

Hyperacusis Alliance Background Information from Recent Grants and Publications

Group 1: Animal Model & Central Neural Function

Kelly Radziwon, University at Buffalo, Hyperacusis and Central Gain

The primary goal of my current research is to develop reliable animal behavioral models of hyperacusis. Using a combination of behavioral metrics to detect changes in loudness perception, sound aversion, and pain sensitivity in animals.

Senthilvelan Manohar, University at Buffalo, Behavioral Model of Loudness Intolerance

One of the critical requirements for understanding and finding a cure for hyperacusis is the development of animal models. I have developed two new animal behavior models to study the pain and annoyance components of hyperacusis. The Active Sound Avoidance Paradigm (ASAP) uses a mouse's innate aversion to a light open area and preference for a dark enclosed box. In the presence of intense noise, the animal shifts its preference to the light area. The Auditory Nociception Test (ANT) is based on a traditional pain threshold assessment. Although animals show an elevated pain threshold in the presence of 90 and 100 dB, at 110 and 115 dB they show a reduced pain tolerance. Using these two tests together will allow me to assess emotional reactions to sound as well as the neural interactions between auditory perception and pain sensation.

Long-Term Goal: To develop and establish a reliable behavioral model to understand the pain and annoyance aspects of hyperacusis and to use these behavioral models to identify the neural and molecular mechanisms underlying hyperacusis and tinnitus.

Guang Di Chen, University at Buffalo, High-Frequency Noise Trauma on Loudness Perception and the Mechanisms

We measured (a) loudness perception & (b) central neural activity in the same animals with high-frequency noise trauma. At the low-frequency in the normal hearing area, the noise-trauma resulted in hyperacusis and correspondingly the neural hyperactivity in the auditory cortex. At the high-frequency in the hearing-loss area, loudness recruitment was observed and the reduced central activity eventually caught up the normal level at high sound level.

Benjamin Auerbach, STATE UNIVERSITY OF NEW YORK AT BUFFALO, THE ROLE OF CENTRAL GAIN CONTROL IN HYPERACUSIS OF DIVERSE ORIGIN

Hyperacusis is a prevalent sensory disorder in which sounds of moderate intensity are perceived as intolerably loud or even painful. Despite the significant societal and economic impact of hyperacusis, treatments for this disorder are lacking. While hearing loss has been identified as the primary risk factor for hyperacusis, many other disorders are also associated with loudness intolerance, suggesting the causes of hyperacusis can be varied. Hyperacusis is particularly prevalent in several neurodevelopmental disorders, such as Williams Syndrome, Fragile X Syndrome (FX), and autism spectrum disorders (ASD). The aim of this proposal is to directly compare the mechanisms underlying hyperacusis of distinct origin to determine if there is a shared neural disruption that manifests as auditory hypersensitivity. Specifically, the proposed work will test the hypothesis that altered central gain control is a common pathophysiological mechanism in two distinct models of hyperacusis: long-term hearing loss and an animal model of FX, the leading inherited cause of ASD. A combination of electrophysiological and behavioral measures will be used to characterize the relationship between central auditory hyperactivity and hyperacusis-like behavior in these models to:

- determine the neural correlates of hyperacusis due to hearing loss;
- characterize hyperacusis and the potential neural correlates in an animal model of FX; and
- identify drugs that may ameliorate measures of hyperacusis in both hearing loss and FX models. Understanding how these distinct forms of hyperacusis are similar and/or different will provide both clinical and basic science insights relevant to understanding and treating hyperacusis."

Group 1 (continued): Animal Model & Central Neural Function

Richard Salvi, STATE UNIVERSITY OF NEW YORK AT BUFFALO, NEURAL BASIS OF HYPERACUSIS

Intense noise exposure and ototoxic drugs cause hearing loss and reduce the neural output of the cochlea. Paradoxically, cochlear damage often enhances neural activity in the central auditory pathway at suprathreshold intensities. This compensatory increase in the central auditory pathway is referred to as Enhanced Central Gain. Enhanced Central Gain is believed to be responsible for hyperacusis (loudness intolerance) and tinnitus. The goal of this project is to experimentally test the Central Gain model to determine if it can account for hyperacusis and tinnitus induced by ototoxic drugs or intense noise exposure. To accomplish this, we will determine if the temporal and spectral properties of noise-induced or drug-induced hyperacusis match time course and spectral features of the electrophysiological metric of increased central gain in auditory cortex (AC), medial geniculate body (MGB), lateral amygdala and inferior colliculus (IC). We will also determine if the time course of noise-induced or drug-induced tinnitus is correlated with the time course and spectral features of hyperacusis and increased central gain in the AC, MGB, LA or IC. Since hyperexcitability disorders can be controlled by drugs that regulate potassium channel permeability, we will test the hypothesis that potassium channel modulators can suppress noise- or drug-induced hyperacusis and enhanced central gain. The proposed studies are designed to increase our understanding of the neural mechanisms of hyperacusis and tinnitus and test the efficacy of novel pharmacological agents to treat these two disorders.

