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Knipper, Marlies; Mazurek, Birgit; van Dijk, Pim; Schulze, Holger

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# Too Blind to See the Elephant? Why Neuroscientists Ought to Be Interested in Tinnitus

MARLIES KNIPPER<sup>1</sup> , BIRGIT MAZUREK<sup>2</sup>, PIM VAN DIJK<sup>3,4</sup>, AND HOLGER SCHULZE<sup>5</sup>

<sup>1</sup> *Molecular Physiology of Hearing, Tübingen Hearing Research Centre (THRC), Department of Otolaryngology, Head & Neck Surgery, University of Tübingen, Elfriede-Aulhorn-Straße 5, 72076 Tübingen, Germany*

<sup>2</sup> *Tinnitus Center Charité, Universitätsmedizin Berlin, Berlin, Germany*

<sup>3</sup> *Department of Otorhinolaryngology/Head and Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

<sup>4</sup> *Graduate School of Medical Sciences (Research School of Behavioural and Cognitive Neurosciences), University of Groningen, Groningen, The Netherlands*

<sup>5</sup> *Experimental Otolaryngology, Friedrich-Alexander Universität Erlangen-Nürnberg, Waldstrasse 1, 91054 Erlangen, Germany*

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## ABSTRACT

A curative therapy for tinnitus currently does not exist. One may actually exist but cannot currently be causally linked to tinnitus due to the lack of consistency of concepts about the neural correlate of tinnitus. Depending on predictions, these concepts would require either a suppression or enhancement of brain activity or an increase in inhibition or disinhibition. Although procedures with a potential to silence tinnitus may exist, the lack of rationale for their curative success hampers an optimization of therapeutic protocols. We discuss here six candidate contributors to tinnitus that have been suggested by a variety of scientific experts in the field and that were addressed in a virtual panel discussion at the ARO round table in February 2021. In this discussion, several potential tinnitus contributors were considered: (i) inhibitory circuits, (ii) attention, (iii) stress, (iv) unidentified sub-entities, (v) maladaptive information transmission, and (vi) minor cochlear deafferentation. Finally, (vii) some potential therapeutic approaches were discussed. The results of this discussion is reflected here in view of potential blind spots that may

still remain and that have been ignored in most tinnitus literature. We strongly suggest to consider the high impact of connecting the controversial findings to unravel the whole complexity of the tinnitus phenomenon; an essential prerequisite for establishing suitable therapeutic approaches.

**Keywords:** tinnitus, hyperacusis, parvalbumin positive interneuron, fast auditory processing, stress, attention

*All authors have shared correspondence.*

Correspondence to: Marlies Knipper · Molecular Physiology of Hearing, Tübingen Hearing Research Centre (THRC), Department of Otolaryngology, Head & Neck Surgery · University of Tübingen · Elfriede-Aulhorn-Straße 5, 72076, Tübingen, Germany. email: marlies.knipper@uni-tuebingen.de

## INTRODUCTION

Questions asked by leading scientists in 2020 around the topic ‘tinnitus’ were the focus of a discussion on the 25th of February, 2021, at the Annual Mid-Winter Meeting of the Association for Research in Otolaryngology which was headed by the authors of the present review. The questions spanned topics around the role of (i) inhibitory circuits, (ii) attention, (iii) stress, (iv) sub-entities, (v) development, (vi) perception, and (vii) successful intervention strategies. During the discussion it was suggested that the ongoing research and modular approach to search for the neural correlates of tinnitus resemble the parable of the ‘blind men and the elephant’, the origins of which have been traced to the Indian subcontinent prior to 500 BCE. We here summarize the questions and answers



process, likely triggered through cochlear damage and reduced auditory input, alters upstream neurotransmitters such as, GABA and changes signal processing via, for example, stochastic resonance (Krauss et al. 2016); this might change the upstream coding underlying normal perception. On that basis, it is unimportant whether the bottom-up mechanism acts through increased spontaneous activity, increased synchrony, increased bursting, adaptive stochastic resonance or neural gain: the crucial open question would be to understand how the ‘higher-order’ top-down mechanism induces a chronic manifestation of tinnitus over time.

A long-standing discussion of numerous tinnitus models deals with the idea of a two-step bottom-up and top-down mechanism during tinnitus generation, albeit from different perspectives: (i) a bottom-up deprivation that leads to a top-down modulation failure of auditory gating and noise cancellation, or an impaired central gate keeper that leads to a tinnitus percept (Leaver et al. 2011; Rauschecker 2010; Rauschecker et al. 2014), (ii) a bottom-up tinnitus development linked to hearing loss that can lead to a tinnitus percept independently of any top-down mechanism. Here, top-down tinnitus results from a network problem between the auditory and non-auditory brain areas, including the pregenual anterior cingulate cortex (Vanneste et al. 2018a, b) linked to thalamocortical dysrhythmia (Vanneste et al. 2018a, b, 2019), (iii) a bottom-up tinnitus precursor that is normally ignored as imprecise evidence against the prevailing percept of ‘silence’ (Sedley et al. 2016) and that is amplified through a top-down mechanism through focused attention (Hullfish et al. 2019; Sedley et al. 2016), fear, anxiety, or stress (Jastreboff et al. 1996), or through a combination of these facilitators. Influences on the individual tinnitus severity depend on the context of their culture and experience (Searchfield 2014).

Thus, if we ask under which circumstances minor cochlear deafferentation – as a starting point in bottom-up tinnitus development – might change GABAergic strength in affected circuits to such a level that it could profoundly alter top-down circuits such that upstream coding of normal percepts is permanently altered, we may already have the answer: fundamental differences in central processing and sound coding are expected between the approx. 40 % of auditory fibers with lower spontaneous discharge rate and high thresholds (low-SR-AF) and the 60 % of auditory fibers with high spontaneous firing rates and lowest thresholds (high-SR-AF) (Bharadwaj et al. 2015; Liberman 1978). Up to now, the low-SR-AF are assumed to be particularly vulnerable to acoustic overexposure and ageing (Liberman and Kujawa 2017; Wu et al. 2019). This auditory fiber type has been suggested to drive shifts in inhibitory responses through enhanced central neural gain that are possibly involved in tinnitus (Schaeffe and McAlpine 2011; Shore et al. 2016). Alternatively, a critical diminution of specifically

fast (high-SR) auditory fiber processing has been suggested to be causally linked to tinnitus through shifts in tonic inhibitory responses that lead to a loss of central neural gain (Hofmeier et al. 2018, 2021; Knipper et al. 2020; Möhrle et al. 2019; Refat et al. 2021; Rüttiger et al. 2013; Singer et al. 2013).

As such, the community might reconsider the lost function of high-SR, low threshold neurons in defined tinnitus frequency channels as a bottom-up mechanism and as a rationale to explain numerous observations:

- (i) Reduced auditory brainstem and cortical responses in tinnitus (Bramhall et al. 2019; Hofmeier et al. 2018; Koops et al. 2020), reduced functional connectivity in the auditory pathway (Boyen et al. 2014; Lanting et al. 2014), and increased latencies in tinnitus (Hofmeier et al. 2018, 2021; Majhi et al. 2019; Milloy et al. 2017; Möhrle et al. 2019) in connection with decreased myelination of the auditory pathway in tinnitus patients (Koops et al. 2021). The latter was observed by fixel<sup>2</sup>-based analysis in which a tinnitus-related atrophy of the left acoustic radiation near the medial geniculate body was the first evidence of a decrease in myelination of the auditory pathway (Koops et al. 2021). This would suggest a more profound peripheral deafferentation of larger-diameter, high-SR auditory fibers that are more robustly myelinated (Bauer et al. 2007).
- (ii) Increased epileptic bursting (Jastreboff et al. 1996), adaptive stochastic resonance (Krauss et al. 2016, 2017, 2018b), and excessive neuronal synchrony in the auditory cortex in tinnitus (Eggermont and Tass 2015; Noreña and Farley 2013) may all be explained through a loss of tonic inhibition that would result in a rapid increase in bursting or epileptic firing and reduced signal-to-noise ratios (Duguid et al. 2012; Hsieh et al. 2017; Rossignol et al. 2013).
- (iii) Diminished activity of the tonic fast-spiking parvalbumin (PV)+ interneuron networks would, in turn, be expected to be linked to enhanced baseline spontaneous gamma power (Mamashli et al. 2017), and thus explain enhanced spontaneous gamma oscillations in tinnitus patients (Ortmann et al. 2011; Vanneste et al. 2018b, 2019; Weisz et al. 2007). This would also be compatible with enhanced variance in stimulus-induced responses and lower signal-to-noise ratios that contribute to tinnitus (Zeng 2020) thereby reducing the gate keeping or noise cancellation linked to dysrhythmia (Leaver et al. 2011; Rauschecker 2010;

<sup>2</sup> Fixel refers to a specific fibre bundle within a specific voxel.



