numerous therapeutic strategies have been proposed or are in use in recent years, using devices, existing drugs for other indications, behavioral therapy, and psychotherapy, alone or in combination. There is a need to differentiate between tinnitus management and treatment in evaluating the success of a strategy. Well-controlled studies of existing and novel strategies are needed to inform and standardize clinical practice guidelines.

PRIORITY RECOMMENDATIONS FOR RESEARCH

The executive panel's most significant recommendations for research are summarized as follows and represent areas that are of high priority for research in the near term.

Fundamental Knowledge Gaps

- Determine the operational readiness impacts of tinnitus in the military.
- Enhance and utilize the Defense Occupational and Environmental Health Readiness System and other medical databases and registries to standardize and obtain the data needed for the conduct of research studies. It is anticipated that policy and regulation issues would need to be addressed.
- Conduct a large-scale longitudinal study of blast-exposed and non-blast-exposed military personnel and veterans to gain insight on tinnitus onset factors and tinnitus progression.
- Determine whether there are key markers for predicting an individual's susceptibility for developing tinnitus, both before and following injury.
- Evaluate the relationships, if any, between tinnitus and other cognitive and psychological disorders.
- Continue to elucidate the mechanisms and contributing factors associated with tinnitus onset and progression to chronic tinnitus.
- Enhance existing and develop additional animal and experimental models and apparatuses to support the study of tinnitus, including blast and traumatic brain injury, tinnitus distress measures, and blast shock tube exposure.

Applied Research and Technology Development

- Identify candidate pharmacologic strategies for early interventions that could prevent the cascade of damage to the cochlea and brain from leading to hearing loss and tinnitus.
- Develop improved and new imaging techniques to identify functional and structural changes that could be used to diagnose and characterize tinnitus.
- Develop improved tools and measures to assess tinnitus loudness, changes in tinnitus, and an individual's reaction to tinnitus.
- Develop tools for the objective diagnosis and characterization of tinnitus.

Clinical Research

- Develop standard protocols and measures for conducting tinnitus-related clinical studies.
- Characterize the performance of existing technologies and modalities, alone and in combination, to diagnose and characterize tinnitus and possible subtypes.
- Conduct well-designed human studies of existing and novel therapies for preventing and treating hearing loss and tinnitus. This would include new uses for existing drugs; nutritional and pharmaceutical-based strategies; and acoustic, electrical, and other stimulation technologies.

RECOMMENDATIONS FOR CURRENT MEDICAL CAPABILITIES

- Develop a centralized education and outreach center to serve both clinicians and patients to support improving care models.
- Establish standardized DoD and VA clinical practice guidelines and information sources for the diagnosis and treatment of tinnitus using currently available technologies and practices; and adjust these guidelines as new technologies and practices are developed and validated.

CONCLUSION

Action can be taken immediately or in the short term to develop and improve the capabilities for diagnosing and treating tinnitus and thus improve the lives of our service members.

Summary of Meeting Proceedings

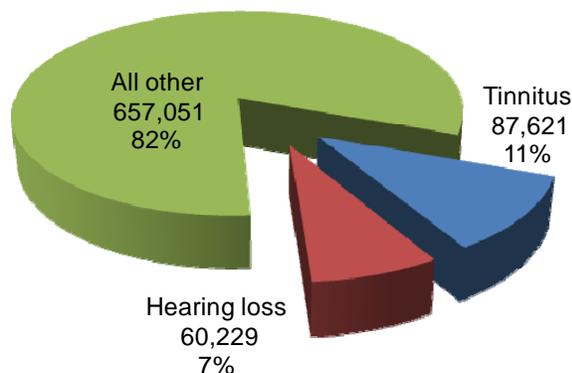
INTRODUCTION

Tinnitus is defined as noise or ringing in one or both ears when no external sound is present. It can be a chronic, debilitating condition. Tinnitus most often results from either acoustic trauma or head and neck injury, which are prevalent injuries in current conflicts. Notably, tinnitus was the most prevalent service-connected disability for veterans (840,865) in fiscal year 2011 (FY11), and hearing loss was second (701,760 veterans).³ Additionally, in FY11, more than 87,000 veterans who began receiving benefits included a diagnosis of tinnitus.

In 2005, Congress mandated that the Institute of Medicine (IOM) carry out a study assessing several issues related to noise-induced hearing loss (NIHL) and tinnitus associated with service in the Armed Forces since World War II. The IOM study recommended the services improve the prevention of, and surveillance for, hearing loss and tinnitus.⁴

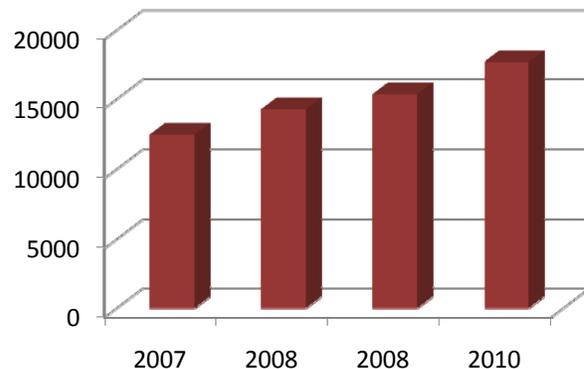
While the Department of Defense (DoD) has actively engaged in hearing conservation efforts over the years, the National Defense Authorization Act for FY09 further directed the DoD to establish a Center of Excellence (CoE) in the prevention, diagnosis, mitigation, treatment, and rehabilitation of hearing loss and auditory system injuries to: (1) ensure collaboration with the Department of Veterans Affairs (VA); (2) track hearing loss and auditory injury data; and (3) use these data for purposes of encouraging and facilitating the conduct of research and the development of best practices and clinical education.⁵

Number of Veterans Who Began Receiving Benefits, Fiscal Year 2011



From: Veterans Benefits Administration, Department of Veterans Affairs. Annual Benefits Report Fiscal Year 2011. (http://www.vba.va.gov/REPORTS/abr/2011_abr.pdf)

Annual Number of Cases of Tinnitus in Active Duty, 2007-2010



From: Helfer, Thomas M. Noise-induced Hearing Injuries, Active Component, U.S. Armed Forces, 2007-2010. Medical Surveillance Medical Report (MSMR) 18(6):7-10, June 2011.

DoD Hearing CoE (HCE)⁶ identified tinnitus as a top research initiative in its organizational concept of operation plan due to the enormous effect tinnitus has on both the warfighter and veteran populations.

The DoD Blast Injury Research Program Coordinating Office (PCO) in collaboration with the HCE and VA hosted the International State-of-the-Science Meeting on Blast-Induced Tinnitus on November 15–17, 2011, in Chantilly, Virginia to review current knowledge regarding the cause, diagnosis, and treatment of tinnitus and to identify research gaps for further investigation.

³ Veterans Benefits Administration, Department of Veterans Affairs. Annual Benefits Report Fiscal Year 2011. (http://www.vba.va.gov/REPORTS/abr/2011_abr.pdf).

⁴ Noise and Military Service: Implications for Hearing Loss and Tinnitus. Committee on Noise-Induced Hearing Loss Associated with Military Service from World War II to the Present, Medical Follow-up Agency; Larry E. Humes, Lois M. Joellenbeck, and Jane S. Durch, editors. Institute of Medicine of the National Academies, 2006.

⁵ Duncan Hunter National Defense Authorization Act for Fiscal Year 2009, Section 721, Public Law 110-417 – Oct. 14, 2008.

⁶ Information on the DoD Hearing Center of Excellence can be found on their web site: <http://hearing.health.mil/Home.aspx>.

The meeting planning committee consisted of clinical, research, and program representatives from the DoD and the VA. A list of committee members can be found in [Appendix A](#). The committee identified an executive panel representing international expertise to facilitate the meeting. Abstract submissions were used to select poster and presentation invitees. A literature search and an analysis on research and clinical trials related to tinnitus were conducted and provided to attendees as reference material. This search included the PubMed, Google Scholar, and the *ClinicalTrials.gov* databases for the period January 2005 to October 2011 and was limited to research involving adult human subjects (ages 19 to 60).

Meeting Objectives

- Identify the cause of tinnitus and determine its association, if any, with post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI).
- Determine if there are existing diagnostic tools that can be used to objectively identify tinnitus.
- Identify and prioritize the research gaps that exist in standardizing methods used in the treatment of tinnitus.

A total of 107 participants representing the DoD, VA, National Institutes of Health (NIH), academia, medicine, and industry attended the meeting. Eight countries were represented at the meeting, including Brazil, Canada, Germany, Italy, the Netherlands, the United Kingdom, the

United States, and Uruguay (see [Appendix B, Meeting Participants](#)). The detailed meeting agenda can be found in [Appendix C](#). The agenda consisted of presentations with panel-facilitated discussions, a poster session, concurrent participant workgroup sessions, panel member report-outs summarizing the workgroup sessions, and a closed executive panel session to review meeting data and formulate recommendations. Links to the presentations and posters presented during the meeting are posted on the DoD Blast Injury Research Program web site at

https://blastinjuryresearch.amedd.army.mil/docs/sos_tinnitus/SoS_Tinnitus_Presentations.pdf.



MEETING PROCESS

The meeting opened with keynote addresses by MG Douglas Robb, Joint Staff Surgeon of the Office of the Chairman of the Joint Chiefs of Staff, and MG James Gilman, Commander of the U.S. Army Medical Research and Materiel Command (USAMRMC), to highlight the importance and need to accelerate the converting of research findings into advanced medical capabilities in support of our warfighters. Additional introductory remarks were provided by the DoD Blast Injury Research PCO, the USAMRMC Military Operational Medicine Research Program (injury prevention), the DoD HCE, and the VA.



