Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

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SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Joel *	Berger *	Dept. Neurosurgery, University of Iowa Hospitals and Clinics

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

Affiliation Uconn Health

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Alice	Burghard	Uconn Health
Douglas	Oliver	Uconn Health

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Signature Emily Fabrizio-Stover

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Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Patrick	Krauss	Neuroscience Lab, University Hospital Erlangen

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

Affiliation University of Michigan

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.
Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.
Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Emily	Fabrizio-Stover	UConn Health Dep of Neuroscience
Christopher	Lee	UConn Health Dep of Neuroscience
Douglas	Oliver	UConn Health Dep of Neuroscience

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Elouise Koops

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Putting Tinnitus Theories to the Test

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Topic Tinnitus

Status Submitted

Submitter Calvin Wu

Affiliation University of Michigan, Otolaryngology - HNS

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

Affiliation Uconn Health

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Alice	Burghard	Uconn Health
Douglas	Oliver	Uconn Health

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Signature Emily Fabrizio-Stover

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Karl	Friston	Wellcome Centre for Human Neuroimaging, Institute of Neurology, University College London, London WC1N 3AR, UK
Patrick	Krauss	Neuroscience Lab, University Hospital Erlangen

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Rui	Cai	SIU School of Medicine
Lynne	Ling	SIU School of Medicine
Kevin	Brownell	SIU School of Medicine
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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

Affiliation University of Michigan

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.

Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.

Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Adam *	Hockley *	University of Michigan

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Emily	Fabrizio-Stover	UConn Health Dep of Neuroscience
Christopher	Lee	UConn Health Dep of Neuroscience
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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Elouise Koops

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Signature EAK

Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

Affiliation University of Michigan, Otolaryngology - HNS

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

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SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

Affiliation Uconn Health

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

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SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

Affiliation University of Michigan

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.
Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.
Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

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SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Signature EAK

Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

Affiliation University of Michigan, Otolaryngology - HNS

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

Affiliation Uconn Health

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

Affiliation University of Michigan

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.

Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.

Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Signature EAK

Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

Affiliation University of Michigan, Otolaryngology - HNS

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.

Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.

Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Signature EAK

Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

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SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

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SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Signature Emily Fabrizio-Stover

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

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SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.

Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.

Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

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SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Signature Emily Fabrizio-Stover

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

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SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.
Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.
Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

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SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Signature Emily Fabrizio-Stover

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

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SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.

Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.

Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

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SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Signature Emily Fabrizio-Stover

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

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SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.

Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.

Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

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SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Signature William Sedley

Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Signature Emily Fabrizio-Stover

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Financial Relationships Details

Commercial Interest	Type of Financial Interest	Individuals Involved

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

Affiliation Neuroscience Lab, University Hospital Erlangen

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Signature AS

Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

Affiliation SIU School of Medicine

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SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

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Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.

Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.

Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

Affiliation UConn Health Dep of Neuroscience

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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Putting Tinnitus Theories to the Test

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Calvin Wu

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SUBMISSION DETAILS

Symposium Description Auditory phantom perception, tinnitus, is extremely common. A highest estimate puts the prevalence between 10–30% in the US, and likely with similar numbers worldwide. Yet, not all tinnitus is equal; etiological heterogeneity and absence of objective diagnostics add to the challenge of reaching a consensus for a unified tinnitus theory. Insights from cognitive, computational, and microcircuit studies in humans and animals have produced various theories at different scales of investigation: from “central gain”, (Schaette and McAlpine) “neural synchrony” (Eggermont), “stochastic resonance” (Schilling and Krauss), “sensory gating” (Rauschecker), to “predictive coding” (Sedley). But how do these theories reconcile? How can they inform future experiments? And, ultimately, are theories falsifiable with empirical evidence? In this symposium, we invite dialogues between theorizing and testing, synthesizing various viewpoints among young investigators in our attempts to tackle and solve one of the most challenging problems in neuroscience.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The invited speakers for this symposium are early-stage investigators, postdocs, and graduate students studying in North American and European institutions. We aim to achieve equal representation of gender. We will prioritize inviting speakers from underrepresented minorities.