- Rauschecker et al. 2014; Vanneste et al. 2019), reducing functional connectivity in the auditory pathway (Boyen et al. 2014; Lanting et al. 2014) (for a review see (Knipper et al. 2020)).
- (iv) Increased susceptibility to a clinical manifestation of tinnitus linked to enhanced tinnitus-related distress, as observed in patients with brain-derived neurotrophic factor (BDNF) Val<sup>66</sup> Met polymorphism (Vanneste et al. 2021). This single-nucleotide polymorphism (SNP) in the BDNF gene (substitution of valine to methionine) leads to a decrease of activity-dependent intracellular trafficking and secretion of the neuronal BDNF (Chen et al. 2004) which is required for balanced hypothalamus-pituitary-adrenal (HPA) axis control (Jeanneteau et al. 2019). During enhanced memory-linked auditory adjustment processes, fast (high-SR) auditory processing is predicted to drive activity-dependent BDNF translation and secretion in the hippocampus (Eckert et al. 2021; Marchetta et al. 2020; Matt et al. 2018).
  - (v) The lower risk of tinnitus in congenital deafness (Eggermont and Kral 2016) and in congenital unilateral deafness (Lee et al. 2017), and the elevated risk of tinnitus in the implanted ear of bilaterally or unilaterally deaf children when CI are switched off (Baguley and Atlas 2007; Chadha et al. 2009; Ramakers et al. 2015) (for a review, see (Knipper et al. 2020)).
  - (vi) Finally, the significantly higher gray matter volume in the lingual gyri observed in hearing loss in the tinnitus group compared to the hearing loss group without tinnitus (Koops et al. 2021), can also be taken as an indicator of the loss of fast auditory processing in tinnitus. The lingual gyrus, also known as the medial occipito-temporal gyrus, is linked preferentially to processing vision (Kozlovskiy et al. 2014). This observation is particularly exciting, as it may point to a loss of clustering of auditory and visual modalities in tinnitus, and provide a rationale for the exuberant connections between the visual and auditory cortex found, for example, in deaf cats, together with an increased visual responsiveness in the auditory cortex (Land et al. 2016). It may support the view that within the frequency channel of the tinnitus percept, the mature, fine-grained wiring that is based on fast (tonic) inhibitory circuits which develops with auditory experience is reversed towards an immature pattern (Knipper et al. 2020). This concept should lead to reconsideration of reported tinnitus-related increases in the connectivity of the left lingual gyrus with the left auditory cortex (Hinkley et al. 2015) and decreased connectivity of the left lingual gyrus with the auditory resting-state network (Schmidt et al. 2013, 2017).

#### *Future Tasks to See and Test for a Possible Blind Spot*

The contribution of fast (high-SR) auditory fiber dysfunction as the trigger of a bottom-up mechanism that, through altered tonic inhibitory strength, leads to top-down activity changes that promote the development of a tinnitus percept could be tested in future studies. A possible approach would be the use of pharmaceutical drugs that either antagonize tonic or phasic GABA receptor units in behavioral animal models of tinnitus, followed by clinical trials. Additionally, morphometric measurements of auditory nerve density could enable to examine the contributions of large-diameter high-SR auditory nerve fibers in tinnitus patients. Moreover, such contributions could then be analysed for associations with changes in top-down cortical oscillatory signatures and dysrhythmia (Lee et al. 2020; van Gendt et al. 2012) or distress and functional-network topology changes, as described in the context of tinnitus (Yoo et al. 2021).

#### Topic 2: Contribution of Attention to Tinnitus and Its Relation to Long-term Habituation and Resilience

There are numerous studies that report impaired or altered *executive attention*, *selective attention*, and working memory in chronic tinnitus (Khan and Husain 2020; Mazurek et al. 2019; Mohamad et al. 2016; Nagaraj et al. 2020). Moreover, no doubt exists that the distress accompanying tinnitus influences general and crystallized intelligence and executive function (Mohamad et al. 2016; Neff et al. 2021). Tinnitus appears to be a symptom of a hyperactive cognitive control network: In this maladaptive network, the negative emotion experienced during tinnitus leads to a consumption of cognitive resources that are typically required for proper functioning of auditory working memory. This imbalanced cognitive control contributes to increased vigilance to the tinnitus tone (Mazurek et al. 2019; Trevis et al. 2016). This concept was confirmed, by previous studies of (Brozowski et al. 2019), who observed that in rats, behaviorally-evidenced tinnitus promotes an increased vigilance to the tinnitus percept, while attention to an auditory-specific task is diminished. In this connection, *long-term habituation* during tinnitus might be associated with a gradual decline of such ‘negative emotions’, or with a decline of factors that contribute to these negative emotions (Elarbed et al. 2021; Luan et al. 2019; Mazurek et al. 2019; Nagaraj et al. 2020).

The contribution of cognitive and perceptual load should also be discussed in this context (Khan and Husain 2020). Perceptual load-tinnitus is an undesired stimulation of the auditory processing pathway, and constant perception of tinnitus affects the cognitive load. Within the same framework, the possible causes of *tinnitus resilience* could be the

same as those that contribute to habituation to tinnitus. In general, resilience is the ability to cope with critical situations through the use of personal and socially mediated resources. Thus, factors for resilience are positive emotions, socio-environmental factors, cognitive flexibility, active coping style, and exercise (Faye et al. 2018). Negative or positive environmental or hereditary conditions, differences in early life-stress, or chronic illness leading to depression or anxiety, and differences in temperament or personality, contribute to the so-called ‘*emotional health*’ that influences tinnitus and span degrees from complete tinnitus resilience to a high risk for tinnitus (Aydin and Searchfield 2019; Marks et al. 2019; Searchfield 2014; Searchfield et al. 2020). On the clinical side, *high resilience* in tinnitus patients is associated with less depression, less anxiety and fewer somatic symptoms, and the relationship between resilience and tinnitus distress is mediated by emotional health (Wallhäusser-Franke et al. 2014). In this sense, the lack of tinnitus *habituation* could be explained as a result of a reduced resilience strategy. Here, for example, the absence of hereditary contributors to enhanced distress, which have been shown to increase susceptibility to tinnitus (Amanat et al. 2020; Lopez-Escamez and Amanat 2020; Ruan et al. 2018; Szczepek et al. 2019), including the BDNF Val 66 Met polymorphism (Vanneste et al. 2021), have to be regarded in the context of a possible contribution to tinnitus resilience and long-term habituation.

#### *Future Tasks to See and Test for a Possible Blind Spot*

The community of tinnitus researchers may reconsider how individual environmental or hereditary differences in attentional/cognitive brain states could contribute to suffering more or less from enhanced ‘noise’ in tinnitus frequency channels that have lost contrast-amplification after reduced fast (high-SR) auditory processing. The strong relation of fast (high-SR) auditory processing as a bottom-up mechanism with attentional/cognitive brain states (Review (Knipper et al. 2020)) needs urgent examination. As additional factors that might directly contribute to hereditary or environmental differences in individuals’ and thereby contribute to either enhanced or decreased habituation or resilience to tinnitus, we suggest to consider also those factors that promote the metabolic fatigue of fast auditory processing. This would include conditions that diminish the function of fast *PV+* interneurons (*PV+IN*) activity (Kann et al. 2016), which require a high action-potential (AP)-related energy budget to maintain high-frequency activity and fast temporally precise transmission (Hu et al. 2018).