Richard Salvi, STATE UNIVERSITY OF NEW YORK AT BUFFALO, HYPERACUSIS AND CENTRAL GAIN

The goals of this project are:

- Determine if Enhanced Central Gain is responsible for the temporal and spectral features of hyperacusis,
- Determine how the acoustic environment (sound enrichment/deprivation) modulates hyperacusis/loudness growth and Central Gain
- Determine how serotonin and GABA agonists/antagonists affect hyperacusis and Central Gain. The proposed studies will increase our understanding of the neural mechanisms of hyperacusis and test the efficacy of pharmacological agents to treat hyperacusis."

Jim Kaltenbach, The Cleveland Clinic, Paper: Attenuation of noise-induced hyperactivity in the dorsal cochlear nucleus by pre-treatment with MK-801.

It has previously been hypothesized that hyperactivity of central auditory neurons following exposure to intense noise is a consequence of synaptic alterations. Recent studies suggest the involvement of NMDA receptors in the induction of this hyperactive state. NMDA receptors can mediate long term changes in the excitability of neurons through their involvement in excitotoxic injury and long term potentiation and depression. In this study, we examined the effect of administering an NMDA receptor blocker on the induction of hyperactivity in the dorsal cochlear nucleus (DCN) following intense sound exposure. Our prediction was that if hyperactivity induced by intense sound exposure is dependent on NMDA receptors, then blocking these receptors by administering an NMDA receptor antagonist just before animals are exposed to intense sound should reduce the degree of hyperactivity that subsequently emerges. We compared the levels of hyperactivity that develop in the DCN after intense sound exposure to activity recorded in control animals that were not sound exposed. One group of animals to be sound exposed received intraperitoneal injection of MK-801 twenty minutes preceding the sound exposure, while the other group received injection of saline. Recordings performed in the DCN 26-28 days post-exposure revealed increased response thresholds and widespread increases in spontaneous activity in the saline-treated animals that had been sound exposed, consistent with earlier studies. The animals treated with MK-801 preceding sound exposure showed similarly elevated thresholds but an attenuation of hyperactivity in the DCN; the attenuation was most robust in the high frequency half of the DCN, but lower levels of hyperactivity were also found in the low frequency half. These findings suggest that NMDA receptors are an important component of the hyperactivity-inducing mechanism following intense sound exposure. They further suggest that blockade of NMDA receptors may offer a useful therapeutic approach to preventing induction of noise-induced hyperactivity-related hearing disorders, such as tinnitus and hyperacusis.

Group 1 (continued): Animal Model & Central Neural Function

Jennifer Resnik, Massachusetts Eye and Ear, Harvard Medical School, Homeostatic modifications in cortical GABA circuits enable states of hyperexcitability and reduced sound level tolerance after auditory nerve degeneration

Sensorineural hearing loss due to noise exposure, aging, ototoxic drugs, or certain diseases reduce the neural activity transmitted from the cochlea to the central auditory system. These types of hearing loss often give rise to hyperacusis, an auditory hypersensitivity disorder in which low- to moderate-intensity sounds are perceived as intolerably loud or even painful. Previously thought as originating in the damaged ear, hyperacusis is emerging as a complex disorder. While it can be triggered by a peripheral injury, it develops from a maladaptation of the central auditory system to the peripheral dysfunction. My research will test the hypothesis that the recovery of sound detection and speech comprehension, may cause an overcompensation that leads to an increase in sound sensitivity and reduced tolerance of moderately loud sounds.

This hypothesis will be tested using a combination of chronic single unit recordings, operant behavioral methods and optogenetic interrogation of specific sub-classes of cortical interneurons. By understanding how brain plasticity is modulated, we will gain deeper insight into the neuronal mechanism underlying aberrant sound processing and its potential reversal.

Long-Term Goal: To better understand the paradoxical role of central auditory system plasticity as both the cause of—and treatment for—the perceptual consequences of hearing loss. A major step to reach this goal is to understand the compensatory mechanisms, following cochlear damage, that allow for basic sound recovery while potentially introducing hypersensitivity and causing chronic sensory impairments such as hyperacusis.

Larry Roberts, McMaster University, Paper: Neural plasticity and its initiating conditions in tinnitus

BACKGROUND AND OBJECTIVE: Deafferentation caused by cochlear pathology (which can be hidden from the audiogram) activates forms of neural plasticity in auditory pathways, generating tinnitus and its associated conditions including hyperacusis. This article discusses tinnitus mechanisms and suggests how these mechanisms may relate to those involved in normal auditory information processing.

MATERIALS AND METHODS: Research findings from animal models of tinnitus and from electromagnetic imaging of tinnitus patients are reviewed which pertain to the role of deafferentation and neural plasticity in tinnitus and hyperacusis.