Subsequently, experts from the scientific, medical, and operational communities provided 12 technical presentations focused on blast-induced tinnitus, covering the topic areas of etiology, diagnostics, treatment, and association with traumatic brain injury and post-traumatic stress disorder (TBI/PTSD). Boxed insets throughout this report highlight the technical presentations. The executive panel listened to each presentation and stimulated post-presentation discussions. The panel consisted of the following experts:

- *Dr. Richard Salvi (Panel Chair), Professor, Department of Communicative Disorders and Sciences and Director of the Center for Hearing and Deafness, State University of New York at Buffalo – Recognized as the national expert on tinnitus. One of the first to use brain imaging techniques to investigate the neural substrate of tinnitus and identify regions of the brain involved with tinnitus.*

- *Dr. Carol Bauer, Professor, Division of Otolaryngology, Southern Illinois School of Medicine – Otolaryngologist specializing in chronic diseases of the ear including hearing loss, balance and problems, and tinnitus. Research interests include the pharmacologic management of tinnitus.*
- *Dr. Anthony Cacace, Professor of Communication Sciences and Otolaryngology, Wayne State University – Chairman of the American Tinnitus Association Scientific Advisory Committee. Research interests include central auditory processing disorders, tinnitus, and magnetic resonance imaging (MRI).*
- *Dr. James Henry, Research Career Scientist, VA National Center for Rehabilitative Auditory Research, and Associate Professor, Department of Otolaryngology, Oregon Health & Sciences University – Research interests include clinical measures of tinnitus, tinnitus treatment, and development and evaluation of comprehensive tinnitus management programs.*
- *Dr. Berthold Langguth, Senior Psychiatrist, Department of Psychiatry and Head of the Tinnitus Center, University of Regensburg, Germany – Chairman of the Tinnitus Research Initiative Executive Committee. Research interests include pharmacotherapy and transcranial magnetic stimulation for tinnitus.*
- *Dr. Pim van Dijk, Professor, School of Behavioral and Cognitive Neurosciences, University Medical Center Groningen, The Netherlands – Member of the American Tinnitus Association Scientific Advisory Committee. Research interests include neuroimaging of tinnitus, biophysics of the inner ear, and experimental tinnitus treatments.*

Workgroup Questions

- What are the current theories concerning the neurobiological basis of tinnitus?
- Is there substantial evidence that tinnitus is associated with PTSD and TBI. If so, what are the common biomarkers?
- What are the current technological approaches to tinnitus diagnosis?
- How can research standardize methods of effective tinnitus treatment?

After the final presentation, meeting participants were divided into five workgroups. Each workgroup was facilitated by a member of the executive panel and was charged with discussing and answering questions regarding the basis of tinnitus, the relation to PTSD and TBI, tinnitus diagnosis, and standardizing tinnitus treatment (see sidebox). Following workgroup discussions, meeting participants reconvened in a general session and each panel member briefed the conclusions of his/her workgroup.

On the final day, the executive panel members and meeting organizers met for a closed session to synthesize information from the meeting and formulate findings, knowledge gaps, and recommendations. The following sections summarize the panel's understanding of the current state of the science, their knowledge gap findings, and their recommendations for further research.

Overview of Tinnitus and Blast-Induced Tinnitus

Tinnitus is the perception of sound in the absence of an acoustic source outside of the body. The origin of tinnitus can be either neurophysiologic, involving auditory and possibly other brain pathways, or somatic, involving structures in the head or neck. Neurophysiologic tinnitus has no corresponding vibratory activity causing the perception. It is unknown what serves as the trigger to cause the onset or the maintenance of neurophysiologic tinnitus. Somatic tinnitus (also referred to as somatosounds) involves vibratory activity in the head or neck that is transmitted to the cochlea via bone conduction, resulting in the perception of sound through the normal auditory mechanism. In some cases, somatic tinnitus can be relieved by surgery although this is relatively uncommon.

The predominant form of tinnitus is the neurophysiologic type. There are no established methods for curing, or even reducing the intensity of, neurophysiologic tinnitus. In many cases, however, the tinnitus perception can be altered by manipulating the temporomandibular joint or facial structures or by moving the eyes (a phenomenon referred to as somatic modulation of tinnitus). These effects are only temporary, but they indicate that somatosensory input has an effect on tinnitus perception. While drugs are often

used to treat tinnitus, no drug has received FDA approval for this purpose. Drugs that have been approved for the treatment of other conditions, such as anti-anxiety medications, have been used as part of tinnitus treatment approaches to affect neural activity and/or comorbidities.

No drug has received FDA approval for treating tinnitus.

Since tinnitus cannot normally be cured and because no drug has been approved for treating the condition, clinicians usually rely on behavioral methodologies to help patients learn how to manage their reactions to their tinnitus. Numerous behavioral methods have been developed for this purpose, and they generally include some combination of education (teaching “coping skills”), stress reduction (relaxation techniques), and various uses of therapeutic sound. These types of therapies are typically offered by audiologists and/or mental health providers.

While NIHL is the most prevalent risk factor for triggering the development of tinnitus, the symptom can also be caused by TBI. When the TBI is blast induced, the onset of tinnitus is even more likely. We do not know why blast-induced TBI can result in tinnitus.

A number of factors can underlie the development of blast-induced tinnitus (see sidebox). The relative contributions of these factors to the development of tinnitus in an individual are unknown. Also, these factors may contribute to varying degrees in the different etiologies of tinnitus. For example, noise-induced tinnitus may be most often associated with cochlear damage while whiplash-induced tinnitus may most often involve the somatosensory system. Notably, factors that give rise to blast-induced tinnitus are unlikely to be homogenous—the same blast wave can produce tinnitus in two individuals by two different mechanisms, depending on predisposing factors and the characteristics of the blast.

Potential Causative Factors for Blast-Induced Tinnitus

- Noise trauma
- Emotional trauma (fear)
- Somatosensory activation
- Brain injury (concussion)
- Neck injury
- Individual susceptibility (genetic)
- Transmission characteristics of the middle ear

NEUROBIOLOGICAL BASIS OF TINNITUS

Current Understanding

Tinnitus is a reaction of the brain to some form of insult or damage. Some pathology within the auditory pathway is necessary, but not sufficient, to induce tinnitus. Of the factors or insults that may be involved in the etiology of tinnitus, NIHL is the most studied. Additional factors or insults include:

- Somatosensory activation (mediated via the dorsal cochlear nucleus or via involvement of the multisensory extralemnic auditory pathways)
- Brain reorganization leading to deficient inhibitory control or excess excitation
- Emotional factors such as stress, anxiety, or depression
- Individual differences in the ability to compensate for direct or indirect injury to the brain or inner ear
- Increased tinnitus susceptibility with age (though beyond a certain age prevalence drops)
- Nonauditory pathologies (e.g., hippocampal damage and metabolic or endocrine changes)
- Retrocochlear tumors and other cochlear pathologies
- Age-related hearing loss
- Ototoxicity

We lack sufficient understanding of the mechanisms and factors involved in the initial onset of tinnitus and the development of chronic tinnitus.

The exact mechanisms for how these factors interact or cause tinnitus is not understood. From the literature review, it is apparent that the contemporary view is that,

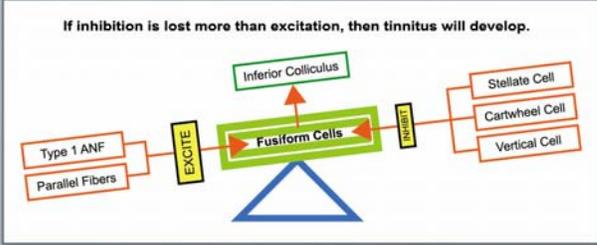
although tinnitus may be triggered by injury to the ear, the neural generators are most readily found centrally. While the neural generators may be primarily auditory, nonauditory centers often participate.⁷ The contemporary theory suggests that plasticity is the main component, with reduced auditory nerve input triggering a shift in the balance of excitation and inhibition centrally.

Presentation Highlight

Dr. Robert Levine
Massachusetts Eye and Ear Infirmary and Harvard Medical School

Implications of the Latest Dorsal Cochlear Nucleus Model for Blast Injury Tinnitus

- ◆ Fusiform cell is the main neural output of the dorsal cochlear nucleus
- ◆ Balance of fusiform cell inhibition and excitation determines if tinnitus develops
- ◆ Tinnitus quieting by GABAergic drugs may be explained by GABA inhibition of the fusiform cell



If inhibition is lost more than excitation, then tinnitus will develop.

This shift leads to changes that are found at multiple levels of the auditory pathway and even in some nonauditory centers, including the somatosensory and limbic regions. For example, using functional MRI (fMRI) and voxel-based morphometry (VBM), Leaver et al. found both functional and structural markers of chronic tinnitus in the limbic and auditory regions of the human brain.⁸ Their data suggest that interactions between the limbic and auditory systems may be the key to understanding chronic tinnitus though additional studies are needed to fully characterize this connection. Paglialonga et al. have investigated the role of outer hair cells and the cochlear-afferent system in tinnitus patients with normal hearing.⁹ They observed abnormal otoacoustic emissions (OAEs) in these patients, suggestive of a higher frequency outer hair cell dysfunction despite normal hearing. A more thorough characterization and mapping of tinnitus-related defects at all levels of the auditory system, including the subcellular and molecular levels are required. We also need to determine how hyperactivity, increased bursting activity, and neural synchrony contribute to the auditory, attentional, and emotional components of tinnitus.