### Topic 3: Contribution of Stress to Tinnitus and Its Link to the Limbic System and Environmental Factors

The list of studies that demonstrate a close relationship of distress and tinnitus is increasing (Boecking et al.

2021; Durai et al. 2018; Elarbed et al. 2021; Park et al. 2020; van Munster et al. 2020). Numerous studies document altered evoked or resting state BOLD fMRI or EEG activity in tinnitus patients, particularly in those brain regions or networks that are involved in attention, distress, and memory functions (Kandeepan et al. 2019; Mohsen et al. 2019; Pattyn et al. 2016; Vanneste et al. 2021; Yoo et al. 2021). The strong contribution of distress culminates in evidence that insomnia, hearing distress, and anxiety are the best predictors of tinnitus severity, and are indeed stronger predictors than any demographic factors (Beukes et al. 2021; Crönlein et al. 2016).

But what do we already know about the mechanism by which distress influences tinnitus? It is important to distinguish the contribution of oxidative stress, stressful acoustic trauma, or mental stress, which has not yet been considered adequately. All forms of stressful events may eventually accumulate to an imbalance within the HPA axis, leading to differential activation of glucocorticoid and mineralocorticoid receptors, and thereby contribute to chronic tinnitus (Kraus and Canlon 2012; Mazurek et al. 2012; Simoens and Hébert 2012). Enhanced tinnitus-related distress, as observed in patient groups with BDNF Val<sup>66</sup> Met polymorphism (Vanneste et al. 2018a) would be compatible with BDNF bridging glucocorticoid effects on brain networks through BDNF driven phosphorylation of glucocorticoid receptor (Jeanneteau et al. 2019). Impaired *glucocorticoid receptor (GR)* phosphorylation following a reduced activity-dependent BDNF recruitment has been shown to lead to impaired long-term memory retention and deficits in forming postsynaptic dendritic spines after, for example, motor-skill training (Arango-Lievano et al. 2019). Thus it is conceivable that, under healthy conditions, fast (high-SR) auditory fiber processing may recruit activity-dependent BDNF to energize contrast amplification and distress levels (Knipper et al. 2020; Matt et al. 2018).

Currently we do not have a good explanation for the potential differential – or combined – impact that acoustic trauma and stress have on different tinnitus groups, which can be clearly distinguished by their distress response. The analysis of 1228 patients led to four distinct patient phenotypes: divided into (i) an ‘avoidant group’, with few affective or psychosomatic symptoms and less tinnitus distress, (ii) a ‘psychosomatic group’ with profound psychosomatic, emotional, and somatic burden, risk of depression and anxiety, and reduced quality of life, (iii) a ‘somatic group’ with physical symptoms that create distress or underlying medical conditions and higher somatic complaints, like pain or headache, and (iv) a ‘distress group’ with a high level of passive stress and physical exhaustion, anxious depressed mood, these patients are often younger and with correlations of neuroticism and anxiety (Bartels et al. 2010; Niemann et al. 2020).

#### *Future Tasks to See and Test for a Possible Blind Spot*

We need to understand how bottom-up mechanisms may be linked to the role that distress plays in tinnitus – which has been judged to be the ‘best predictor of tinnitus severity’ (Beukes et al. 2021; Crönlein et al. 2016). Here, BDNF signaling needs to be considered as a potential bridge linking bottom-up changes in tinnitus with an altered distress network. Deficits in BDNF driven GR phosphorylation and LTP retention should be considered in the context of enhanced tinnitus-related distress in patients suffering from the BDNF Val66Met polymorphism (Vanneste et al. 2021).

#### Topic 4: Contribution of Non-identified Sub-entities of Tinnitus to Current Controversial Views on the Neural Correlate of Tinnitus

Previous studies analyzing patients with tinnitus and hyperacusis (T+H group) and patients without hyperacusis (T-group) revealed evidence for the existence of tinnitus subcategories (Hofmeier et al. 2018, 2021). When tinnitus co-occurred with hyperacusis, stimuli-evoked increases in sound-evoked, supra-threshold ABR amplitudes and fMRI BOLD responses in the medial geniculate body (MGB) as well as in the auditory cortex were found (Hofmeier et al. 2021; Koops and van Dijk 2021; Refat et al. 2021). While a higher sound-evoked fMRI BOLD activity in cortical and subcortical auditory structures was observed in the tinnitus group with hyperacusis compared to the tinnitus group without hyperacusis, an enhanced response to sound was not found in the tinnitus frequency regions (Koops and van Dijk 2021). On the other hand, in tinnitus patients without hyperacusis the auditory responsiveness, including spontaneous and evoked fMRI BOLD responses was reduced (Hofmeier et al. 2021; Refat et al. 2021). Not only the annoyance, tinnitus loudness and bilateral tinnitus are higher in the T+H group (Hofmeier et al. 2021; Ralli et al. 2017; Refat et al. 2021; Schecklmann et al. 2014), but the co-occurrence of tinnitus with hyperacusis also leads to an increase of tinnitus duration over time (Refat et al. 2021; Vielsmeier et al. 2020). Moreover, when chirp stimuli of different frequency spectra were employed (Hofmeier et al. 2021), the results pointed to reduced auditory response activity in T-groups to higher-frequency stimuli and to enhanced auditory response patterns to lower-frequency stimuli in T+H groups (Hofmeier et al. 2021). The more widespread signal amplification process in patients with tinnitus and hyperacusis is supposed to proceed through an excessive thalamo-cortical activity that may trigger an excitation spread to limbic and pain regions, and ultimately results in an over-attention to increased loudness at all sound frequencies (Hofmeier et al. 2021; Koops et al. 2020). It is conceivable that the enhanced distress levels in T+H patients (Hofmeier et al.

2021; Ralli et al. 2017; Refat et al. 2021; Schecklmann et al. 2014) affect wider frequency ranges, including the pain network (Hofmeier et al. 2021; Refat et al. 2021) and contribute directly to the enhanced annoyance to the ‘noise’ in higher-frequency tinnitus channels.

Overall, the hypothesis that sub-entities of tinnitus exist, and can possibly co-occur in different frequency channels, needs to be validated in larger cohort groups.

We may speculate that even controversial findings of deficits of speech-in-noise intelligibility of tinnitus patients may have their origin in different prevalence of sub-entities of tinnitus. Accordingly, a study of (Zeng 2020) did not find any differences in speech-in-noise intelligibility using a group of young adults (mean age 22.6 years) as a normal-hearing control compared to a heterogeneous group of 45 adults (mean age 44 years) with chronic tinnitus (Zeng 2020). In contrast, (Bureš et al. 2019), who found a poorer ability to detect tones in noise and a higher sensitivity to intensity changes and interaural time differences, used a more harmonized group of 51 tinnitus subjects aged around 66 years, and 68 controls around 69 years. It is feasible that a difference in the prevalence of patients with T+H co-occurrence between both studies explain the difference in speech-in-noise intelligibility between the groups.

#### *Future Tasks to See and Test a Possible Blind Spot*

The current evidence suggests that hyperacusis and tinnitus pathologies may co-exist in parallel frequency channels of the bottom-up auditory pathways. There is an urgent need to consider that in patients with tinnitus and hyperacusis parallel bottom-up changes exist that differentially affect top-down circuits (Eggermont 2021; Martel and Shore 2020) this hypothesis needs to be validated in larger cohort groups and through multi-center clinical trials.