RESULTS: Auditory neurons compensate for deafferentation by increasing their input/output functions (gain) at multiple levels of the auditory system. Forms of homeostatic plasticity are believed to be responsible for this neural change, which increases the spontaneous and driven activity of neurons in central auditory structures in animals expressing behavioral evidence of tinnitus. Another tinnitus correlate, increased neural synchrony among the affected neurons, is forged by spike-timing-dependent neural plasticity in auditory pathways. Slow oscillations generated by bursting thalamic neurons verified in tinnitus animals appear to modulate neural plasticity in the cortex, integrating tinnitus neural activity with information in brain regions supporting memory, emotion, and consciousness which exhibit increased metabolic activity in tinnitus patients.

DISCUSSION AND CONCLUSION: The latter process may be induced by transient auditory events in normal processing but it persists in tinnitus, driven by phantom signals from the auditory pathway. Several tinnitus therapies attempt to suppress tinnitus through plasticity, but repeated sessions will likely be needed to prevent tinnitus activity from returning owing to deafferentation as its initiating condition.

Group 2: Cochlea & Central Neural Function

Adam Shephard, University at Buffalo, Low-level Noise and Central Gain (SYNAPTOPATHY AND NEURAL GAIN FOLLOWING LOW-LEVEL NOISE EXPOSURE)

Determine if low-level noise inhibits neural responses to noise at the level of the Auditory Midbrain.

Paul Fuchs, Johns Hopkins University, Excitability and Synaptic Function of Type II Cochlear Afferents

Determine the responsiveness; signaling and pharmacology of type II cochlear afferents that have until recently been entirely mysterious.

- By intracellular recording from type II afferents in cochlear segment, an anatomically-correct, compartmental model will be built to estimate of the acoustic stimulus required to activate the type II afferent. To explore further a possible role in cochlear trauma, type II recordings will be made in cochleae that have been damaged by loud sound and/or exposure to ototoxins.
- Auditory pathogenesis may result from an altered balance of activity between small type II; and large type I afferents; by analogy to neuropathic pain in the somatic nervous system; thus providing the type II afferent as a novel therapeutic target."

Paul Fuchs, Johns Hopkins University, TYPE II AFFERENTS AND COCHLEAR DAMAGE

Test the hypothesis that type II afferents serve as cochlear nociceptors. From the complaint of hyperacusis after hearing loss, we will examine the structure and function of type II afferents in normal and post trauma cochleas. The hypothesis is that painful hyperacusis, noxacusis, includes hyperactivity of type II afferents. Thus we will examine type II structure and function in normal and post trauma cochleas of rats and mice. In parallel we will investigate the properties of surviving outer hair cells in post trauma cochleas. Our methods include: ex vivo electrophysiology, light and electron microscopy, utilization of optogenetic and chemogenetic tools, and validation and quantification of mouse models in which type II specific bio markers are expressed We will compare damaging sound, ototoxic antibiotics and genetically encoded biotoxins to produce experimentally tractable effects on tissue for ex vivo experiments. The properties and synaptic connections of type II afferents and outer hair cells will be examined in the excised cochlear tissue of these animals. We will continue to explore type II specific genetic mouse models. Genetically encoded reporter proteins, voltage and calcium sensitive indicators, biotoxins, and opto and chemo genetic modulators have become informative tools in neurobiology. With such transgenic models it becomes possible to study innervation patterns by expression of fluorescent reporter proteins, and to activate, eliminate, or modulate type II activity for anatomical and physiological studies. Cre dependent expression of genetically modified G protein coupled receptors (DREADDS) will provide mice in which type II activity can be increased or decreased by injection of a novel synthetic ligand, depending on the specific construct. Varying combinations of systemic and round window drug delivery will be employed to increase the specificity of experimental manipulations. The goal of this program is to complete the description of type II afferent and the hypothesis that these serve as cochlear nociceptors. If correct these are a likely neurobiological substrate for noxacusis (painful hyperacusis).

Catherine Weisz, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS, SYNAPTIC CIRCUITRY OF AUDITORY NEURONS

Two major research aims: 1) Intrinsic electrical properties and synaptic inputs of medial olivocochlear (MOC) neurons in the brainstem, and 2) Influence of synaptic outputs of MOC neurons in the cochlea.

- Aim 1: Synaptic inputs of olivocochlear neurons in the brainstem and synaptic outputs in the cochlea Medial olivocochlear (MOC) neurons have cell bodies in the brainstem, where they receive synaptic inputs conveying sound information from the cochlea via the cochlear nucleus. We aim to understand how the MOC neurons are activated, modulated, and how their properties may contribute to neuronal hyperactivity that has shown to occur with tinnitus or hyperacusis. By using a computational model of MOC neurons, we investigate the role of hyperpolarization activated current I_h in affecting synaptic integration in MOC neurons.
- Aim 2: Investigating synaptic inputs to MOC neurons in brainstem slices from mice. The experiments will elucidate the mechanisms of synaptic activation and inhibition of MOC neurons, which drives their inhibition of mechanical