The onset and maintenance of tinnitus may involve different mechanisms. We will need to differentiate between the factors that are involved in the onset of tinnitus (acute tinnitus) and the factors involved in the maintenance of the symptom (chronic tinnitus). For example, noise trauma may be pertinent for the onset of tinnitus, whereas emotional and psychological distress may become relevant factors in the chronification of tinnitus (i.e., the transition from acute to chronic tinnitus).

Current specific theories of the neurobiological mechanisms of tinnitus include:

- Neuroplastic, reactive changes in brain pathways and areas as a consequence of altered afferent input. These changes may be a consequence of gain adaptation to compensate for reduced input or the consequence of the lack of lateral inhibition, or both, and can include:
 - Hyperactivity in some brain regions and hypoactivity in others
 - Neural hypersynchrony
 - Tonotopic reorganization (pathological plasticity)
 - Changes in gene and protein expression that give rise to aberrant tinnitus-related neural activity

⁷Kaltenbach JA. *Hear Res.* 2011 Jun; 276(1-2):52-60.

⁸Leaver et al. *Neuron.* 2011 Jan 13;69(1):33-43.

⁹Paglialonga et al. *Auris Nasus Larynx.* 2010 Jun;37(3):291-8.

- Mechanisms by which nonauditory brain areas interact with auditory pathways:
 - Somatosensory modulation
 - Conditioned association (fear conditioning)
 - Involvement of extralemniscal auditory pathways
 - Gating or attentional mechanisms in nonauditory structures that influence auditory perception
 - Dynamic interaction of coactivated brain networks
 - Memory mechanisms

Knowledge Gaps

The general theory of tinnitus perception or annoyance is that it represents a change in the balancing act between inhibitory and excitatory inputs induced by one or more factors, both auditory and nonauditory. An example is a change in the auditory input from cochlear cells due to NIHL. However, the exact interplay that induces and maintains tinnitus is unknown.

The executive panel identified the following key questions or gaps to be addressed in the study of tinnitus:

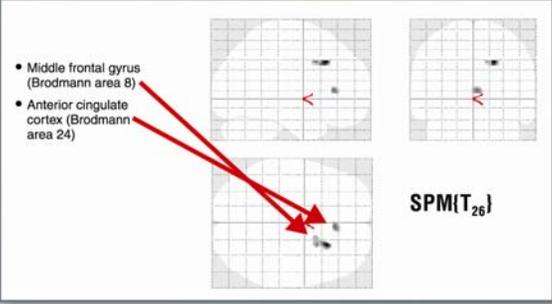
Presentation Highlight

Dr. Wolfgang Delb
Heidelberg University

What Brain Centers Are Linked to Tinnitus-Induced Distress?

- ◆ fMRI studies to determine brain centers linked to tinnitus distress
- ◆ Prefrontal cortex (Brodmann Area [BA] BA8) and anterior cingulate cortex (ACC, BA24) involved, with BA24 influenced by depressive symptoms and anxiety but not BA8
- ◆ May support objective evaluations of tinnitus-related distress and sub-classification of tinnitus patients

- Middle frontal gyrus (Brodmann area 8)
- Anterior cingulate cortex (Brodmann area 24)



- What factors and combinations of factors can induce or potentiate tinnitus, and what are their mechanisms of actions?
- When an individual sustains damage to the auditory system:
 - What is the mechanism that *causes the onset* of tinnitus?
 - What is the mechanism that mediates the *conversion* of acute tinnitus into a chronic condition?
 - How could that damage result in the onset of chronic tinnitus years or decades later?
- How do different manifestations of tinnitus relate to different underlying mechanisms?
- What are the relative contributions of cochlear injury and brain injury to the development of tinnitus and are there genetic or biological markers of tinnitus that can be identified?
- What are the factors involved and the mechanisms underlying why (1) under the same exact conditions, some individuals develop tinnitus while others do not, and (2) for those who develop tinnitus, it becomes bothersome for some and not for others?

- What parts of the brain other than the classical auditory pathway are involved in tinnitus?
- What are the mechanisms by which the emotional parts of the brain become involved in individuals with bothersome tinnitus?
- Are there gender differences that affect the onset or maintenance of tinnitus, and if so, how are these explained at the neurobiological level?
- What are the contributions of continuous background noise and other biological and emotional stressors or factors to the onset and/or maintenance of tinnitus?
- What is the prevalence of tinnitus in relationship to age and gender?

The panel further differentiated key questions on blast-induced tinnitus. These questions could be grouped into characterizing blast-induced tinnitus and experimental models. It is of interest to determine whether there are unique factors and mechanisms involved in blast-induced tinnitus, or whether blast injuries simply alter the balance of inputs and auditory processing and the same mechanism is at play as for other tinnitus-inducing factors. Animal and experimental models for blast-induced tinnitus will need to be refined and standardized to address some of these questions. The executive panel identified the following key questions/gaps to be addressed in the study of blast-induced tinnitus:

- What are the clinical characteristics and co-morbidities of blast-induced tinnitus?
 - Are there different subforms of blast-induced tinnitus?
 - How is blast-induced tinnitus associated with hyperacusis, headache, depression, anxiety, and somatic modulation of tinnitus?
 - How is blast-induced tinnitus related to other blast-induced symptoms (e.g., migraines, memory impairment, or PTSD)?

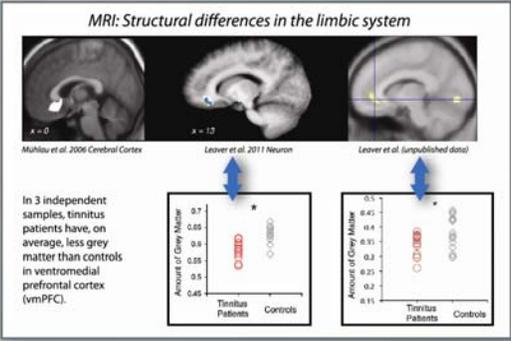
Presentation Highlight

Dr. Josef Rauschecker
Georgetown University Medical Center

Tinnitus – A Combination of Noise Trauma and Damage to Medial Prefrontal Cortex

- ◆ Cortical reorganization hypothesis supported by fMRI data
- ◆ Damage to the limbic system can lead to chronic tinnitus
- ◆ Tinnitus results from peripheral auditory damage followed by central auditory changes and lack of limbic suppression due to medial frontal damage

MRI: Structural differences in the limbic system



In 3 independent samples, tinnitus patients have, on average, less grey matter than controls in ventromedial prefrontal cortex (vmPFC).

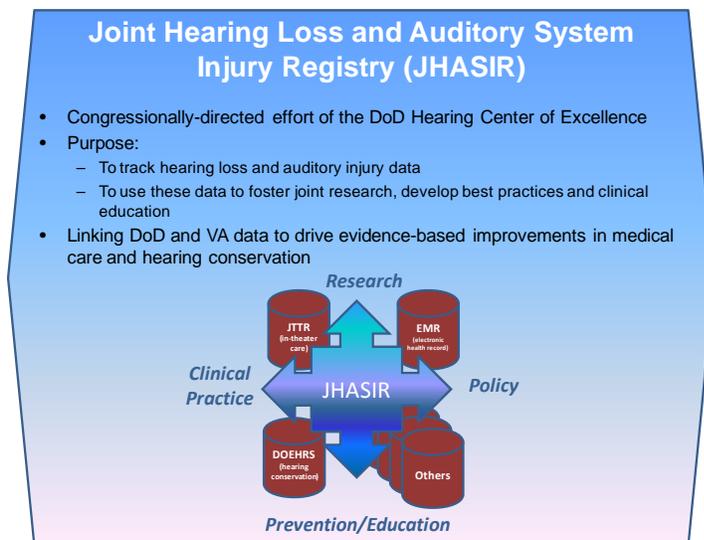
- What are the effects of blast alone, blast plus concussion, and concussion alone on the development of tinnitus?
- Are there other factors or conditions that induce or potentiate tinnitus in combination with blast or noise?
 - While limited data exist, need to determine why nonauditory areas of the brain are involved such as those related to attention and emotional processing.
- Do trauma-induced changes in the brain (e.g., microvascular, neurochemical, inflammatory, and gray or white matter lesions) cause or contribute to the onset of tinnitus, and if so, what are the mechanisms?

- Are there unique factors involved in blast-induced tinnitus (e.g., specific microvascular, gray and/or white matter changes in the brain)? Studies were suggested that leverage newer, noninvasive MRI modalities, which may include VBM (group comparison studies), susceptibility weighted imaging (SWI), or diffusion tensor imaging (DTI). Studying individual differences, potentially identified using individual morphological segmentation techniques, was also suggested.
- What are the physical parameters of blast exposure that are relevant to tinnitus? It is anticipated that this will require blast shock tube studies using well-characterized systems; however, consideration could be given to applying direct low-level blast exposures as was done by Rubovitch et al. recently.¹⁰
 - Need standard metrics for quantifying and characterizing blast exposure and the orientation of the subject with respect to the blast wavefront.
 - Need to elucidate the temporal and spectral characteristics of shock tubes used in animal experiments.
 - Need to leverage the effort to standardize the design and use of shock tubes for blast-induced TBI and apply lessons learned to study blast-induced tinnitus.
- Need to determine the best animal model to utilize for blast-related tinnitus studies. For example, should we utilize animals that have audibility characteristics similar to humans? While mice and rats may be expedient and cost-effective, these species may in part be protected against tinnitus and may be shock tube specific.