#### Topic 5: Contribution of Maladaptive Information Transmission to Tinnitus?

This question may need to be considered in the context of the brain’s overall ability to constantly try to optimize information transmission from the periphery into the brain (Krauss et al. 2016, 2017, 2018a). In the various disciplines in neuroscience, the optimization of information transmission from the periphery into the brain can be (i) realized through *stochastic resonance*, where added neuronal noise lifts *spontaneous firing rate (SFR)* above the threshold, causing a sensory percept (Krauss et al. 2016; Schilling et al. 2021; White et al. 2019). (ii) Alternatively, based on the *Bayesian model*, the brain is conceived as a prediction machine that informs its memory-based predictions through sensory updating (Hemmer et al. 2015). In this view, tinnitus is the result of a prediction error between the predicted and the actual auditory input. The decrease in sensory updating is reflected by decreased

alpha activity, while the prediction error is believed to result in altered theta-gamma and beta-gamma coupling (De Ridder et al. 2015; Durai et al. 2019; Hullfish et al. 2019; Mohebbi et al. 2019). Both models may be covered in another (iii) view that the information transfer from the periphery into the brain operates in a so-called ‘reverberating regime,’ (Cramer et al. 2020; Wilting et al. 2018). This describes an information process that, for example, enables cortical networks to interpolate between the asynchronous-irregular and the critical state by small changes in effective synaptic strength or by the excitation-inhibition ratio (Cramer et al. 2020; Wilting et al. 2018).

In these information processing models, we may miss determinants that define (i) the thresholds for action potentials lowered by stochastic resonance, (ii) the set point or threshold to which predictions are typically made (memory or detection threshold?), (iii) the baseline at which the system reverberates.

#### *Future Tasks to See and test a Potential Blind Spot*

Considering tinnitus as a diminution of fast (high-SR fiber dependent) auditory processing (Knipper et al. 2020; Zeng 2020), the baseline signal-to-noise ratio would be lost in affected frequency channels. In this view, the brain’s advantage having tinnitus in deprived frequency channels would be to lower the energy budget of the brain. The reversal from a mature fast-processing circuit to a presumably immature state within the affected frequency channels would prevent further metabolic fatigue. Thus, fast inhibitory PV+ interneurons and fast (high-SR) auditory processing (Knipper et al. 2020), comprise of only 2.6–4.6 % of interneurons - but require 14–25 % of the total AP related energy budget of the brain (Hu et al. 2014, 2018). This might explain the high vulnerability for metabolic fatigue of PV+ interneurons (Kann et al. 2016). The evolutionary gain in separately clustering sensory modalities to enhance fast information processing and sensory-specific acuity may create a risk of losing it. On a fast time scale, a mechanism like stochastic resonance, which constantly optimizes information transmission from the periphery to the brain, would improve auditory processing at the cost of generating a tinnitus percept. In that view, tinnitus would be a side effect of the brain’s effort to improve hearing (Gollnast et al. 2017).

#### Topic 6: Contribution of Deafferentation to a Tinnitus Percept?

It is still unclear how, through altered GABAergic circuit strength or differential tonic or phasic GABA receptor activation, a bottom-up activity might lead to a tinnitus percept? Bottom-up activity must change activity spreading from the thalamus through a canonical propagation to the different cortical layers, from layer IV to supra-granular layer I–II, and subsequently through a top-down mechanism from the infra-granular layer V/VI to the

limbic system (Norena et al. 2021), finally leading to a conscious sound percept. Here, the Bayesian models, including predictive coding, attentional modulation and cortical oscillatory band activity, as neurophysiological substrates for auditory predictions, were suggested to contribute through incomplete top-down processing during auditory scene analysis to the conscious tinnitus percept (Durai et al. 2018; Hullfish et al. 2018). It has been speculated that during the perception of tinnitus, spatio-temporal activity patterns in the auditory cortex must be specific to the quality of the percept, and different from patterns that may be recorded during silence but without any phantom percept (Krauss et al. 2018b).

The discussion included the idea that in a chronically perceived tinnitus percept, minor undetectable changes may also contribute, and propagate, possibly as an adaptive response to a transient signal that has occurred only for a few milliseconds within the bottom-up path. In an attempt to illustrate the scenario of a host of existing tinnitus researchers currently hypothesizing several hundreds of different tinnitus decisive factors, the example of “*the Blind men and the Elephant*” was brought up:

Blind to see the coherent whole behind a tinnitus percept, being too fixated on one individual part.

#### *Future Tasks to See and test for a Possible Blind Spot*

Here, we dare to suggest one factor that the tinnitus community may still be too ‘blind’ to, and that could explain most of the different existing tinnitus models and theories, to wit: the observation that the conscious percept of an auditory stimulus requires a proper maturation of a baseline. On top of this baseline, the auditory stimuli can be facilitated via integration into a fronto-striatal contrast amplification circuit to lead to a percept (Irvine 2018; Oxenham 2018). When we assume that the baseline is lost in ascending bottom-up circuits in distinct frequency channels (Knipper et al. 2020), the top-down circuit will now amplify the ‘enhanced noise’ that is generated as a result of lost contrast amplification in the affected region. The intensity of the ‘amplification process’ may, in turn, heavily depend on the individual’s ‘emotional stage’.

#### Topic 7: Future Therapy Approaches on the Basis of Ongoing Controversies About the Neural Correlate of Tinnitus

The strong contribution of distress as the best predictor of tinnitus severity (Beukes et al. 2021; Crönlein et al. 2016) may explain why cognitive behavioral therapy (CBT) has the highest effectiveness in the therapy of chronic tinnitus (European Guideline) (Aazh et al. 2019; Cima et al. 2019). The numerous studies that report stress as a co-factor for tinnitus (Brüggemann et al. 2017; Knopke et al. 2017; Ramakers et al. 2015) justify cognitive behavioral therapy as the currently



most effective therapy with the best reduction of tinnitus burden.

Besides the gold standard of rather unspecific CBT, which has been propagated for many years, the concept of bimodal neuromodulation has currently gained attention in tinnitus research through various studies that apparently provide surprisingly good results (Conlon et al. 2020; Riffle et al. 2020). Regarding the contributing factor of general health on tinnitus, efforts to reduce tinnitus by diet (Spankovich and Le Prell 2019) or physical activity (Carpenter-Thompson et al. 2015; Michiels et al. 2016) need further thought. The benefit of invasive tinnitus treatment may outweigh its risks, but with one exception: the extraordinarily invasive method of cochlear implantation. Indeed, increasing evidence suggests that tinnitus can be silenced in most of the implanted tinnitus patients with deafness or severe hearing loss (Baguley and Atlas 2007; Kleine Punte et al. 2013; Knopke et al. 2017; Li et al. 2019; Mertens et al. 2018; Pillsbury et al. 2018; Tyler et al. 2008). This would, of course, still not justify cochlear implantation in tinnitus patients that have little or no hearing loss. A brainstem auditory implant would possibly be beneficial in such cases (Van Den Berge et al. 2019).

The potential of vagus nerve stimulation (VNS) to drive neural plasticity to reduce or eliminate the neural drivers of ongoing tinnitus, although recently judged as a successful approach (De Ridder et al. 2020), may have too many side effects. Effects of pairing of the vagus stimulation with non-tinnitus or tinnitus-matched sounds still has to be determined (De Ridder et al. 2020).

Despite their potential to silence intermittent tinnitus under distinct conditions, other therapies, including, for example, lidocaine, (Vielsmeier et al. 2021), may have too severe side effects. These include psychotropic effects, or effects on blood pressure (Tran and Koo 2014), and their benefits do not seem to outweigh their risks.

#### *Future Tasks to See and Test for a Possible Blind Spot*

As noted previously, it may be conceivable to work on strategies that specifically trigger stochastic resonance. Alternatively, acoustic stimulation may be re-considered, consistent with previous findings that reported the suppression or relief of the tinnitus percept by electric-acoustic stimulation or by hearing aids (Kleine Punte et al. 2013; Knopke et al. 2017; Li et al. 2019; Mertens et al. 2018; Peters et al. 2020; Pillsbury et al. 2018; Searchfield et al. 2010; Shekhawat et al. 2013).