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Signature Calvin Wu

Putting Tinnitus Theories to the Test

The Elusivity of an Objective Test for Tinnitus in Humans

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Joel Berger

Affiliation Dept. Neurosurgery, University of Iowa Hospitals and Clinics

Participant(s) Calvin Wu (Chair), Alice Burghard (Co-chair), Amarins Heeringa (Co-chair), William Sedley (Presenter), Emily Fabrizio-Stover (Presenter), Joel Berger (Presenter), Achim Schilling (Presenter), Madan Ghimire (Presenter), Adam Hockley (Presenter), Alice Burghard (Presenter), Elouise Koops (Presenter)

SUBMISSION DETAILS

Individual Abstract Tinnitus assessment in humans currently still relies on self-report, often based on frequency matching procedures. Contrastingly, in animals, objective assessment of tinnitus is the only method for detecting the presence of a phantom percept following either noise exposure or administration of a drug such as sodium salicylate. Development of objective assessments that can be used in both animals and humans would allow bridging of the oft-mentioned gap between animal and human studies, thus linking potential theories of tinnitus to the human experience. Previous data have demonstrated that the most commonly-used behavioral test for tinnitus in animals - the gap pre-pulse inhibition of the acoustic startle paradigm – can be adapted to neural recordings in awake animals (Berger et al., 2017; 2018). I will discuss these studies, along with attempts to bring this paradigm to humans and report rare data that we recorded from an intracranially-implanted epilepsy patient with intermittent tinnitus. Ultimately, although a clinically-useful objective test for tinnitus in humans remains elusive at present, the development and validation of one would provide corroboration of animal behavioral studies and allow for more accurate assessment of a phantom percept.

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Signature Joel Berger

Putting Tinnitus Theories to the Test

Emergence of Tinnitus in a Bayesian System of Signal and Noise

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter William Sedley

Affiliation Newcastle University

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SUBMISSION DETAILS

Individual Abstract Many contemporary frameworks characterise the brain's perceptual systems as engines for Bayesian inference, which generate, maintain and update internal models of the sensory environment so as to optimise the detection of meaningful signals whilst minimising noise and error within the system. As such, sensitivity can be maximised for sensory information that is salient, familiar, anticipated, sought, contextually relevant or reliable, whilst information that is irrelevant, unfamiliar or unreliable can be minimised or ignored altogether. In some ways, this can be considered a way of distinguishing signal from noise, with signals being incorporated into generative models and prior predictions, and noise being explained away as prediction error. However, prediction errors generated by sensory information with sufficiently high precision lead to the modification of existing priors or the formation of new ones. Here, I summarise existing arguments and models for how tinnitus can appear as an emergent property of an otherwise normally functioning perceptual system acting to compensate for hearing loss. I then consider the question of whether tinnitus is a 'signal' that is detected with excessive sensitivity, or whether it is 'noise' misinterpreted as a signal, and therefore whether tinnitus is the sign of a better or worse functioning perceptual inference system. I go on to consider how tinnitus due to hearing loss might compare to tinnitus without hearing loss that occurs as part of the visual snow syndrome, and whether this informs the debate about central noise vs. central gain as the origin of the tinnitus signal. Finally, I discuss a range of research avenues (some already underway) that might support, refute or refine Bayesian models of tinnitus, ranging from psychophysical testing through neurophysiological oddball responses to biologically informed computational models.

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Putting Tinnitus Theories to the Test

Sound Evoked Changes after Long Duration Sound as a Test for Tinnitus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Emily Fabrizio-Stover

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SUBMISSION DETAILS

Individual Abstract An objective, non-invasive, electrophysiological test is needed for efficient tinnitus research. In wild type, CBA/CaJ mice, a long-duration sound (LDS) can alter both spontaneous firing rate and responses to sound in the inferior colliculus (IC). Specifically, the majority of sound-driven responses are suppressed while a subset are facilitated after the LDS. We believe that because tinnitus animals show increased spontaneous activity in the auditory system, the LDS-generated changes will be less apparent than in non-tinnitus animals. Here, we recorded auditory brainstem responses (ABRs) before and after the LDS and show that there are tinnitus-specific differences. Awake CBA/CaJ mice received a unilateral sound exposure that resulted in mice with and without behavioral evidence of tinnitus. ABR responses to tone pips at three or more frequencies were collected from tinnitus, non-tinnitus, and unexposed control mice. We quantified the effect of LDS-changes and calculated a tinnitus score based on peak-trough amplitudes for each ABR wave. The tone-pip ABRs evoked by sounds in the exposed ear for tinnitus and non-tinnitus mice showed that non-tinnitus mice had significantly lower scores than tinnitus mice. That is, non-tinnitus mice had more suppression after LDS than tinnitus mice. At higher frequencies at later waves, the effect was more significant. However, there was no significant difference between tinnitus and the control. A correlation analysis of pre-LDS and post-LDS waveforms showed a significantly bigger difference in non-tinnitus mice than in tinnitus mice. A differential time frequency analysis analyzing the spectrum of the ABR waveforms over time showed tinnitus specific ‘hotspots’ at tinnitus frequencies, but not at non-tinnitus frequencies. Responses to the LDS show tinnitus specific changes that may be a basis for an electrophysiological test for tinnitus.