Recommendations for Research

The meeting participants and the executive panel placed a strong emphasis on the need for clinical datasets. These datasets could be analyzed to identify factors associated with tinnitus susceptibility, onset, and progression. In particular, long-term epidemiological studies and expanded databases of military and veteran hearing-related data are needed. The DoD HCE has been charged with establishing a clinical data registry (see following figure). It is anticipated that DoD and VA policy changes may be needed to address data access barriers. This information, combined with targeted animal and human studies, will help elucidate the mechanisms involved in tinnitus progression and ultimately identify candidate targets for therapies.

Capture of and access to acute and long-term hearing-related clinical data for military personnel and veterans are needed.



¹⁰Rubovitch V, Ten-Bosch M, Zohar O, Harrison CR, et al. A mouse model of blast-induced mild traumatic brain injury. *Exp Neurol*. 2011 Dec;232(2):280-9.

Registries and Databases

- Modify and make accessible for research the existing Defense Occupational Environmental and Health Readiness System (DOEHRS) registry.
 - Temporally characterize patients who are suffering from tinnitus—individuals with NIHL, age-related hearing loss.
 - Leverage the pre- and post-deployment data in the Automated Neuropsychological Assessment Metrics database, especially the data on neuropsychological and neurocognitive status to correlate with other data.
- **✎ Establish a DoD/VA/NIH working group that includes experts on tinnitus who also know about the relevant databases to identify the data required. Specific functions would include:**
 - Determining the kinds of data that would be useful and whether we have an existing database with those data.
 - Identifying barriers to obtaining the data requires policy subject matter expertise. For example, it may be necessary to expand the current policy (Directive-Type Memorandum) for blast exposure to include tinnitus.
 - Determining the best way to characterize tinnitus from a psychoacoustic perspective.

Research Studies

- **✎ Conduct a large-scale longitudinal epidemiological study comparing new veterans who have been exposed to blast injury to new veterans who have not been. Also compare to non-veterans.**
 - Characterize tinnitus from a psychoacoustic perspective and its relationship to other symptoms and conditions in these individuals.
 - Stratify veterans based on different levels of noise exposure.
 - Perform a complete assessment on the veterans and follow them for 20–30 years.
 - Find more effective ways to capture what veterans are experiencing (e.g., their comorbidities).
 - Establish a joint DoD/VA effort that leverages existing DoD datasets on blast exposures.
 - Obtain data that would be directly relevant to mechanisms research.
 - Obtain data that could address ancillary questions (e.g., the prevalence of tinnitus in relation to age).
 - Evaluate how different manifestations of tinnitus relate to different underlying mechanisms.
- **✎ Determine whether there are any biomarkers for susceptibility to developing tinnitus (e.g., genetic factors for stress, psychoacoustic, imaging-related, or age-related).**
- Determine if there are any cognitive deficits (e.g., psychoacoustic and central auditory processing) that are related to some forms of tinnitus.
- Conduct an epidemiological study that characterizes early life stressors/triggers and correlates them with the risk of developing an illness later in life.¹¹
 - The Adverse Childhood Experiences (ACEs) Study is investigating the association between childhood maltreatment and later-life health and well-being. This study has demonstrated that certain experiences are major risk factors for poor quality of life, illnesses, and early

Lack understanding of the full relationship between blast-induced brain injury and tinnitus.

¹¹Note the article by Heim and Binder (*Exp Neurol*. 2011 Nov 7. [Epub ahead of print]) that summarizes current research trends in early life stress and depression, and the article by Heim and Nemeroff (*Biol Psychiatry*. 2001 Jun 15;49(12):1023-39), which covers the role of childhood trauma in the neurobiology of mood and anxiety disorders.

death.¹² Therefore, the impact of ACEs on developing bothersome, disruptive tinnitus later in life should be included in any epidemiology study of tinnitus and TBI.

- Determine whether an enriched acoustic environment immediately after exposure ameliorates maladaptive cortical plasticity and reduces hearing loss in blast-induced tinnitus.¹³
- Use brain imaging techniques (e.g., electroencephalography [EEG], fMRI, positron emission tomography [PET], and magnetoencephalography [MEG]) to examine the relationships between tinnitus and distress, tinnitus and depression, etc.¹⁴
- Determine whether there is an effective pharmacologic intervention that could provide early rescue from blast injury damage to the brain and the cochlea, which in turn would prevent the development of tinnitus. The ideal candidate would be an existing, benign agent (e.g., a nutraceutical, steroid, or antioxidant).
- **Determine the efficacy of brief educational counseling on hearing loss and tinnitus mechanisms for both primary and secondary prevention. Develop educational programs to make patients aware of existing tinnitus therapies (e.g., sound therapy, counseling, and hearing aids).**
- **While animal models can address many of these gaps (e.g., specific variables can be isolated in animal models), the behavioral validation of tinnitus distress still remains to be developed in animal models of tinnitus.**

ASSOCIATION OF TINNITUS TO PTSD AND TBI

Current Understanding

Clinical evidence and the scientific literature indicate that TBI can cause the onset of tinnitus. The prevalence of tinnitus after blast-induced TBI is substantially higher than after non-blast-induced TBI. Lew et al. conducted a review of medical records at a VA TBI inpatient unit and found tinnitus reported in 18% of non-blast-related and 38% of blast-related TBI cases.¹⁵ Hearing loss was reported at higher rates in blast-related TBI cases (62%) compared to non-blast TBI cases (44%). Regarding PTSD, the incidence of tinnitus varies depending on whether the PTSD is a result of head/brain injury. Fagelson reviewed charts of tinnitus patients from a 4-year period in a VA medical center population.¹⁶ Of these, 34% of the tinnitus patients also had a PTSD diagnosis. While there appears to be a correlative relationship between PTSD and tinnitus, a causative relationship has not been demonstrated. It is not clear whether tinnitus causes distress, whether distress causes tinnitus, or whether there are other factors that cause or predispose individuals to both tinnitus and PTSD. Studies show that soldiers with tinnitus have a higher stress level in general.

Knowledge Gaps

The ability to document the linkages between tinnitus and brain injury and psychological disorders, such as PTSD, is in part hampered by the lack of sufficient objective data to characterize tinnitus onset and presence over time. Therefore, the knowledge gaps identified by the executive panel are focused more on obtaining this information to begin to correlate with other potentially confounding or

PTSD and Tinnitus

- There is insufficient evidence to define a contributory linkage between tinnitus and PTSD in either direction.
- An indirect relationship may exist through an association of PTSD and tinnitus with brain injury.

Need animal models of brain injury that address blast-induced tinnitus.

¹² Anda et al. *Eur Arch Psychiatry Clin Neurosci*. 2006 Apr;256(3):174-86.

¹³ Norena AJ and Eggermont JJ. *Journal of Neuroscience* 2005 25(3):699-705.

¹⁴ Weisz et al. *PLoS Med*. 2005 Jun;2(6):e153; Weisz et al. *J Neurosci*. 2007 Feb 7;27(6):1479-84; Schlee et al. *PLoS One*. 2008;3(11):e3720; Schlee et al. *BMC Neurosci*. 2009 Feb 19;10:11; Schlee et al. *BMC Biol*. 2009 Nov 23;7:80; Vanneste et al. *Neuroimage*. 2010 Aug 15;52(2):470-80; De Ridder et al. *PLoS One*. 2011;6(10):e24273.

¹⁵ Lew et al. *J Rehabil Res Dev*. 2007 44(7):921-8; Cave et al. *Mil Med*. 2007 172(7):726-30.

¹⁶ Fagelson MA. *Am J Audiol*. 2007 16(2):107-17.

related variables. These knowledge gaps (see sidebox) include defining/measuring tinnitus and evaluating the relationships with other injuries/disorders.

Presentation Highlight

Dr. Marc Fagelson
East Tennessee State University

Bi-Directional Effects of Tinnitus and PTSD

- ◆ Investigated relationship between tinnitus and PTSD
- ◆ Hyperarousal causes mislabeling of sensory information (central to PTSD and hyperacusis)
- ◆ Tinnitus symptoms rated more severe by PTSD patients
- ◆ Tinnitus self-efficacy lower in PTSD patients than other psychological conditions or tinnitus alone

Category	Tinnitus	Tinnitus and PTSD
Tinnitus Loudness	~6.5	~7.5
Sound Tolerance Problems	~4.5	~7.5

Fagelson, (2007). The Association between tinnitus and PTSD; AJA.

- What are the consensual definitions for temporary, acute, and chronic tinnitus?
- What are the guidelines for the differential assessment of TBI (especially mild TBI [mTBI]) and PTSD?
- What are the guidelines for the differential assessment of tinnitus?¹⁷ This would consider both time course (temporary, acute, and chronic) and severity level.
- How can objective measures of tinnitus be developed?
- How can biomarkers for objectifying the severity of tinnitus be developed?
 - Potential biomarkers include neuroimaging (MRI, fMRI, PET, EEG, MEG, and infrared spectroscopy), neuroendocrine measures, blood tests, heart rate variability, and neuropsychologic tests.
- How can neurobehavioral assessments for tinnitus be validated?
- How can distress be assessed in tinnitus patients with EEG and other brain imaging techniques?
- What is the co-incidence of PTSD, mTBI, and tinnitus?
- What are the temporal relationships between PTSD, TBI, and tinnitus?
- Is PTSD a risk factor for developing tinnitus and/or bothersome tinnitus?
- How are severity levels of TBI related to tinnitus?
- What animal model can be used to assess distress and/or anxiety associated with tinnitus?
- Can chronic tinnitus be “rescued” by reversing the underlying pathology or performing therapeutic interventions such as counseling and sound therapy?