## CONCLUSION

We suggest that the tinnitus percept resulting from the amplification of ‘enhanced noise’ that is generated as a result of lost contrast amplification subsequent to a loss of fast (high-SR) auditory processing is compatible with

numerous apparently controversial findings. In this view certain forms of tinnitus may result from loss of fast (high-SR) auditory fibers and subsequent diminished capacity to suppress intrinsic noise levels in affected frequency channels through PV-IN driven fronto-striatal contrast amplification circuits. This signal is required to energize gate keeping, contrast amplification, neural gain, and adjustments, but when reduced as a result of diminished fast (high-SR) auditory fiber processing, would entail dysfunctions in affected frequency channels that themselves result in elevated noise levels and tinnitus percept. Tinnitus percept is amplified through increased vigilance to the noise following imbalanced cognitive control and lost contrast amplification. Tinnitus percept is amplified through increased vigilance to the noise following imbalanced cognitive control and lost contrast amplification. The tinnitus loudness and burden may differ in individuals, depending on their individual ‘emotional stage’ and distress level. Important to emphasize that this viewpoint may hold only for a small minority of tinnitus sufferers, regarding that likely a great variety of tinnitus forms exists. The authors are however convinced that the search for the most comprehensive possible concrete therapy forms is doomed to failure at least as long as we do not succeed in enabling a better clinical characterization of single forms of tinnitus in patients. In a unified effort across the tinnitus community, tinnitus research could focus on examination of this suggested concept, and find new curative approaches to silence tinnitus.

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## REFERENCES

- AAZH H, LANDGREBE M, DANESH AA, MOORE BC (2019) Cognitive behavioral therapy for alleviating the distress caused by tinnitus, hyperacusis and misophonia: current perspectives. *Psychol Res Behav Manag* 12:991–1002. <https://doi.org/10.2147/PRBM.S179138>
- AMANAT S, GALLEGU-MARTINEZ A, LOPEZ-ESCAJAZ JA (2020) Genetic inheritance and its contribution to tinnitus. *Curr Top Behav Neurosci*. [https://doi.org/10.1007/7854\\_2020\\_155](https://doi.org/10.1007/7854_2020_155)
- ARANGO-LIEVANO M, BORIE AM, DROMARD Y, MURAT M, DESARMENIEN MG, GARABEDIAN MJ, JEANNETEAU F (2019) Persistence of learning-induced synapses depends on neurotrophic priming of glucocorticoid receptors. *Proc Natl Acad Sci USA* 116(26):13097–13106. <https://doi.org/10.1073/pnas.1903203116>
- AYDIN N, SEARCHFIELD GD (2019) Changes in tinnitus and physiological biomarkers of stress in response to short-term broadband noise and sounds of nature. *Complement Ther Med* 46:62–68. <https://doi.org/10.1016/j.ctim.2019.07.018>
- BAGULEY DM, ATLAS MD (2007) Cochlear implants and tinnitus. *Prog Brain Res* 166:347–355. [https://doi.org/10.1016/S0079-6123\(07\)66033-6](https://doi.org/10.1016/S0079-6123(07)66033-6)
- BARTELS H, MIDDEL B, PEDERSEN SS, STAAL MJ, ALBERS FWJ (2010) The distressed (type D) personality is independently associated with tinnitus: a case-control study. *Psychosomatics* 51(1):29–38. <https://doi.org/10.1176/appi.psy.51.1.29>
- BAUER CS, WOOLLEY RJ, TESCHEMACHER AG, SEWARD EP (2007) Potentiation of exocytosis by phospholipase C-coupled G-protein-coupled receptors requires the priming protein Munc13-1. *J Neurosci* 27(1):212–219. <https://doi.org/10.1523/JNEUROSCI.4201-06.2007>
- BEUKES EW, MANCHAIH V, ALLEN PM, ANDERSSON G, BAGULEY DM (2021) Exploring tinnitus heterogeneity. *Prog Brain Res* 260:79–99. <https://doi.org/10.1016/bs.pbr.2020.05.022>
- BHARADWAJ HM, MASUD S, MEHRAEI G, VERHULST S, SHINN-CUNNINGHAM BG (2015) Individual differences reveal correlates of hidden hearing deficits. *J Neurosci* 35(5):2161–2172. <https://doi.org/10.1523/JNEUROSCI.3915-14.2015>
- BOECKING B, ROSE M, BRÜGGEMANN P, MAZUREK B (2021) Two birds with one stone—addressing depressive symptoms, emotional tension and worry improves tinnitus-related distress and affective pain perceptions in patients with chronic tinnitus. *PLoS One*. <https://doi.org/10.1371/journal.pone.0246747>
- BOYEN K, DE KLEINE E, VAN DIJK P, LANGERS DRM (2014) Tinnitus-related dissociation between cortical and subcortical neural activity in humans with mild to moderate sensorineural hearing loss. *Hear Res* 312:48–59. <https://doi.org/10.1016/j.heares.2014.03.001>
- BRAMHALL NF, McMILLAN GP, GALLUN FJ, KONRAD-MARTIN D (2019) Auditory brainstem response demonstrates that reduced peripheral auditory input is associated with self-report of tinnitus. *J Acoust Soc Am* 146(5):3849–3862. <https://doi.org/10.1121/1.5132708>
- BROZOSKI T, WISNER K, RANDALL M, CASPARY D (2019) Chronic sound-induced tinnitus and auditory attention in animals. *Neuroscience* 407:200–212. <https://doi.org/10.1016/j.neuroscience.2018.10.013>
- BRÜGGEMANN P, SZCZEPEK AJ, KLEE K, GRÄBEL S, MAZUREK B, OLZE H (2017) In patients undergoing cochlear implantation, psychological burden affects tinnitus and the overall outcome of auditory rehabilitation. *Front Hum Neurosci*. <https://doi.org/10.3389/fnhum.2017.00226>
- BUREŠ Z, PROFANT O, SVOBODOVÁ V, TÓTHOVÁ D, VENCOVSKÝ V, SYKA J (2019) Speech comprehension and its relation to other auditory parameters in elderly patients with tinnitus. *Front Aging Neurosci*. <https://doi.org/10.3389/fnagi.2019.00219>
- CARPENTER-THOMPSON JR, MCAULEY E, HUSAIN FT (2015) Physical activity, tinnitus severity, and improved quality of life. *Ear Hear* 36(5):574–581. <https://doi.org/10.1097/AUD.0000000000000169>
- CHADHA NK, GORDON KA, JAMES AL, PAPSIN BC (2009) Tinnitus is prevalent in children with cochlear implants. *Int J Pediatr Otorhinolaryngol* 73(5):671–675. <https://doi.org/10.1016/j.ijporl.2008.12.032>
- CHEN ZY, PATEL PD, SANT G, MENG CX, TENG KK, HEMPSTEAD BL, LEE FS (2004) Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci* 24(18):4401–4411. <https://doi.org/10.1523/JNEUROSCI.0348-04.2004>
- CIMA RFF, MAZUREK B, HAIDER H, KIKIDIS D, LAPIRA A, NORENA A, HOARE DJ (2019) A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment. *HNO* 67(1):10–42. <https://doi.org/10.1007/s00106-019-0633-7>
- CONLON B, LANGGUTH B, HAMILTON C, HUGHES S, MEADE E, CONNOR CO, SCHECKLMANN M, HALL DA, VANNESTE S, LEONG SL, SUBRAMANIAM T, D'ARCY S, LIM HH (2020) Bimodal neuromodulation combining sound and tongue stimulation reduces tinnitus symptoms in a large randomized clinical study. *Sci Transl Med*. <https://doi.org/10.1126/scitranslmed.abb2830>
- CRAMER B, STÖCKEL D, KREFT M, WIBRAL M, SCHEMMELE J, MEIER K, PRIESEMANN V (2020) Control of criticality and computation in spiking neuromorphic networks with plasticity. *Nat Commun*. <https://doi.org/10.1038/s41467-020-16548-3>
- CRÖNLEIN T, LANGGUTH B, PREGLER M, KREUZER PM, WETTER TC, SCHECKLMANN M (2016) Insomnia in patients with chronic tinnitus: cognitive and emotional distress as moderator variables. *J Psychosom Res* 83:65–68. <https://doi.org/10.1016/j.jpsychores.2016.03.001>
- DE RIDDER D, VANNESTE S, LANGGUTH B, LLINAS R (2015) Thalamocortical dysrhythmia: a theoretical update in tinnitus. *Front Neurol*. <https://doi.org/10.3389/fneur.2015.00124>
- DE RIDDER D, LANGGUTH B, VANNESTE S (2020) Vagus nerve stimulation for tinnitus: a review and perspective. *Prog Brain Res*. <https://doi.org/10.1016/bs.pbr.2020.08.011>
- DUGUID I, BRANCO T, LONDON M, CHADDERTON P, HÄUSSER M (2012) Tonic inhibition enhances fidelity of sensory information transmission in the cerebellar cortex. *J Neurosci* 32(32):11132–11143. <https://doi.org/10.1523/JNEUROSCI.0460-12.2012>
- DURAI M, O'KEEFE MG, SEARCHFIELD GD (2018) A review of auditory prediction and its potential role in tinnitus perception. *J Am Acad Audiol* 29(6):533–547. <https://doi.org/10.3766/jaaa.17025>
- DURAI M, SANDERS M, KOBAYASHI K, SEARCHFIELD GD (2019) Auditory streaming and prediction in tinnitus sufferers. *Ear Hear* 40(2):345–357. <https://doi.org/10.1097/AUD.0000000000000620>
- ECKERT P, MARCHETTA P, MANTHEY MK, WALTER MH, JOVANOVIĆ S, SAVITSKA D, SINGER W, JACOB MH, RÜTTIGER L, SCHIMMANG T,