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Putting Tinnitus Theories to the Test

Towards a Unified Theory of Auditory (phantom) Perception

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Achim Schilling

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SUBMISSION DETAILS

Individual Abstract Background and Aim
“What are the neural mechanisms of auditory (phantom) perception and how could this complex set of various neuronal mechanisms be meaningfully understood by humans?” The answer of this question needs a highly interdisciplinary approach based on computational neuroscience, experimental neuroscience and artificial intelligence. We argue that the most promising way of understanding tinnitus, is to tackle the problem on an algorithmic level, which means that we try to understand tinnitus mechanisms on an intermediate level between the molecular mechanisms (implementational level) and the computational level (formulation of the task to be solved).

Methods
To do so, we created a hybrid computational model of the auditory pathway consisting of a simple cochlear and DCN model, which we combined with a deep neural network. Thus, the deep neural network could be interpreted as a model of the higher auditory processing stages up to the cerebral cortex, but is also a tool to quantify meaningful information in the DCN output. We trained the deep neural network on speech recognition and used the accuracy as an objective function of speech comprehension ability of the auditory pathway. Finally, we distorted the system by adding a simulated hearing loss and fed in intrinsic neural noise to the DCN.

Results
We were able to show that indeed the addition of neural noise can partly compensate the hearing loss and can increase the speech comprehension ability by a factor of 2, an effect called stochastic resonance (SR). We hypothesize that the origin of that neural noise is the somato-sensory system innervating the dorsal cochlear nucleus. Despite of the explanatory power of the model, one crucial question remains unsolved: Why does (nearly) everyone with tinnitus suffer from hearing loss, but

not everyone with hearing loss suffers from tinnitus?

Discussion and Conclusion
We argue that the bottom-up model described above is only the first part of the big picture. A second part, namely a complementary top-down model is needed to account for the influence of stress, attention, and experience on tinnitus perception. We argue that potentially the increase of sensory precision due to Bayesian inference as described by Sedley and Friston could be caused by intrinsic neural noise and lead to a prediction error in the cortex. The combination of our bottom-up model with this top-down model based on predictive coding provides a unified framework of the neural algorithms underlying tinnitus perception.

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Putting Tinnitus Theories to the Test

Attentional Deficit in tinnitus—Symptom or Cause?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Madan Ghimire

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SUBMISSION DETAILS

Individual Abstract Incidence of chronic tinnitus has progressed to impact more than 15 percent of the global population. Tinnitus pathology is believed to be initiated by damage to the auditory periphery resulting in maladaptive plastic changes, altering central auditory, limbic and attentional systems. Individuals most disturbed by their tinnitus, show bimodal abnormalities of selective attention. For example, Norena and colleagues (2004) showed that individuals with tinnitus are bound to their tinnitus percept and are unable to divert their attention away from the sound in their heads. Similar attentional deficits were observed in an animal model of tinnitus (Brozoski et al., 2019). Based on this hypothesis, several therapeutic approaches employing sound were devised to divert attention away from tinnitus and have been used in tinnitus patients with modest success. Later, Roberts and colleagues (2013) proposed that a partial deafferentation induced loss of signal, creates a mismatch between the predicted and experienced inputs into the auditory cortex (A1), recruiting attentional resources and reinforcing the phantom signals. It is yet unclear what role attentional systems play in the tinnitus pathology. Present studies were designed to examine the tinnitus-related changes in attentional resources in the A1. The role of nicotinic signaling in the regulation of attention in the central nervous system has been well studied. When attention is required, cholinergic neurons of basal forebrain are found to increase release of acetylcholine (ACh) to the target cortical region and administration of nicotinic agents are found to heighten attention. Using a well-established animal model of tinnitus, we examined tinnitus-related changes in nicotinic acetylcholine receptors (nAChR) signaling in A1 layer 5 pyramidal neurons (PNs) and vasointestinal peptide positive (VIP) neurons. In vitro whole-cell patch-clamp studies revealed a significant tinnitus-related loss of nAChR signaling in layer 5 PNs. In contrary, puffed ACh evoked a significantly greater number of action potentials in VIP neurons from animals with behavioral evidence of tinnitus. Since, increased VIP neuron activity favors excitation of PNs through disinhibition, tinnitus-related increases in nAChR evoked excitability of VIP neurons may tip the

balance toward increased excitability of principle cortical neurons.