Recommendations for Research

- **Develop a standardized assessment instrument for tinnitus that is validated and includes measures to rule out inconsistent or false responses and data.**
- Conduct a series of studies to discover and validate biomarkers for blast-induced tinnitus. These studies would include:

¹⁷Langguth et al. *Prog Brain Res* 2007;166:525-36 for a standardized assessment of tinnitus based on a consensus meeting.

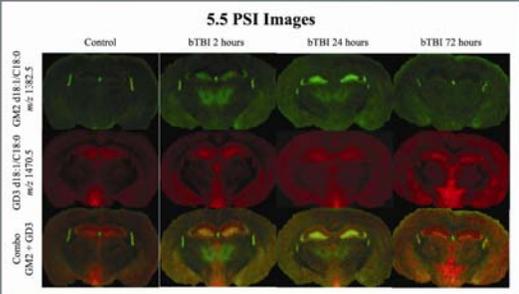
- A large-scale longitudinal epidemiological study comparing new veterans who have been exposed to blast injury to new veterans who have not been (described previously). Sub-efforts in this study would obtain and analyze available data (blood, genetics, etc.), hypothesize what the biomarkers may be, and then start looking for them.
- A data-mining study from military records that could elucidate biomarkers for tinnitus.
- A well-designed, hypothesis-driven prospective study focused on confirming the biomarkers identified in the data-mining study.

Presentation Highlight

Dr. Carey Balaban
University of Pittsburgh

Tinnitus Associated with Blast-Induced TBI: Patterns and Changes Over Time

- ◆ Need to determine relationship of tinnitus to central auditory processing disorders and headache syndromes, long-term tinnitus relation to blast and noise exposure, and the impact of early intervention on long-term tinnitus
- ◆ Mouse model of low-level blast-induced brain injury shows both short- and long-term changes



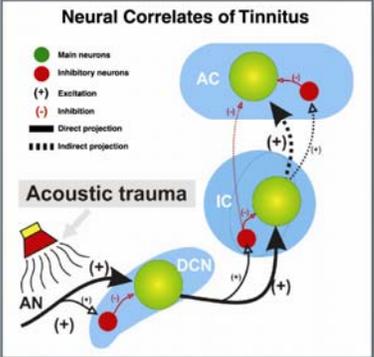
- *Determine whether the location of the structural brain lesions or the aberrant brain activity after TBI is related to the risk of tinnitus.*
- Establish animal models with discrete brain lesions (e.g., cerebellum, prefrontal cortex, or amygdala) to determine whether such lesions increase the likelihood of the development of tinnitus.
- Develop an animal model of tinnitus that correlates behavior with discrete injuries to develop cause-and-effect relationships.
- *Conduct neuroimaging (e.g., structural, functional, or neurobiochemical) in combination with behavioral (e.g., auditory stimulation) or brain stimulation challenges.*

Presentation Highlight

Dr. Jinsheng Zhang
Wayne State University School of Medicine

Blast-Induced Tinnitus and Its Treatment Strategies

- ◆ Rat model using Gap-Acoustic Startle Response measures following blast exposure
- ◆ Observed early-onset tinnitus at multiple frequencies that converged toward the high-frequency over time
- ◆ Changes in inferior colliculus and medial geniculate body suggest tinnitus mediated by plasticity in auditory brainstem and thalamus
- ◆ Auditory cortex and nonauditory center changes take longer to appear and may be involved in chronic tinnitus



APPROACHES TO TINNITUS DIAGNOSIS

Current Understanding

The diagnosis of tinnitus, and the differential diagnosis of tinnitus, are currently based primarily on the case history and the clinical and audiological examination of a patient. The instruments and methods available to general physicians and audiologists to detect tinnitus or tinnitus-related sequelae include validated questionnaires, audiological evaluations, and psychoacoustic tests. These detection instruments are applied to evaluate a patient's tinnitus in an attempt to determine the cause(s) of the tinnitus (i.e., etiologic assays and prognostics) and guide treatment approaches (i.e., predictive tests), evaluate patient distress to guide overall patient care, and monitor the efficacy of therapies for tinnitus and tinnitus-associated distress.

A variety of technologies are under development for the diagnosis of tinnitus in humans. Landgrebe et al. reported on the Tinnitus Research Initiative Database.¹⁸ This effort uses standardized formats for data reporting and has resulted in a larger dataset to support tinnitus investigations. It is anticipated that this dataset can be mined in studies focused on characterizing tinnitus subtypes and identifying predictors of individual treatment response. Santos Filha and Matas conducted a cross-sectional cohort prospective study of 60 individuals who were exposed to occupational noise.¹⁹ They found significant differences in long latency auditory evoked potentials when comparing subjects with tinnitus to those without the symptom. An evaluation by Singh et al. of auditory brainstem responses, middle latency responses, and OAEs in normal-hearing individuals with and without tinnitus revealed some significant differences in several measures (e.g., wave I latency prolongation, enlargement of wave Na and Pa amplitude, and transient evoked OAE signal-to-noise ratios).²⁰

Additional examples of approaches being investigated include:

- Psychoacoustic measures that are specific for characterizing tinnitus, including:
 - Loudness and pitch-matching techniques
 - Noise matching and spectral matching techniques
 - Minimum masking levels and residual inhibition

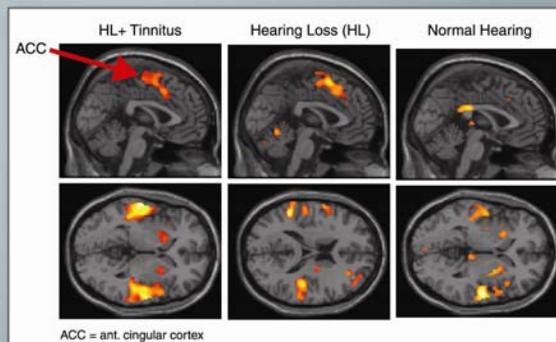
Presentation Highlight

Dr. Fatima Husain

University of Illinois at Urbana-Champaign

Functional and Anatomical Neural Networks of Chronic Tinnitus and Hearing Loss

- ◆ Imaging suggests large-scale neural networks governing attention, cognition, and emotion are affected by tinnitus
- ◆ Compared tinnitus with/without hearing loss using fMRI studies of auditory perception and cognitive processing
- ◆ Observed a differential engagement of a presumed auditory attention and short-term memory network (regions of the frontal, parietal, temporal cortices, and anterior cingulate)



¹⁸ Landgrebe M. et al. *BMC Med Inform Decis Mak.* 2010 Aug 3;10:42.

¹⁹ Santos Filha VA and Matas CG. *Braz J Otorhinolaryngol.* 2010 Apr;76(2):263-70.

²⁰ Singh S et al. *J Laryngol Otol.* 2011 Jul;125(7):668-72, Epub 2011 Apr 19.

- Structural and functional imaging, including:
 - Magnetic resonance imaging
 - Positron emission tomography
 - Electroencephalography
 - Event-related potential
 - Magnetoencephalography
 - Functional contrast agents (e.g., the application of Teslascan as applied to humans in manganese-enhanced MRI)
- Gap detection/startle reflex and EEG component

Presentation Highlight

Dr. Paul Davis
University of Miami

Bilateral and Contralateral OAE Suppression Testing in Tinnitus Patients

- ◆ Otoacoustic emission (OAE) suppression model
- ◆ OAEs provide a measure of efferent neural pathway functioning
- ◆ Contralateral OAE suppression is decreased in ear suffering from tinnitus (compared to ear without or with less tinnitus)
- ◆ Negative correlation between awareness of tinnitus and OAE suppression

OAE Suppression and Tinnitus Models

```

graph TD
    HL[Hearing Loss] --> B[Brain tries to increase sound perception]
    HL --> TP[Tinnitus perception]
    B --> LES[Less effective efferent system]
    LES --> H[Hyperacusis]
    LES --> DOS[Decreases OAE suppression]
    TP --> PE[Psychological effects]
  
```

- Audiometric testing, including:
 - High-frequency audiometry
 - OAE – transient and distortion products – and OAE suppression (relates to some theories, but range of response is limited)
 - Auditory brainstem response
 - Loudness discomfort levels
- Biomarkers of hearing loss and tinnitus

Knowledge Gaps

The primary knowledge gap is the discovery of biomarkers and other measures that can be used to objectively diagnose and characterize tinnitus, both in humans and in animal models. Clinical trials of novel approaches need validated, objective measures to avoid the subjective nature of tinnitus reporting by patients. Distress and impacts on the patient associated with tinnitus needs validated measures. Analytical methods and strategies being considered based on existing human methods, e.g., imaging and stimulation/response paradigms, need to be translated into animal models that can be used to investigate tinnitus mechanisms and discover novel approaches to the treatment of tinnitus. The questions to be addressed focus on the types of tools that can be used and types of diagnostic decisions that are needed:

Lack standardized, objective diagnostic and characterization tools to support tinnitus evaluation and provide measures for clinical trials.