Group 2 (continued): Cochlea & Central Neural Function

activity in the cochlea. Synaptic outputs of olivocochlear neurons in the cochlea project to the cochlea, where they decrease the movement of the basilar membrane by inhibiting cochlear OHCs. OHC activity enhances signaling to cochlear IHCs & shapes cochlear tuning curves & gain. MOC synapses onto OHCs are implicated in inhibiting OHC via coupling of cholinergic channel coupling to an SK potassium conductance. This enable improved hearing in background noise, and protection of the cochlea from sound trauma. MOC neurons are also thought to release other neuro-transmitters in the cochlea. The medial olivocochlear system, a component of the final stage of the descending auditory system may have altered activity in tinnitus & hyperacusis. Working with Dr. Seal of Pittsburgh, we developed a mouse line that will provide better control of afferent signaling through type II spiral ganglion afferent neurons. Working with Dr. Tracy Fitzgerald, we will test the function of the MOC system. These experiments will elucidate the pathways through which the MOC reflex is activated, distinguishing between inputs from type I vs type II spiral ganglion afferents. DPOAE will test OHC function. The change in DPOAE strength by contralateral suppression, a measure of MOC activity, will be used to assess the MOC function. This will determine whether type II spiral ganglion afferent neurons contribute to or modulate the MOC reflex. VGLUTs in OHCs, and the central innervation patterns of type II cochlear afferent neurons. Working with Dr. Rebecca Seal at the University of Pittsburgh, we developed mutant mice lacking the VGLUTs from either inner hair cells (IHC) or OHC, or both. Use of these mutant mice allows isolation of afferent signaling by either type of hair cell, in order to determine the unique contribution that each pathway makes to perception of sound."

Charles Liberman, MASSACHUSETTS EYE AND EAR INFIRMARY, SINGLE-NEURON MARKING IN THE STUDY OF ABNORMAL COCHLEAS (Selective low-SR fiber loss role in hyperacusis, tinnitus and hyperactivity in central circuits.)

Preliminary results suggest neuropathy is elicited by moderate-level exposure (84 dB SPL), especially in the absence of olivocochlear (OC) feedback, and that selective low-SR fiber loss may lead to hyperacusis, tinnitus and hyperactivity in central circuits. Recent human studies also suggest that low-SR neuropathy may be associated with tinnitus; and AN masking studies in animals suggest it should contribute to difficulties hearing in a noisy background. We pursue these issues, from cochlea to colliculus and from mouse to human, in 5 Aims:

- Aim 1 uses the confocal to examine AN/IHC synapses in humans to ask whether the low/high SR dichotomy is present in our ears and to quantify primary neuropathy in the aging ear.
- Aim 2 is a neurophysiological study of masking in the AN of noise-damaged ears designed to assess the impact of low-SR neuropathy on coding of signals in noise and to develop an ABR-based assay to diagnose the loss of low-SR fibers.
- Aim 3 uses tract-tracing techniques to examine the central projections of low-SR fibers, to test the hypothesis that they represent the major ascending input to OC reflex circuitry.
- Aim 4 uses selective OC lesions to test the hypothesis that a major role of the OC system is to minimize primary neuropathy in everyday acoustic environments.
- Aim 5 combines neurophysiological studies of the inferior colliculus with behavioral measures based on the acoustic startle responses to test the hypothesis that low-SR neuropathy leads to central hyperactivity, hyperacusis and tinnitus.

Group 2 (continued): Cochlea & Central Neural Function

CJ Plack, The University of Manchester,

The physiological bases and perceptual consequences of 'hidden' noise-induced hearing loss

Hidden loss may also be associated with tinnitus and hyperacusis. Together, these deficits lead to a reduced quality of life for the individuals concerned. It is vital that we understand the mechanisms and consequences of hidden hearing loss so that we can:

- Adequately assess hearing ability, and provide appropriate treatments
- Identify at-risk individuals and provide personalised healthcare advice to prevent further damage
- Re-evaluate EU noise-exposure regulations Our proposal is far-reaching and multidisciplinary, combining animal histology, neurophysiology, electrophysiology, and psychophysics, with human electrophysiology, psychophysics, and neuroimaging.

By using overlapping methodologies across the animal and human experiments, it will be possible to make inferences regarding the physiological bases of noise-induced damage in the human auditory system; information that will be vital for the diagnosis and treatment of hidden hearing loss. The animal noise-exposure experiments will also be invaluable in the determination of safe noise levels for humans."

US Wilson, JT Lichtenhan, Washington University, Efferent inhibition strength is a physiological correlate of hyperacusis in children with autism spectrum disorder

Autism spectrum disorder (ASD) is a developmental disability that is poorly understood. Children with ASD often have sensory hypersensitivities, including auditory hypersensitivity (hyperacusis). In adults with hyperacusis who are otherwise neurotypical, the medial olivocochlear (MOC) efferent reflex is stronger than usual. In children with ASD, the MOC reflex has been measured, but without also assessing hyperacusis.