- MILENKOVIC I, PILZ PKD, KNIPPER M (2021) Deletion of BDNF in Pax2 lineage-derived interneuron precursors in the hindbrain hampers the proportion of excitation/inhibition, learning, and behavior. *Front Mol Neurosci*. <https://doi.org/10.3389/fnmol.2021.642679>
- EGGERMONT JJ (2021) Separate auditory pathways for the induction and maintenance of tinnitus and hyperacusis? *Prog Brain Res* 260:101–127. <https://doi.org/10.1016/bs.pbr.2020.01.006>
- EGGERMONT JJ, TASS PA (2015) Maladaptive neural synchrony in tinnitus: origin and restoration. *Front Neurol*. <https://doi.org/10.3389/fneur.2015.00029>
- EGGERMONT JJ, KRAL A (2016) Somatic memory and gain increase as preconditions for tinnitus: insights from congenital deafness. *Hear Res* 333:37–48. <https://doi.org/10.1016/j.heares.2015.12.018>
- ELARBED A, FACKRELL K, BAGULEY DM, HOARE DJ (2021) Tinnitus and stress in adults: a scoping review. *Int J Audiol* 60(3):171–182. <https://doi.org/10.1080/14992027.2020.1827306>
- FAYE C, MCGOWAN JC, DENNY CA, DAVID DJ (2018) Neurobiological mechanisms of stress resilience and implications for the aged population. *Curr Neuropharmacol* 16(3):234–270. <https://doi.org/10.2174/1570159x15666170818095105>
- GOLLNAST D, TZIRIDIS K, KRAUSS P, SCHILLING A, HOPPE U, SCHULZE H (2017) Analysis of audiometric differences of patients with and without tinnitus in a large clinical database. *Front Neurol*. <https://doi.org/10.3389/fneur.2017.00031>
- HEMMER P, TAUBER S, STEYVERS M (2015) Moving beyond qualitative evaluations of Bayesian models of cognition. *Psychon Bull Rev* 22(3):614–628. <https://doi.org/10.3758/s13423-014-0725-z>
- HINKLEY LB, MIZUURI D, HONG O, NAGARAJAN SS, CHEUNG SW (2015) Increased striatal functional connectivity with auditory cortex in tinnitus. *Front Hum Neurosci* 9(OCTOBER):568. <https://doi.org/10.3389/fnhum.2015.00568>
- HOFMEIER B, WOLPERT S, ALDAMER ES, WALTER M, THIERICKE J, BRAUN C, ZELLE D, RÜTTIGER L, KLOSE U, KNIPPER M (2018) Reduced sound-evoked and resting-state BOLD fMRI connectivity in tinnitus. *NeuroImage Clin* 20:637–649. <https://doi.org/10.1016/j.nicl.2018.08.029>
- HOFMEIER B, WERTZ J, REFAT F, HINRICHS P, SAEMISCH J, SINGER W, RÜTTIGER L, KLOSE U, KNIPPER M, WOLPERT S (2021) Functional biomarkers that distinguish between tinnitus with and without hyperacusis. *Clin Transl Med* 11(5):e378. <https://doi.org/10.1002/ctm2.378>
- HSIEH TH, CHEONG LEE HH, HAMEED MQ, PASCUAL-LEONE A, HENSCH TK, ROTENBERG A (2017) Trajectory of parvalbumin cell impairment and loss of cortical inhibition in traumatic brain injury. *Cereb Cortex* 27(12):5509–5524. <https://doi.org/10.1093/cercor/bhw318>
- HU H, GAN J, JONAS P (2014) Fast-spiking, parvalbumin+ GABAergic interneurons: from cellular design to microcircuit function. *Science*. <https://doi.org/10.1126/science.1255263>
- HU H, ROTH FC, VANDAELE D, JONAS P (2018) Complementary tuning of Na+ and K+ channel gating underlies fast and energy-efficient action potentials in GABAergic interneuron axons. *Neuron* 98(1):156–165. e6. <https://doi.org/10.1016/j.neuron.2018.02.024>
- HULLFISH J, ABENES I, KOVACS S, SUNAERT S, DE RIDDER D, VANNESTE S (2018) Functional brain changes in auditory phantom perception evoked by different stimulus frequencies. *Neurosci Lett* 683:160–167. <https://doi.org/10.1016/j.neulet.2018.07.043>
- HULLFISH J, SEDLEY W, VANNESTE S (2019) Prediction and perception: insights for (and from) tinnitus. *Neurosci Biobehav Rev* 102:1–12. <https://doi.org/10.1016/j.neubiorev.2019.04.008>
- IRVINE DRF (2018) Plasticity in the auditory system. *Hear Res* 362:61–73. <https://doi.org/10.1016/j.heares.2017.10.011>
- JASTREBOFF PJ, GRAY WC, GOLD SL (1996) Neurophysiological approach to tinnitus patients. *Am J Otol* 17(2):236–240
- JEANNETEAU F, BORIE A, CHAO MV, GARABEDIAN MJ (2019) Bridging the gap between brain-derived neurotrophic factor and glucocorticoid effects on brain networks. *Neuroendocrinology* 109(3):277–284. <https://doi.org/10.1159/000496392>
- KANDEEPAN S, MAUDOUX A, RIBEIRO DE PAULA D, ZHENG JY, CABAY JE, GÓMEZ F, CHRONIK BA, RIDDER D, VANNESTE S, SODDU A (2019) Tinnitus distress: a paradoxical attention to the sound? *J Neurool* 266(9):2197–2207. <https://doi.org/10.1007/s00415-019-09390-1>
- KANN L, MCMANUS T, HARRIS WA, SHANKLIN SL, FLINT KH, HAWKINS J, QUEEN B, LOWRY R, OLSEN EOM, CHYEN D, WHITTLE L, THORNTON J, LIM C, YAMAKAWA Y, BRENER N, ZAZA S (2016) Youth risk behavior surveillance—United States, 2015. *MMWR Surveill Summ* 65(6):1–180. <https://doi.org/10.15585/mmwr.ss6506a1>
- KHAN RA, HUSAIN FT (2020) Tinnitus and cognition: can load theory help us refine our understanding? *Laryngosc Invest Otolaryngol* 5(6):1197–1204. <https://doi.org/10.1002/lio2.501>
- KLEINE PUNTE A, DE RIDDER D, VAN DE HEYNING P (2013) On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. *Hear Res* 295:24–29. <https://doi.org/10.1016/j.heares.2012.08.003>
- KNIPPER M, VAN DIJK P, SCHULZE H, MAZUREK B, KRAUSS P, SCHEPER V, WARNECKE A, SCHLEE W, SCHWABE K, SINGER W, BRAUN C, DELANO PH, FALLGATTER AJ, EHLIS AC, SEARCHFIELD GD, MUNK MHJ, BAGULEY DM, RÜTTIGER L (2020) The neural bases of tinnitus: lessons from deafness and cochlear implants. *J Neurosci* 40(38):7190–7202. <https://doi.org/10.1523/JNEUROSCI.1314-19.2020>
- KNOPKE S, SZCZEPEK AJ, HAÜSSLER SM, GRABEL S, OLZE H (2017) Cochlear implantation of bilaterally deafened patients with tinnitus induces sustained decrease of tinnitus-related distress. *Front Neurol*. <https://doi.org/10.3389/fneur.2017.00158>
- KOOPS EA, VAN DIJK P (2021) Hyperacusis in tinnitus patients relates to enlarged subcortical and cortical responses to sound except at the tinnitus frequency. *Hear Res*. <https://doi.org/10.1016/j.heares.2020.108158>
- KOOPS EA, RENKEN RJ, LANTING CP, VAN DIJK P (2020) Cortical tonotopic map changes in humans are larger in hearing loss than in additional tinnitus. *J Neurosci* 40(16):3178–3185. <https://doi.org/10.1523/JNEUROSCI.2083-19.2020>
- KOOPS EA, HAYKAL S, VAN DIJK P (2021) Macrostructural changes of the acoustic radiation in humans with hearing loss and tinnitus revealed with fixel-based analysis. *J Neurosci* 41(18):3958–3965. <https://doi.org/10.1523/jneurosci.2996-20.2021>
- KOZLOVSKIY SA, PYASIK MM, KOROTKOVA AV, VARTANOV AV, GLOZMAN JM, KISELNIKOV AA (2014) Activation of left lingual gyrus related to working memory for schematic faces. *Int J Psychophysiol* 94(2):241. <https://doi.org/10.1016/j.ijpsycho.2014.08.928>
- KRAUS KS, CANLON B (2012) Neuronal connectivity and interactions between the auditory and limbic systems. Effects of noise and tinnitus. *Hear Res* 288(1–2):34–46. <https://doi.org/10.1016/j.heares.2012.02.009>
- KRAUSS P, TZIRIDIS K, METZNER C, SCHILLING A, HOPPE U, SCHULZE H (2016) Stochastic resonance controlled upregulation of internal noise after hearing loss as a putative cause of tinnitus-related neuronal hyperactivity. *Front Neurosci*. <https://doi.org/10.3389/fnins.2016.00597>
- KRAUSS P, METZNER C, SCHILLING A, SCHÜTZ C, TZIRIDIS K, FABRY B, SCHULZE H (2017) Adaptive stochastic resonance for unknown and variable input signals. *Sci Rep*. <https://doi.org/10.1038/s41598-017-02644-w>
- KRAUSS P, METZNER C, SCHILLING A, TZIRIDIS K, TRAXDORF M, WOLLBRINK A, RAMPP S, PANTEV C, SCHULZE H (2018a) A statistical method for analyzing and comparing spatiotemporal cortical activation patterns. *Sci Rep*. <https://doi.org/10.1038/s41598-018-23765-w>
- KRAUSS P, TZIRIDIS K, SCHILLING A, SCHULZE H (2018b) Cross-modal stochastic resonance as a universal principle to enhance sensory processing. *Front Neurosci* 12(AUG):578. <https://doi.org/10.3389/fnins.2018.00578>