- What objective diagnostic tools can be used to measure tinnitus?
 - Tinnitus is currently described by patient report, and there are very few tests or tools (other than high-frequency audiometry and pitch matching) that have been empirically proven to be useful for the differential diagnosis of the condition.
 - Need better differentiation of the different types of tinnitus so that diagnosis can be type specific.²¹
- How would tinnitus be diagnosed using a standardized case history? A standard set of questions and standardized methods are needed.²² Adaptations for military and veterans should include blast exposure questions and age ranges. A data registry could be used to identify connections.²³
- How would diagnostics for clinical purposes (i.e., diagnosing specific patients) differ from diagnostics for assessing claims (i.e., determining whether someone who complains of tinnitus really has tinnitus)?
- Which of several available questionnaires should be used for measuring the level of clinical distress of tinnitus?
 - Need better methods of assessing the impact of tinnitus on patients (e.g., their quality of life, amount of suffering, and ability to concentrate).
 - Need to more accurately quantify symptoms.
 - Need to obtain pertinent follow-up data.
 - Need a severity scale with high validity and a broad range of values to be able to make correlations.

Recommendations for Research

There is a need to develop diagnostic tools that consider the unique exposures/characteristics of the military and veteran populations. Additionally, existing technologies need to be evaluated for their validity and accuracy to support near-term recommendations for diagnostics. New biomarkers and modalities will need to be investigated for their diagnostic potential.

- **Develop a military- and veteran-specific questionnaire for assessing the impact of tinnitus.**

Presentation Highlight

Dr. Erik Viire
Naval Health Research Center

Prevalence and Auditory Effects of Blast-Related Ear Injury in Operation Iraqi Freedom

- ◆ Linked Expeditional Medical Encounter Database (EMED) data with 1-year post-injury auditory status records
- ◆ Overall prevalence of hearing loss was 31% in 3,981 patients
- ◆ Recommended that ear injuries be closely monitored in-theater and in all follow-up care to identify hearing-related morbidity that can impact service members' operational readiness

Blast-Related Ear Injury Diagnosed in Theater in Operation Iraqi Freedom (Navy-Marine Corps Data for 2004-2008)

Injury Type	% of patients
Inner/middle ear injury w/ tinnitus	19%
Tympanic membrane rupture	8%
Ear injury, other/unspecified	7%
Any ear injury	31%

Within one year of injury for those with no prior history of hearing loss or tinnitus (n=3824):

- 12% (444) diagnosed with hearing loss
- 6% (233) diagnosed with tinnitus

From: Presentation by Dr. Erik Viire, Department of Medical Modeling, Simulation and Mission Support and Weightier Performance, Naval Health Research Center

²¹Note the four subgroups of tinnitus patients identified in: Tyler et al. *Am J Audiol*. 2008 Dec;17(2):S176-84.

²²Can add to the list in: Languth et al. *Prog Brain Res* 2007;166:525-36.

²³An example for a database can be found in: Landgrebe et al. *BMC Med Inform Decis Mak*. 2010 Aug 3;10:42.

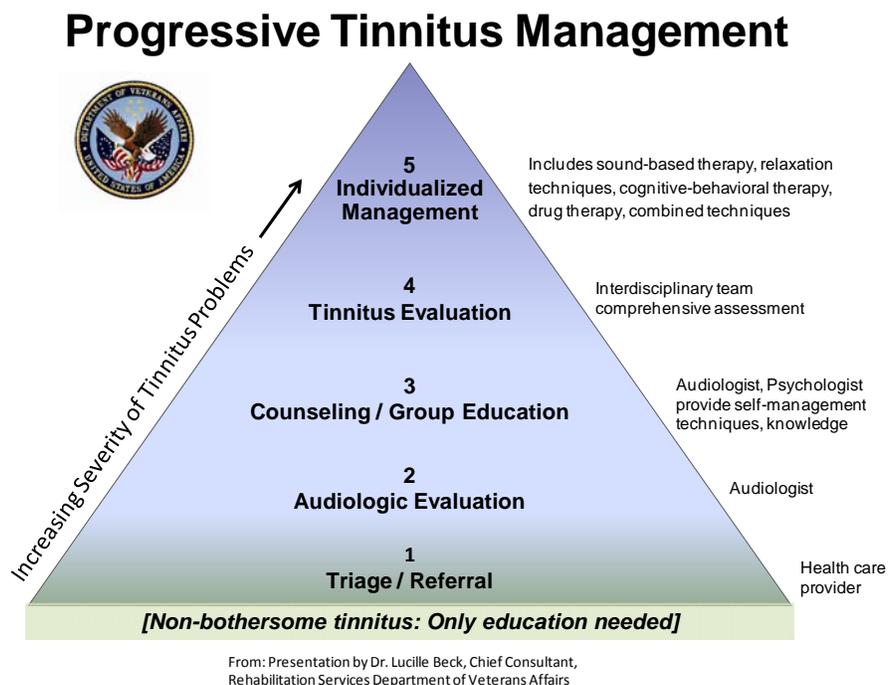
- Use matched tasks and multimodalities to demonstrate the specificity of the deficit. In particular, determine if central processing deficits are modality specific (i.e., auditory, visual, olfactory, and vestibular), multimodal, or supra-modal (i.e., attentional).
- **Determine specificity, sensitivity, reliability, and validity of existing technologies and combine techniques to make improvements in these areas. This should include multivariate statistical analysis to identify specific subtypes of tinnitus.**
- Identify biomarkers of hearing loss and tinnitus (e.g., genetic or biochemical).
- **Develop improved imaging techniques for identifying aberrant functional and structural changes in the brain that are linked to tinnitus, which may also be feasible in combat areas.**
- Leverage newer, noninvasive MRI modalities (e.g., SWI, DTI, or VBM).

STANDARDIZING METHODS OF EFFECTIVE TINNITUS TREATMENT

Current Understanding

As noted earlier in this report, there is no reliable clinical methodology for either reducing the intensity of tinnitus or eliminating/curing it. There are no drugs that can change the loudness of tinnitus. While drugs exist that treat comorbidities (e.g., depression, anxiety, and insomnia) and can reduce global suffering, none of the existing drugs is specific for tinnitus. The VA audiology clinics use the Progressive Tinnitus Management (PTM) protocol developed by the VA's National Center of Rehabilitative Auditory Research.

Clinical providers lack reliable methods to reduce the intensity of or eliminate the tinnitus phenomena.



The methods that are currently used to treat tinnitus are primarily behavioral, including sound therapy, stress reduction, and counseling. A reduction in tinnitus loudness has been attained with transcranial magnetic stimulation in some patients versus sham, although data are very limited to date.²⁴

Methods with clinical observational evidence for efficacy either individually or in combination include:

²⁴Meng et al. *Cochrane Database Syst Rev*. 2011 Oct 5;(10):CD007946.

- Tinnitus masking (e.g., Vernon/Meikle masking technique)
- Tinnitus Retraining Therapy
- Auditory stimulation (e.g., hearing aids and cochlear implants)
- Progressive tinnitus management (used by the VA)
- Sound therapy with counseling (including educational)
- Cognitive behavioral therapy (CBT; used by mental health providers)

Presentation Highlight

Dr. Craig Formby
University of Alabama

The Tinnitus Retraining Therapy Trial (TRTT)

- ◆ TRTT combines directed counseling and sound therapy
- ◆ Phase 3 multicenter trial involving military centers, 18-month follow-up planned; non-TBI patients

TRTT Treatment Groups

Treatment Group	Components
TRT	Directive Counseling, Sound Generator
Partial TRT	Directive Counseling, Placebo Sound Generator
Standard of Care	Standard of Care

©TRTT

Presentation Highlight

Dr. Pawel Jastreboff
Emory University School of Medicine

Tinnitus Retraining Therapy (TRT) for Noise Trauma-Induced Tinnitus

- ◆ Blast evokes a startle reaction, which increases arousal and can lead to the development of conditioned reflexes linking tinnitus perception with negative reinforcement
- ◆ TRT goal is to habituate to the tinnitus signal by removing the negative association – block tinnitus-related neuronal activity before it reaches the level of consciousness

Perception Reaction Perception Reaction

Stimulus Reinforcement Stimulus e.g., Tinnitus Reinforcement

Specific forms of tinnitus may be treatable with drugs and/or surgery, for example:

- Typewriter tinnitus
- Tinnitus related to vascular abnormalities
- Vascular diverticulum in temporal bone

The ideal approach is to have a standard protocol for treating tinnitus. As mentioned previously, differential diagnostic capabilities will be important for a clinician to identify the appropriate treatment approach. It is unlikely that all people with tinnitus will respond to a single intervention approach. But it may be possible to have a single intervention for preventing the chronification of tinnitus.

There is no established program in the military for treating tinnitus. The VA has developed a comprehensive protocol on PTM, which is gradually being adapted in VA hospitals and clinics. In the DoD, some audiologists have received the VA training and they are conducting PTM. Primary care physicians need to receive training in tinnitus management. The VA program addresses alleviating reactions to tinnitus but not curing it. Research is needed to discover cures for tinnitus. While such research is ongoing, the findings are not organized in a structured or systematized way that would allow for a global assessment of effectiveness. The VA has recently adapted its structured, educational counseling protocol on tinnitus management for patients with TBI in a format that can be delivered via the telephone, and it is achieving good results.²⁵ There have been some efforts in Europe aimed at developing an electronic version of CBT so it may be possible in the future to expand the VA's telehealth protocol to a web-based program.