We assessed the MOC reflex in children with ASD by measuring the strength of MOC-induced inhibition of transient-evoked otoacoustic emissions (TEOAEs), a noninvasive physiological measure that reflects cochlear amplification. MOC activity was evoked by contralateral noise. Hyperacusis was assessed subjectively on the basis of the children's symptoms. We found a significant correlation between hyperacusis scores and MOC strength in children with ASD. When children were divided into ASD-with-severe-hyperacusis (ASDs), ASD-with-not-severe-hyperacusis (ASDns), and neurotypical (NT) groups, the last two groups had similar hyperacusis and MOC reflexes, whereas the ASDs group, on average, had hyperacusis and MOC reflexes that were approximately twice as strong. The MOC inhibition of TEOAEs averaged larger at all frequencies in the ASDs compared with ASDns and NT groups. The results suggest that the MOC reflex can be used to estimate hyperacusis in children with ASD and might be used to validate future questionnaires to assess hyperacusis. Our results also provide evidence that strong MOC reflexes in children with ASD are associated with hyperacusis and that hyperacusis is a comorbid condition and is not a necessary, integral part of the abnormal neural processing associated with ASD.

NEW & NOTEWORTHY Children with autism spectrum disorder (ASD) are a heterogeneous group, some with hyperacusis and some without. Our research shows that hyperacusis can be estimated in children with ASD by using medial olivocochlear (MOC) reflex measurements. By establishing that an objective measure correlates with attributes of hyperacusis, our results enable future work to enable subtyping of children with ASD to provide improved individualized treatments to at-risk children and those without adequate language to describe their hyperacusis symptoms."

Group 3: Peripheral Function & Literature Review

Xiyang Guan, Massachusetts Eye and Ear, Harvard Medical School

Hyperacusis caused by abnormalities in auditory mechanics

To understand how mechanical disturbances in the ear result in hypersensitive hearing.

- Superior canal dehiscence (SCD) results in increased cochlear input drive for bone conducted (BC) sound.
- Abnormal middle ear can cause bone conduction hyperacusis.
- Assess the efficacy of the round window reinforcement as a treatment to hyperacusis.

Damien Ponsot, Phillipe Fournier, Académie de Lyon, Lycée Germaine Tillion. France,

Paper: A Brief Review of the Anatomy, Physiology and Function of the tensor tympani muscle

The middle ear is composed of two small skeletal muscles that play an important role in controlling the movement of the tympano-ossicular chain: the stapedian muscle and the tensor tympani muscle. Of the two middle ear muscles, the tensor tympani muscle has been the subject of few in-depth studies on its function in the auditory system. Recently, its putative involvement has been cited in pathologies such as acoustic shock and temporomandibular joint disorders. Klockhoff has associated phenomena of tonic contraction of the TTM with a tonic tensor tympani syndrome (TTTS) that causes many symptoms: feeling of fullness in the ear, otalgia, tinnitus, dysacusis, tension headaches and dizziness. This brief review reviews the state of knowledge about this muscle.

Peter Drummand, Murdoch University, Western Australia,

Paper: Hyperacusis in chronic pain: neural interactions between the auditory and nociceptive systems

Objective: Sensory disturbances are common in chronic pain patients. Hyperacusis can be an especially debilitating experience. Here, we review published work on how the auditory and nociceptive systems might interact in chronic pain syndromes to produce pain-hyperacusis.

Design: Literature review. Study sample: The PubMed and Scopus databases were searched for relevant articles published between 2000 & 2017 using the primary search terms “hyperacusis”/“hyperacousis” and “pain”. Ten papers were found using this strategy.

Results: The importance of central mechanisms in pain-hyperacusis was highlighted in the 10 selected papers.

Hyperacusis is a significant but under-recognised symptom in conditions such as complex regional pain syndrome and fibromyalgia, and an integral feature of migraine.

Conclusions: Nociceptive circuits become hypersensitive in acute and chronic pain; this sensitivity spreads from the periphery to spinal neurons and higher centres in the brain, leading to hyperalgesia or spontaneous pain even in the absence of peripheral nociceptive input. This “central sensitisation” may alter activity at sensory convergence points in the thalamus and brainstem centres such as the locus coeruleus, and give rise to hyperacusis in certain pain syndromes.

David Baguley, University of Nottingham, Paper: Clinical Interventions for Hyperacusis in Adults: A Scoping Review to Assess the Current Position and Determine Priorities for Research

Background: There is no universally accepted definition for hyperacusis, but in general it is characterised by decreased sound tolerance to ordinary environmental sounds. Despite hyperacusis being prevalent and having significant clinical implications, much remains unknown about current management strategies.

Purpose: To establish the current position of research on hyperacusis and identify research gaps to direct future research.