- LAND R, BAUMHOFF P, TILLEIN J, LOMBER SG, HUBKA P, KRAL A (2016) Cross-modal plasticity in higher-order auditory cortex of congenitally deaf cats does not limit auditory responsiveness to cochlear implants. *J Neurosci* 36(23):6175–6185. <https://doi.org/10.1523/JNEUROSCI.0046-16.2016>
- LANTING CP, DE KLEINE E, LANGERS DRM, VAN DIJK P (2014) Unilateral tinnitus: changes in connectivity and response lateralization measured with fMRI. *PLoS One*. <https://doi.org/10.1371/journal.pone.0110704>
- LEAVER AM, RENIER L, CHEVILLET MA, MORGAN S, KIM HJ, RAUSCHER JP (2011) Dysregulation of limbic and auditory networks in tinnitus. *Neuron* 69(1):33–43. <https://doi.org/10.1016/j.neuron.2010.12.002>
- LEE SY, NAM DW, KOO JW, DE RIDDER D, VANNESTE S, SONG JJ (2017) No auditory experience, no tinnitus: lessons from subjects with congenital- and acquired single-sided deafness. *Hear Res* 354:9–15. <https://doi.org/10.1016/j.heares.2017.08.002>
- LEE SY, CHOI BY, KOO JW, DE RIDDER D, SONG JJ (2020) Cortical oscillatory signatures reveal the prerequisites for tinnitus perception: a comparison of subjects with sudden sensorineural hearing loss with and without tinnitus. *Front Neurosci*. <https://doi.org/10.3389/fnins.2020.596647>
- LI C, KUHLMAY M, KIM AH (2019) Electroacoustic stimulation. *Otolaryngol Clin North Am* 52(2):311–322. <https://doi.org/10.1016/j.otc.2018.11.008>
- LIBERMAN MC (1978) Auditory-nerve response from cats raised in a low-noise chamber. *J Acoust Soc Am* 63(2):442–455. <https://doi.org/10.1121/1.381736>
- LIBERMAN MC, KUJAWA SG (2017) Cochlear synaptopathy in acquired sensorineural hearing loss: manifestations and mechanisms. *Hear Res* 349:138–147. <https://doi.org/10.1016/j.heares.2017.01.003>
- LOPEZ-ESCAMEZ JA, AMANAT S (2020) Heritability and genetics contribution to tinnitus. *Otolaryngol Clin North Am* 53(4):501–513. <https://doi.org/10.1016/j.otc.2020.03.003>
- LUAN Y, WANG C, JIAO Y, TANG T, ZHANG J, TENG GJ (2019) Prefrontal-temporal pathway mediates the cross-modal and cognitive reorganization in sensorineural hearing loss with or without tinnitus: a Multimodal MRI Study. *Front Neurosci*. <https://doi.org/10.3389/fnins.2019.00222>
- MAJHI SK, KHANDELWAL K, SHAREEF M (2019) Auditory brainstem response in patients of tinnitus with sensorineural hearing loss. *Indian J Otolaryngol Head Neck Surg* 71(Suppl 2):1495–1499. <https://doi.org/10.1007/s12070-018-1568-0>
- MAMASHLI F, KHAN S, BHARADWAJ H, MICHMIZOS K, GANESAN S, GAREL KLA, ALI HASHMI J, HERBERT MR, HÄMÄLÄINEN M, KENET T (2017) Auditory processing in noise is associated with complex patterns of disrupted functional connectivity in autism spectrum disorder. *Autism Res* 10(4):631–647. <https://doi.org/10.1002/aur.1714>
- MARCHETTA P, SAVITSKA D, KÜBLER A, ASOLA G, MANTHEY M, MÖHRLE D, SCHIMMANG T, RÜTTIGER L, KNIPPER M, SINGER W (2020) Age-dependent auditory processing deficits after cochlear synaptopathy depend on auditory nerve latency and the ability of the brain to recruit ltp/bdnf. *Brain Sci* 10(10):1–26. <https://doi.org/10.3390/brainsci10100710>
- MARKS E, SMITH P, MCKENNA L (2019) Living with tinnitus and the health care journey: an interpretative phenomenological analysis. *Br J Health Psychol* 24(2):250–264. <https://doi.org/10.1111/bjhp.12351>
- MARTEL DT, SHORE SE (2020) Ventral cochlear nucleus bushy cells encode hyperacusis in guinea pigs. *Sci Rep*. <https://doi.org/10.1038/S41598-020-77754-Z>
- MATT L, ECKERT P, PANFORD-WALSH R, GEISLER HS, BAUSCH AE, MANTHEY M, MÜLLER NIC, HARASZTOSI C, ROHBOCK K, RUTH P, FRIAUF E, OTT T, ZIMMERMANN U, RÜTTIGER L, SCHIMMANG T, KNIPPER M, SINGER W (2018) Visualizing BDNF transcript usage during sound-induced memory linked plasticity. *Front Mol Neurosci*. <https://doi.org/10.3389/fnmol.2018.00260>
- MAZUREK B, HAUPT H, OLZE H, SZCZEPK AJ (2012) Stress and tinnitus—from bedside to bench and back. *Front Syst Neurosci*. <https://doi.org/10.3389/fnsys.2012.00047>
- MAZUREK B, BOECKING B, BRUEGGEMANN P (2019) Association between stress and tinnitus—new aspects. *Otol Neurotol* 40(4):e467–e473. <https://doi.org/10.1097/MAO.0000000000002180>
- MERTENS G, VAN ROMPAEY V, VAN DE HEYNING P (2018) Electric-acoustic stimulation suppresses tinnitus in a subject with high-frequency single-sided deafness. *Cochlear Implants Int* 19(5):292–296. <https://doi.org/10.1080/14670100.2018.1473940>
- MICHELIS S, NAESSENS S, VAN DE HEYNING P, BRAEM M, VISSCHER CM, GILLES A, DE HERTOOGH W (2016) The effect of physical therapy treatment in patients with subjective tinnitus: a systematic review. *Front Neurosci*. <https://doi.org/10.3389/fnins.2016.00545>
- MILLOY V, FOURNIER P, BENOIT D, NOREÑA A, KORAVAND A (2017) Auditory brainstem responses in tinnitus: a review of who, how, and what? *Front Aging Neurosci*. <https://doi.org/10.3389/fnagi.2017.00237>
- MOHAMAD N, HOARE DJ, HALL DA (2016) The consequences of tinnitus and tinnitus severity on cognition: a review of the behavioural evidence. *Hear Res* 332:199–209. <https://doi.org/10.1016/j.heares.2015.10.001>
- MOHEBBI M, DANESI A, ASADPOUR A, MOHSEN S, FARHADI M, MAHMOUDIAN S (2019) The potential role of auditory prediction error in decompensated tinnitus: an auditory mismatch negativity study. *Brain Behav* 9(4):1–14. <https://doi.org/10.1002/brb3.1242>
- MÖHRLE D, HOFMEIER B, AMEND M, WOLPERT S, NI K, BING D, KLOSE U, PICHLER B, KNIPPER M, RÜTTIGER L (2019) Enhanced central neural gain compensates acoustic trauma-induced cochlear impairment, but unlikely correlates with tinnitus and hyperacusis. *Neuroscience* 407:146–169. <https://doi.org/10.1016/j.neuroscience.2018.12.038>
- MOHSEN S, MAHMOUDIAN S, TALBIAN S, POURBAKHT A (2019) Research paper: correlation analysis of the tinnitus handicap inventory and distress network in chronic tinnitus: an EEG Study. *Basic Clin Neurosci* 10(5):499–514. <https://doi.org/10.32598/bcn.9.10.215>
- NAGARAJ MK, BHASKAR A, PRABHU P (2020) Assessment of auditory working memory in normal hearing adults with tinnitus. *Eur Arch Otorhinolaryngol* 277(1):47–54. <https://doi.org/10.1007/s00405-019-05658-4>
- NEFF PKA, SCHOISSWOHL S, SIMOES J, STAUDINGER S, LANGGUTH B, SCHECKLMANN M, SCHLEE W (2021) Prolonged tinnitus suppression after short-term acoustic stimulation. *Prog Brain Res*. <https://doi.org/10.1016/bs.pbr.2021.02.004>
- NIEMANN U, BRUEGGEMANN P, BOECKING B, MEBUS W, ROSE M, SPILIOPOULOU M, MAZUREK B (2020) Phenotyping chronic tinnitus patients using self-report questionnaire data: cluster analysis and visual comparison. *Sci Rep*. <https://doi.org/10.1038/s41598-020-73402-8>
- NOREÑA A, LACHER-FOUGÈRE S, FRAYSSE M-J, BIZAGUET E, GREVIN P, THAI-VAN H, MOATI L, LE PAJOLEC C, FOURNIER P, OHRESSER M (2021) A contribution to the debate on tinnitus definition. *Prog Brain Res*. <https://doi.org/10.1016/bs.pbr.2021.01.029>
- NOREÑA AJ, FARLEY BJ (2013) Tinnitus-related neural activity: theories of generation, propagation, and centralization. *Hear Res* 295:161–171. <https://doi.org/10.1016/j.heares.2012.09.010>
- ORTMANN M, MÜLLER N, SCHLEE W, WEISZ N (2011) Rapid increases of gamma power in the auditory cortex following noise trauma in humans. *Eur J Neurosci* 33(3):568–575. <https://doi.org/10.1111/j.1460-9568.2010.07542.x>
- OXENHAM AJ (2018) How we hear: the perception and neural coding of sound. *Annu Rev Psychol* 69:27–50. <https://doi.org/10.1146/annurev-psych-122216-011635>
- PARK E, KIM H, CHOI IH, HAN HM, HAN K, JUNG HH, IM GJ (2020) Psychiatric distress as a common risk factor for tinnitus and joint pain: a national population-based survey. *Clin Exp*