A wide variety of treatment modalities are currently being investigated, including pharmacotherapy, neural stimulations, cognitive-behavioral therapy, devices (e.g., hearing aids and sound generators), therapeutic sound (music or ambient white noise to direct the patients' attention away from tinnitus), surgical interventions, and hyperbaric oxygen treatments for tinnitus. A few examples are mentioned here to show the breadth of approaches being considered. Hurtuk et al. reported on the effectiveness of melatonin in reducing tinnitus intensity and improving quality of sleep.²⁶ In a study of pramipexole (indicated for Parkinson's symptoms), Sziklai et al. observed that tinnitus annoyance was reduced.²⁷ Transcranial magnetic stimulation (TMS) is being studied by many researchers,²⁸ with positive effects noted suggesting the usefulness of various TMS approaches in reducing tinnitus measures. Bauer and Brozoski observed clinically significant effects of Tinnitus Retraining Therapy on tinnitus loudness and annoyance measures.²⁹ Okamoto et al., using a notched music (lacking sound at tinnitus frequencies) treatment over 12 months, reported a reduction in tinnitus loudness.³⁰

Sixty clinical trials relevant to tinnitus are currently listed in the *ClinicalTrials.gov* database as being in progress, either partially or fully, during the period of January 2005 to October 2011. Thirty-eight of the trials fall into the category of pharmacotherapy or device-based interventions. The pharmacotherapies examined in these trials include: neramexane, AM-101, Caroverin, cilostazol, NST-101, BGG492, vardenafil, acamprosate, paroxetine plus vestipitant, Deanxit plus Rivotril, gabapentin, and piribedil. Device-related trials include studies of TMS, transcutaneous noninvasive nerve stimulation, electrical stimulation of the auditory cortex, and phase shift sound cancelling, as well as studies of conventional therapies including device use (e.g., sound generators with tinnitus counseling).

Knowledge Gaps

While much research has been done on tinnitus and a number of treatment strategies are in use with limited or mixed success, there generally appears to be less rigor in the validation of many of these techniques.

Additionally, parameters to measure to consider a treatment successful must be considered—what is the goal of the treatment? Goals can range from eliminating the tinnitus phenomenon or reducing the

Well-controlled studies of existing and novel strategies are needed to inform and standardize clinical practice guidelines.

²⁵Research Leading to PTM (http://www.ncrar.research.va.gov/Education/Documents/TinnitusDocuments/02_HenryPTM-HB_11-20.pdf).

²⁶Hurtuk et al. *Ann Otol Rhinol Laryngol*. 2011 Jul;120(7):433-40.

²⁷Sziklai et al. *Laryngoscope*. 2011 Apr;121(4):888-93. doi: 10.1002/lary.21461.

²⁸Examples include: Anders et al. *Neuro Endocrinol Lett*. 2010;31(2):238-49.; Khedr et al. *Eur J Neurol*. 2010 Jul;17(7):976-83, Epub 2010 Mar 4; Lorenz et al. *J Neurophysiol*. 2010 Sep;104(3):1497-505, Epub 2010 Jun 30; and Marcondes et al. *Eur J Neurol*. 2010 Jan;17(1):38-44. Epub 2009 Jul 9.

²⁹Bauer CA and Brozoski TJ. *Ear Hear*. 2011 Mar-Apr;32(2):145-55.

³⁰Okamoto et al. *Proc Natl Acad Sci U S A*. 2010 Jan 19;107(3):1207-10, Epub 2009 Dec 28.

loudness or interference of tinnitus, to reducing the distress caused by tinnitus. These goals may differ among the military, veteran, and civilian medical communities. The availability of objective measures tied to these goals is critical to evaluating existing and novel treatment strategies. The knowledge gaps identified indicate a lack of effective diagnostic support tools/characterization; less emphasis was placed on specific knowledge gaps related to improving treatment capabilities.

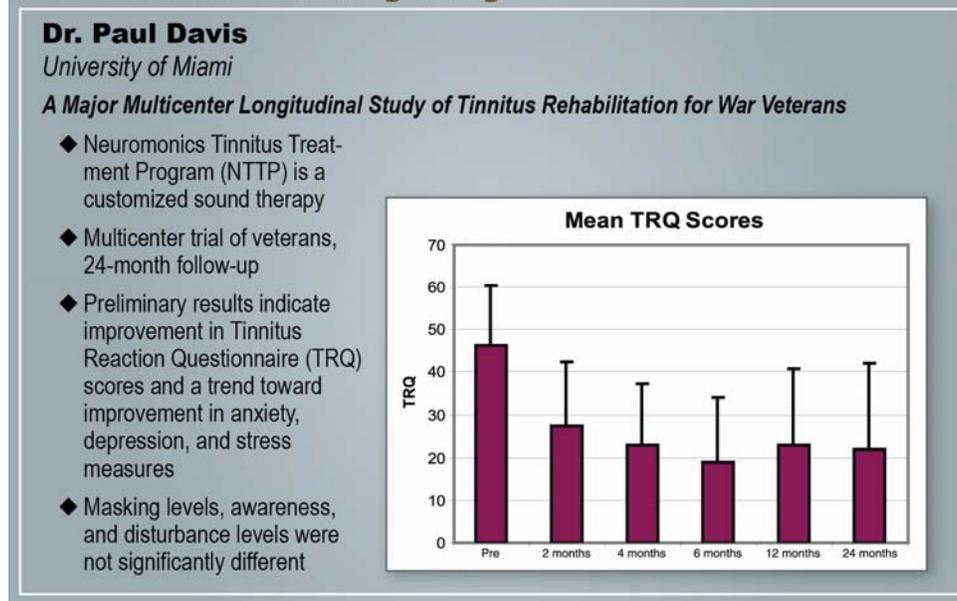
Supporting Tools/Characterization

- To what extent do tinnitus and tinnitus-related comorbidities such as hyperacusis affect operational readiness?
- How can we standardize psychoacoustic measures? To date, such measures have not been proven to reflect clinically relevant changes with treatment.
- We need to develop improved tools/measures for assessing tinnitus loudness, changes in tinnitus, and an individual's reaction to tinnitus.

Treatment

- How can we create educational training models for patients to self-manage their tinnitus?
- How can drug treatments be developed that are specifically targeted to tinnitus?
- We need to understand the parameters of electrical stimulation that can be effective in reducing tinnitus.

Presentation Highlight



Recommendations for Research

The bottom line is a strong need by the clinical community for effective, evidence-based treatments for tinnitus. We need to validate, or repudiate, both existing and novel approaches to tinnitus treatment. Both animal models and human studies need to be refined. Standardized methodology for the conduct of tinnitus-related clinical trials, including tinnitus measures, will be critical to achieving the innovations needed to improve medical practice. In addition to focusing research on treatments to eliminate tinnitus, means are needed to prevent the initial onset of tinnitus following injury as well as the subsequent chronification of tinnitus.



Tinnitus Retraining Therapy Trial

A randomized, placebo-controlled, multi-center trial that is testing the efficacies of TRT and its component parts, directive counseling and sound therapy, versus standard of care treatment in individuals who have self-perceived debilitating tinnitus.

Clinical Study Sites	Administration
 Wilford Hall Ambulatory Surgical Center (TX) David Grant Medical Center (CA)	 Study Chair's Office University of Alabama <i>Craig Formby, PhD, Study Chair</i>
 Walter Reed National Military Medical Center Bethesda (MD)	 Data Coordinating Center Johns Hopkins University <i>Roberta W. Scherer, PhD, Director</i>
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From: Presentation by Dr. Craig Formby, University of Alabama

Programmatic Initiatives

- ***Develop a tinnitus education model. Establish a centralized, DoD/VA tinnitus education center that will serve both clinicians and patients. The first goal of the center would be to help clinicians take care of their patients, and the second goal would be to provide access for patients in remote areas.***
 - Consider the DoD HCE and VA partnership.
 - Consider combining this with the hearing loss/tinnitus data registry to compare hearing loss/tinnitus with treatment and outcomes and patient satisfaction.
 - Determine the best modality for delivering treatment to patients based on their individual circumstances.
- ***Establish a multidisciplinary (i.e., otology, neuro-otology, audiology, neurology, psychiatry, psychology/psychotherapy, neurosurgery, and/or pharmacology) working group that guides the field and that will review existing models in other fields (e.g., pain, PTSD, cancer, and Alzheimer's disease) to determine if techniques in those fields could be applied to tinnitus.***
- ***Explore the possibility of expanding upon the Tinnitus Research Initiative (www.tinnitusresearch.org) to develop a global group to address blast-induced tinnitus.***

Research Studies

- Conduct a controlled clinical study focusing on the effectiveness of hearing aids in treating tinnitus.
- ***Conduct controlled clinical studies aimed at evaluating current therapy methodologies as well as developing therapies (e.g., vagal nerve stimulation in combination with acoustic stimulation of ears, repetitive transcranial magnetic and electric stimulation, and notched noise and notched music).***
- Evaluate the potential for micronutrients, antioxidants, herbal formulas, and specific pharmaceutical agents to protect against hearing loss and tinnitus and to potentially reduce tinnitus.

- Perform human and animal drug studies aimed at preventing or reducing hearing loss after noise trauma³¹ and preventing the chronification of tinnitus.
- Conduct well-designed human and animal studies aimed at evaluating new uses of existing drugs (e.g., cyclobenzaprine) in human or animal models and studies to develop and evaluate new drugs in reducing tinnitus.
- Develop methods aimed at improving the specificity of drug delivery systems since many pharmaceuticals may be effective if delivered by means other than through systemic applications.

SUMMARY OF RECOMMENDATIONS

The number of cases of tinnitus reported by the DoD and VA is staggering. While much progress has been made in understanding tinnitus mechanisms, treatment strategies remain widely varied in approach and success rate. This State-of-the-Science meeting brought together an international group of tinnitus researchers to discuss current findings and future approaches. From the presentations, discussions, and focused working groups, the executive panel developed its findings and recommendations for further research. The most significant recommendations for research are summarized in the following paragraphs and represent areas that are high priority for research in the near-term.