Design and Sample: Using an established methodological framework, electronic and manual searches of databases and journals identified 43 records that met our inclusion criteria. Incorporating content and thematic analysis approaches, the definitions of hyperacusis, management strategies, and outcome measures were catalogued.

Results: Only 67% of the studies provided a definition of hyperacusis, such as “reduced tolerance” or “oversensitivity to sound.” Assessments and outcome measures included Loudness Discomfort Levels, the Hyperacusis Questionnaire, and Tinnitus Retraining Therapy (TRT) interview. Management strategies reported were Cognitive Behavioural Therapy, TRT, devices, pharmacological therapy, and surgery.

Group 3 (continued): Peripheral Function & Literature Review

Conclusions: Management strategies were typically evaluated in patients reporting hyperacusis as a secondary complaint or as part of a symptom set. As such the outcomes reported only provided an indication of their effectiveness for hyperacusis. Randomised Controlled Trials are needed to evaluate the effectiveness of management strategies for patients experiencing hyperacusis."

Derick Hoare, University of Nottingham, Priority Setting Partnership to identify treatment uncertainties for hyperacusis

Initiate a James Lind Alliance (JLA) Priority Setting Partnership (PSP) to identify and prioritise unanswered research questions on hyperacusis. The method aims to identify questions which are of direct relevance to patients and clinicians, and to change how research funding is allocated as a consequence. Using standard JLA methodology, the research team will convene a steering group to initiate and promote the project, open an online survey to all clinicians, patients and the public asking them to nominate hyperacusis research uncertainties, process the responses and survey clinicians, patients and the public on the relative importance of the unanswered questions identified, before finalising the Top 10 Priorities. These priorities will be turned into research questions and disseminated widely. The grant will enable the research team to work with people who are or have been affected by hyperacusis, with clinicians, representatives from professional bodies, learned societies, and third sector organisations/support groups, to identify and prioritise uncertainties about the prevention, diagnosis, and treatment of hyperacusis. The main outcome of this activity will be the Top 10 priority research questions in hyperacusis agreed by consensus

J. Berger, University of Nottingham, Effects of the cannabinoid CB1 agonist ACEA on salicylate ototoxicity, hyperacusis and tinnitus in guinea pigs.

Cannabinoids have been suggested as a therapeutic target for a variety of brain disorders. Despite the presence of their receptors throughout the auditory system, little is known about how cannabinoids affect auditory function. We sought to determine whether administration of arachidonyl-2'-chloroethylamide (ACEA), a highly-selective CB1 agonist, could attenuate a variety of auditory effects caused by prior administration of salicylate, and potentially treat tinnitus. We recorded cortical resting-state activity, auditory-evoked cortical activity and auditory brainstem responses (ABRs), from chronically-implanted awake guinea pigs, before and after salicylate + ACEA. Salicylate-induced reductions in click-evoked ABR amplitudes were smaller in the presence of ACEA, suggesting that the ototoxic effects of salicylate were less severe. ACEA also abolished salicylate-induced changes in cortical alpha band (6-10 Hz) oscillatory activity. However, salicylate-induced increases in cortical evoked activity (suggestive of the presence of hyperacusis) were still present with salicylate + ACEA. ACEA administered alone did not induce significant changes in either ABR amplitudes or oscillatory activity, but did increase cortical evoked potentials. Furthermore, in two separate groups of non-implanted animals, we found no evidence that ACEA could reverse behavioural identification of salicylate- or noise-induced tinnitus. Together, these data suggest that while ACEA may be potentially otoprotective, selective CB1 agonists are not effective in diminishing the presence of tinnitus or hyperacusis.

Group 4: Diagnostic Assessments & Clinical Options

Sarah M. Theodoroff, NCRAR Investigator, OHSU, A New Approach to Diagnosing Hyperacusis

- Long-term goal: Develop an effective paradigm to diagnose and assess hyperacusis
- Primary aim of current work: Develop multi-dimensional framework and identify sensitive behavioral & physiological metrics
- Help resolve a barrier that exists regarding defining hyperacusis based on where dysfunction might be present
- No “gold standard test” to diagnose hyperacusis: Framework concept to find a better approach to evaluate sound tolerance problems”

Naomi Bramhal, PORTLAND VA MEDICAL CENTER

UNCOVERING PHYSIOLOGICAL MARKERS OF HIDDEN HEARING LOSS

Synaptic loss may be associated with tinnitus and hyperacusis. But ,synaptic loss can exist even when auditory thresholds are normal, making it difficult to detect. There is a need to identify individuals suffering from noise-induced cochlear synaptic degeneration. Individuals with a significant history of noise exposure should show physiological differences in the auditory nerve, brainstem, and cortex when compared to individuals with less noise exposure which may be associated with hyperacusis and tinnitus. Preliminary data shows differences in the amplitude of wave I of the auditory brainstem response (a measure of the synchronous firing of the auditory nerve) between individuals with differing levels of noise exposure. Research suggests that noise exposure and tinnitus/hyperacusis may be associated with additional changes in auditory physiology. The rationale is that identification of physiological markers of hidden hearing loss and the resulting perceptual changes will facilitate the development of methods for preventing or treating this condition. Four specific aims:

- 1) Identify envelope following response (a measure of the brainstem's ability to phase-lock to the envelope of a stimulus) abnormalities present in Veterans with normal pure tone thresholds & high levels of noise exposure
- 2) Identify elements of the middle & late latency responses (auditory evoked potentials generated by the cortex) that differentiate noise-exposed Veterans with normal auditory thresholds from those with less noise exposure
- 3) Evaluate Veterans with high noise exposure and normal pure tone thresholds for differences in contralateral suppression of distortion product otoacoustic emissions (a measure of the strength of the medialolivocochlear efferent feedback pathway)
- 4) Investigate the relationship between hyperacusis & tinnitus and the physiological measures described in aims 1-

Martin Feeney, PORTLAND VA MEDICAL CENTER, NATIONAL CENTER FOR REHABILITATIVE AUDITORY RESEARCH

The National Center for Rehabilitative Auditory Research (NCRAR) funds infrastructure that supports core investigators. Further development is planned for NCRAR's OtoID, a patent-pending high-frequency portable audiometer, and for an upgrade to a recently patented Tinnitus Evaluation System, which will be used in a study to standardize tinnitus evaluation. Some RELEVANT examples of studies planned:

- Diagnosis and Assessment 1) standardization of assessment for tinnitus and hyperacusis; 3)clinical assessment of central auditory deficits resulting from blast exposure, traumatic brain injury (TBI), and their interaction with post-traumatic stress disorder; 4) new physiologic and behavioral methods to identify hidden hearing loss resulting from noise exposure; 7) use of behavioral methods to assess the effects of imprecise temporal processing and reduced frequency selectivity associated with sensorineural hearing loss.
- Rehabilitation 1) refinement of Progressive Tinnitus Management (PTM) as a stepped-care program that combines acoustic therapy and Cognitive-Behavioral Therapy. In collaboration with Health Services Research and Development (HSR&D) and researchers at the VAPORHCS, PTM will be readied for implementation throughout VA; 2) a multi-center clinical trial of repetitive transcranial magnetic stimulation(rTMS) for the relief of tinnitus, along with efforts to identify best methods for magnet placement.

Group 4 (continued): Diagnostic Assessments & Clinical Options

- Prevention 1) continuation of an epidemiology study on noise induced hearing loss and tinnitus in recently discharged Veterans with the goal of developing algorithms for predicting risk of tinnitus and hearing loss.

Stéphane Maison, MASSACHUSETTS EYE AND EAR INFIRMARY, NEURAL PATHOPHYSIOLOGY AND SUPRATHRESHOLD PROCESSING IN YOUNG ADULTS WITH NORMAL THRESHOLDS

Extend our pilot study into large-scale cross-sectional (Aim 1) and longitudinal I (Aim 2) studies of hidden hearing loss in college students with normal audiometric thresholds and widely differing lifestyles.

- Aim 1: Test the hypotheses that hidden hearing loss, defined as performance deficits on difficult word-recognition tasks, is correlated with physiologic response deficits consistent with cochlear synaptopathy and with lifetime noise dose. A statistical model will test the correlation of these outcomes with noise-exposure history and with a battery of physiological or psychophysical measures chosen to probe different stages of auditory processing, i.e. distortion product otoacoustic emissions and high-frequency audiometry, SP/AP ratio and envelope following responses to tones at high modulation frequencies, middle ear muscle or medial olivocochlear reflexes, several variants of frequency following response probing monaural and binaural temporal fine-structure processing, a temporal integration test of theories on stochastic undersampling in cochlear synaptopathy, and tinnitus severity/handicap and loudness discomfort level/hyperacusis. Using principal components analysis, cluster analysis and adaptive LASSO, we will find the test combination that best predicts the outcome measures and assess the relative contributions of peripheral vs. central pathophysiology to performance deficits.
- Aim 2: Test the hypothesis that hidden hearing loss progresses in young adults with regular and continued acoustic over exposure by tracking a cohort of students over the five-year period of this project using the above test battery

S Yilmaz, Trakya University, Edirne, Turkey,

Assessment of Reduced Tolerance to Sound (Hyperacusis) in University Students.

Hyperacusis is defined as a reduction in tolerance to ordinary environmental sounds. Although there is no objective test to accurately diagnose hyperacusis, questionnaires are useful for the assessment of hyperacusis. The aim of this study was to explore the reduced sound tolerance in university students using a hyperacusis questionnaire (HQ).

MATERIALS AND METHODS: A total of 536 university students (300 females and 236 males) aged between 18 and 25 years, with a mean age of 21.34 ± 1.87 years, were assessed using an HQ developed by Khalfa. The mean total score of all the participants was 16.34 ± 7.91 , and 5.78% of the participants had total scores indicating hyperacusis, where a majority of them were females.