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Signature MG

Putting Tinnitus Theories to the Test

Nitric Oxide as a Mechanism of Central Gain in the Ventral Cochlear Nucleus

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Adam Hockley

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SUBMISSION DETAILS

Individual Abstract One theory proposes that tinnitus is produced by central gain enhancement following cochlear damage. This theory is often based on ABRs (sound-evoked activity) which may not be a good measure for tinnitus (spontaneous activity). Furthermore, the cellular mechanisms of this gain enhancement are unknown, though often are attributed to either: 1) reduced inhibition; 2) increased excitation; or 3) altered intrinsic excitability.
Here, I analyse these possibilities with a focus on the function of nitric oxide (NO) in the ventral cochlear nucleus. NO is increased in the VCN in animals with behavioural evidence of tinnitus, and is capable of bidirectionally altering driven and spontaneous rates. Blocking NO production has shown that NO supports the increased driven rates in tinnitus animals compared to no-tinnitus animals. NO also increases spontaneous rates, however this occurs in a similar proportion of neurons in tinnitus and control animals. One possible mechanism for NO mediating potentiation is the novel functional role discovered in T-stellate cell interconnections (Cao et al., 2019). This circuit can produce positive feedback in a network of T-stellate cells, and due to increased NO levels, is likely strengthened during tinnitus.
Altered excitability by NO-mediated neuromodulation is potential regulator of cellular gain within the VCN, however the conclusive link to the tinnitus percept is still enigmatic.

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Signature AdamHockley

Putting Tinnitus Theories to the Test

Long-Duration Sound Induced Plasticity is Altered in Mice with Tinnitus.

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

Submitter Alice Burghard

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SUBMISSION DETAILS

Individual Abstract A presentation of a long-duration sound (LDS) can lead to a change in both spontaneous activity as well as sound-driven activity in the inferior colliculus (IC) in non-sound exposed mice. While the majority of sound-driven responses are suppressed, a subset is potentiated after the LDS. This potentiation is more likely in channels with higher spontaneous activity. Since tinnitus is associated with increased activity in the auditory system, we are hypothesizing that tinnitus animals will have more facilitation/less suppression than animals without tinnitus. Exposing awake CBA/CaJ mice to a unilateral sound exposure, resulted in mice with and without behavioral signs of tinnitus. We recorded from both IC, ipsi- and contra-lateral to the sound exposed ear. The spontaneous activity in the IC contralateral to the sound exposure was higher in the tinnitus group than in the sound-exposed non-tinnitus and the control (not sound-exposed) group. When comparing LDS-driven plasticity in mice with and without behavioral signs of tinnitus, we find that the sound exposed non-tinnitus animals show more suppression than tinnitus animals exposed to the same sound. The tinnitus animals show a response that is more similar to control (not sound-exposed) animals. Taken together this indicates an electrophysiological detectable LDS-induced difference in sound-exposed tinnitus vs non-tinnitus animals that might serve as an objective test to differentiate between hearing loss with or without tinnitus.

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Signature Alice Burghard

Putting Tinnitus Theories to the Test

Central gain: A Closer Fit to Hyperacusis than to Tinnitus?

Submission ID 3003147

Submission Type Young Investigator Symposia

Topic Tinnitus

Status Submitted

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SUBMISSION DETAILS

Individual Abstract Central gain refers to the increase of spontaneous activity observed in hierarchically higher auditory pathway areas after hearing loss induction (Schaette & Kempter, 2006). The upregulation of neuronal activity in central auditory regions is interpreted as a homeostatic plasticity response to decreased peripheral input. In the context of hyperacusis (Auerbach et al., 2014; Diehl & Schaette, 2015) and tinnitus (Norena, 2011; Schaette & McAlpine, 2011), the central gain framework has been extended to include sound-evoked activation. Whereas tinnitus is the most extensively studied condition co-occurring with hearing loss, 59% of those with hyperacusis have co-occurring hearing loss (Paulin et al., 2016), and the majority of those with hyperacusis also report tinnitus (Anari et al., 1999; Dauman & Bouscau-Faure, 2005; Schecklmann et al., 2014). Even though hyperacusis frequently co-occurs with hearing loss and tinnitus, it is often not taken into account in experimental studies, hampering adequate characterization of the neural signatures of these conditions.

In an fMRI study, we investigated the subcortical and cortical BOLD-responses in a group (n=35) that often reports hyperacusis: individuals with hearing loss and tinnitus. Additionally, we characterized the frequency tuning of cortical voxels in the primary auditory cortex of those with and without hyperacusis. In this study, hyperacusis was indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ).

In the group with hyperacusis, sound-evoked activity was higher in both cortical and subcortical auditory structures. This increase in responsivity extended to frequencies not affected by hearing loss, and the higher subcortical and cortical activity in response to sound appears to be a marker of hyperacusis. The frequency tuning of auditory cortical voxels was not significantly different in those with hyperacusis. In contrast, the auditory cortex BOLD signal was reduced in response to the presentation of the tinnitus frequency in those with higher hyperacusis scores. Overall, the

heightened subcortical and cortical activity can reflect an increase in neural gain along the auditory pathway in those with hyperacusis, but may not capture cortical responses that are involved in tinnitus.

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