PRIORITY RECOMMENDATIONS FOR RESEARCH

Fundamental Knowledge Gaps

- Determine the operational readiness impacts of tinnitus in the military.
- Enhance and utilize the DOEHS and other medical databases/registries to standardize and obtain the data needed for the conduct of research studies. It is anticipated that policy and regulation issues would need to be addressed.
- Conduct a large-scale longitudinal study of blast-exposed and non-blast-exposed military personnel and veterans to gain insight on tinnitus onset factors and tinnitus progression.
- Determine if there are key markers for predicting an individual's susceptibility for developing tinnitus, both before and following injury. Included in this is the need to develop appropriate animal models.
- Evaluate the potential relationships between tinnitus and other cognitive and psychological disorders.
- Continue to elucidate the mechanisms and contributing factors associated with tinnitus onset and progression to chronic tinnitus.
- Enhance existing and develop additional animal and experimental models/apparatus to support the study of tinnitus, including blast and traumatic brain injury, tinnitus distress measures, and blast shock tube exposure.

Applied Research and Technology Development

- Identify candidate pharmacologic strategies for early interventions to prevent the cascade of damage to the cochlea and brain from leading to hearing loss and tinnitus.
- Develop new and improved imaging techniques to identify functional and structural changes to diagnose and characterize tinnitus.
- Develop improved tools and measures to assess tinnitus loudness, changes in tinnitus, and an individual's reaction to tinnitus.
- Develop tools for the objective diagnosis and characterization of tinnitus.

³¹Elgoyhen et al. *Biochem Pharmacol.* 2009 Oct 1;78(7):712-9.

Clinical Research

- Develop standard protocols and measures for conducting tinnitus-related clinical studies.
- Characterize the performance of existing technologies and modalities, alone and in combination, to diagnose and characterize tinnitus and possible subtypes.
- Conduct well-designed human studies of existing and novel therapies for preventing and treating hearing loss and tinnitus. This would include new uses for existing drugs; nutritional and pharmaceutical-based strategies; and acoustic, electrical, and other stimulation technologies.

RECOMMENDATIONS FOR CURRENT MEDICAL CAPABILITIES

- Develop a centralized education and outreach center to serve both clinicians and patients to support improving care models.
- Establish standardized DoD and VA clinical practice guidelines and information sources for the diagnosis and treatment of tinnitus using currently available technologies and practices; and adjust these guidelines as new technologies and practices are developed and validated.

CONCLUSION

The International State-of-the-Science Meeting on Blast-Induced Tinnitus reviewed current knowledge regarding the cause, diagnosis, and treatment of tinnitus and identified research gaps for further investigation. The meeting also served to foster collaboration among researchers and inform DoD research investment strategies. Continued research and development are needed to resolve key barriers in the ability to effectively diagnose and treat tinnitus, and thereby reduce the impact of tinnitus on the DoD and VA.

APPENDICES

- A. Meeting Planning Committee
- B. Meeting Participants
- C. Meeting Agenda
- D. Welcome Letter
- E. DoD Blast Injury Research Program Coordinating Office Contact Information

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Dr. Patricia Dorn	Headquarters VA Washington, DC
LTC Marjorie Grantham	U.S. Army Public Health Command Aberdeen Proving Ground, Maryland
Dr. Caton Harris	Branch Medical Clinic Marine Corps Air Station Miramar
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Appendix C – Meeting Agenda

Links to copies of the presentations and posters presented during the meeting are posted on the DoD Blast Injury Research Program web site at https://blastinjuryresearch.amedd.army.mil/docs/sos_tinnitus/SoS_Tinnitus_Presentations.pdf.

Tuesday, 15 November 2011

Time	Schedule	Presenter
7:00	Registration	
8:00	Introduction	Mr. Michael Leggieri, Jr.
8:15	Office of the Chairman, Joint Chiefs of Staff	MG Douglas Robb
8:30	U.S. Army Medical Research and Materiel Command (USAMRMC)	MG James Gilman
8:45	U.S. Department of Veterans Affairs	Dr. Lucille Beck
9:00	Hearing Center of Excellence	Lt Col Mark Packer
9:15	Military Operational Medicine Research Program Hearing Injury Prevention and Protection Research	Dr. Roy Vigneulle
9:30	Break	
Etiology:		
10:00	Implications of the latest dorsal cochlear nucleus model for blast injury tinnitus	Dr. Robert Levine
10:30	Tinnitus – a combination of noise trauma and damage to the medial prefrontal cortex	Dr. Josef Rauschecker
11:00	What brain centers are linked to tinnitus-induced distress? –An f-MRI study	Dr. Wolfgang Delb
11:30	Lunch	
12:30	Poster Session	
Diagnostics:		
1:30	Bilateral and contralateral OAE suppression testing in tinnitus patients	Dr. Paul Davis
2:00	Functional and Anatomical Neural Networks of Chronic Tinnitus and Hearing Loss	Dr. Fatima Husain
2:30	Prevalence and auditory effects of blast-related ear injury in Operation Iraqi Freedom	Dr. Erik Viirre
3:00	Break	
Treatment:		
3:30	The Tinnitus Retraining Therapy Trial (TRTT)	Dr. Craig Formby
4:00	A Major Multicenter Longitudinal Study of Tinnitus Rehabilitation for War Veterans	Dr. Paul Davis
4:30	Tinnitus Retraining Therapy for noise trauma-induced tinnitus	Dr. Pawel Jastreboff
5:00	Daily wrap-up	Lt Col Mark Packer

Wednesday, 16 November 2011

Time	Schedule	Presenter
7:30	<i>Registration</i>	
8:00	Administration and Goals for the Day	Mr. Michael Leggieri, Jr.
<i>TBI/PTSD-Related:</i>		
8:15	Tinnitus associated with blast-induced traumatic brain injury: Patterns and changes over time	Dr. Carey Balaban
9:15	Blast-induced tinnitus and its treatment strategies	Prof. Jinsheng Zhang
9:45	Bi-directional effects of tinnitus and PTSD	Dr. Marc Fagelson
10:15	Orientation to workgroups	Mr. Michael Leggieri, Jr.
10:30	<i>Break</i>	
10:45	Workgroups: 1. Adams 2. Hamilton 3. Jeffersonian IV 4. Jeffersonian VI 5. Washingtonian	Dr. Carol Bauer Dr. Pim van Dijk Dr. Anthony Cacace Dr. James Henry Dr. Berthold Langguth
12:00	<i>Lunch</i>	
1:00	Workgroups: (1), (2), (3), (4), (5)	
2:30	<i>Break & Return to Plenary Session</i>	
3:00	Brief Back: Workgroup 1	Dr. Carol Bauer
3:20	Brief Back: Workgroup 2	Dr. Pim van Dijk
3:40	Brief Back: Workgroup 3	Dr. Anthony Cacace
4:00	Brief Back: Workgroup 4	Dr. James Henry
4:20	Brief Back: Workgroup 5	Dr. Berthold Langguth
4:40	Wrap-up and Closing Remarks	Mr. Michael Leggieri, Jr.

Thursday, 17 November 2011
(Expert Panel & PCO Staff Only)

Time	Schedule	Presenter
8:00	Introduction	Dr. Richard Salvi
8:15	Executive Session	
10:00	<i>Break</i>	
10:30	Executive Session	
12:00	<i>Lunch</i>	
1:00	Executive Session	
2:30	Closing Remarks	Mr. Michael Leggieri, Jr.

Appendix D – Welcome Letter

Dear Colleague,

On behalf of the DoD Executive Agent for Medical Research for Prevention, Mitigation, and Treatment of Blast Injury, the U.S. Department of Veterans Affairs, and the DoD Hearing Center of Excellence, welcome to the third meeting in the International State-of-the-Science Meeting series. This meeting will focus on identifying what is known and what is unknown about blast-induced tinnitus. Approximately 105 subject matter experts have volunteered to participate in the meeting, and I look forward to the important work that we will accomplish. Scientific information gained from this meeting will be used to shape and guide future medical science and technology strategy.

Acoustic trauma is the most frequently observed injury in our warfighters returning from Afghanistan and Iraq. Not surprisingly, hearing loss and tinnitus are the respective 1 and 2 compensatory illnesses reported by the U.S. Department of Veterans Affairs. In 2005, Congress mandated that the Institute of Medicine (IOM) carry out a study assessing several issues related to noise-induced hearing loss and tinnitus associated with service in the Armed Forces since World War II. The IOM study recommended the Services improve the prevention of, and surveillance for, hearing loss and tinnitus. The DoD Hearing Center of Excellence identified tinnitus as a top research initiative in its organizational concept of operation plan due to the enormous effect tinnitus has on the warfighter and veteran populations.

During the meeting, experts from the scientific, medical, and operational communities will present their work and participate in working groups. Your participation will help achieve the objectives of the meeting that are to:

1. Identify the cause of tinnitus and determine its association, if any, with post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI).
2. Determine if there are existing diagnostic tools that can be used to objectively identify tinnitus.
3. Identify and prioritize the research gaps that exist in standardizing methods used in the treatment of tinnitus.

The key questions to be addressed during the meeting are:

1. What are the current theories concerning the neurobiological basis of tinnitus?
2. Is there substantial evidence that tinnitus is associated with PTSD and TBI. If so, what are the common biomarkers?
3. What are the current technological approaches to tinnitus diagnosis?
4. How can research standardize methods of effective tinnitus treatment?

Please accept my gratitude for your active participation in this meeting.

Michael J. Leggieri, Jr.
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