RESULTS: Females had significantly higher scores than men in terms of both the total and the attentional and emotional dimensions. The scores of the participants who reported noise exposure or a decrease in their tolerance to noise were significantly higher than those of the other participants. Even among young adults, there was a group of participants suffering from some problems related to decreased tolerance to everyday sounds.

DISCUSSION: Although the Turkish translation of the HQ seems to be a reliable tool for evaluating hyperacusis in young adults, further work with various populations of different age groups is required to establish validity and to assess the psychometric qualities of the Turkish form"

M. Ralli, Richard Salvi, University of Rome, Rome, Italy, University at Buffalo, Characteristics of somatic tinnitus patients with and without hyperacusis

OBJECTIVE: Determine if somatic tinnitus patients with hyperacusis have different characteristics from those without hyperacusis.

PATIENTS AND METHODS: 172 somatic tinnitus patients with ($n = 82$) and without ($n = 90$) hyperacusis referred to the Tinnitus Unit of Sapienza University of Rome between June 2012 and June 2016 were compared for demographic characteristics, tinnitus features, self-administered questionnaire scores, nature of somatic modulation and history.

Group 4 (continued): Diagnostic Assessments & Clinical Options

RESULTS: Compared to those without hyperacusis, patients with somatic tinnitus and hyperacusis: (a) were older (43.38 vs 39.12 years, $p = 0.05$), (b) were more likely to have bilateral tinnitus (67.08% vs 55.56%, $p = 0.04$), (c) had a higher prevalence of somatic modulation of tinnitus (53.65% vs 36.66%, $p = 0.02$) and (d) scored significantly worse on tinnitus annoyance (39.34 vs 22.81, $p < 0.001$) and subjective hearing level (8.04 vs 1.83, $p < 0.001$).

CONCLUSION: Our study shows significantly higher tinnitus modulation and worse self-rating of tinnitus and hearing ability in somatic tinnitus patients with hyperacusis versus somatic tinnitus patients without hyperacusis. These differences could prove useful in developing a better understanding of the pathophysiology and establishing a course of treatment for these two groups of patients"

H. Aazh, Brian Moore, Royal Surrey County Hospital, UK, University of Cambridge, UK, Incidence of Discomfort During Pure-Tone Audiometry and Measurement of Uncomfortable Loudness Levels Among People Seeking Help for Tinnitus and/or Hyperacusis.

Purpose: The aim of this study was to assess the proportion of patients seen in a tinnitus and hyperacusis therapy clinic for whom presentation levels based on the British Society of Audiology (BSA)-recommended procedures for pure-tone audiometry and determination of uncomfortable loudness levels (ULLs) exceed ULLs, leading to discomfort during administration of these procedures.

Method: This was a retrospective cross-sectional study of 362 consecutive patients who attended a National Health Service audiology clinic for tinnitus and/or hyperacusis rehabilitation.

Results: For 21% of the patients, presentation levels based on the BSA procedure for pure-tone audiometry exceeded the ULL for at least 1 of the measured frequencies (excluding the first frequency tested, 1 kHz): 0.25, 0.5, 2, 3, 4, 6, and 8 kHz. For 24% of patients, the starting presentation level of 60 dB hearing level recommended for determination of ULLs exceeded the ULL for at least 1 frequency.

Conclusion: The starting presentation levels used for pure-tone audiometry and measurement of ULLs should be lower than those recommended by the BSA for people with tinnitus and hyperacusis."

Ann Hoffman, UC Los Angeles,

CONTRIBUTIONS OF AUDITORY SENSITIVITY TO TRAUMATIC BRAIN INJURY ENHANCED FEAR LEARNING

Our findings demonstrate that diffuse Traumatic brain injury (TBI) causes dynamic changes in plasticity within amygdala neurocircuitry known to underlie stress, emotion, and fear learning processes and that TBI-induced changes within auditory fear circuitry correspond to robustly enhanced contextual fear when foot shocks are paired with white noise auditory stimuli. This proposal will test the hypothesis that 'auditory sensitivity following diffuse TBI underlies enhanced fear learning to white noise.

- Aim 1: We will first determine whether diffuse TBI heightens sensitivity in emotional-auditory networks in a series of convergent anatomical, immunohistochemical, and behavioral approaches.
- Aim 2: Using novel viral mediated technology that allows direct manipulation of activity in specific target projections, we will causally determine the involvement of auditory-amygdala network function during white noise fear conditioning on the observed enhanced fear phenotype after TBI."

Craig Formby, University of Alabama, Toward a Transitional Intervention for Debilitating Hyperacusis

- Develop a hybrid device with extreme amplitude compression to facilitate desensitization of debilitated hyperacusis patients with customized combination hearing-aid/noise generator devices.
- Aim 2, the device, used as a transitional tool to replace hearing protection, will be assessed with enriching sound therapy from noise generators in a repeated-measures within-subject design to track treatment effects and dynamics in patients with debilitating hyperacusis."