- Otorhinolaryngol 13(3):234–240. <https://doi.org/10.21053/ceo.2019.00563>
- PATTYN T, VAN DEN EEDE F, VANNESTE S, CASSIERS L, VELTMAN DJ, VAN DE HEYNING P, SABBE BCG (2016) Tinnitus and anxiety disorders: a review. *Hear Res* 333:255–265. <https://doi.org/10.1016/j.heares.2015.08.014>
- PETERS TTA, VAN DEN BERGE MJC, FREE RH, VAN DER VLIET AM, KNOPPEL H, VAN DIJK P, HOFMAN R (2020) The relation between tinnitus and a neurovascular conflict of the cochleovestibular nerve on magnetic resonance imaging. *Otol Neurotol* 41(1):E124–E131. <https://doi.org/10.1097/MAO.0000000000002432>
- PILLSBURY HC, DILLON MT, BUCHMAN CA, STAECKER H, PRENTISS SM, RUCKENSTEIN MJ, BIGELOW DC, TELISCHI FF, DI MARTINEZ M, RUNGE CL, FRIEDLAND DR, BLEVINS NH, LARKY JB, ALEXIADES G, KAYLIE DM, ROLAND PS, MIYAMOTO RT, BACKOUS DD, WARREN FM ET AL (2018) Multicenter US Clinical Trial with an electric-acoustic stimulation (EAS) system in adults: final outcomes. *Otol Neurotol* 39(3):299–305. <https://doi.org/10.1097/MAO.0000000000001691>
- RALLI M, SALVI RJ, GRECO A, TURCHETTA R, DE VIRGILIO A, ALTISSIMI G, ATTANASIO G, CLANFRONE G, DE VINCENITIS M (2017) Characteristics of somatic tinnitus patients with and without hyperacusis. *PLoS One*. <https://doi.org/10.1371/journal.pone.0188255>
- RAMAKERS GGJ, VAN ZON A, STEGEMAN I, GROLMAN W (2015) The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: a systematic review. *Laryngoscope* 125(11):2584–2592. <https://doi.org/10.1002/lary.25370>
- RAUSCHHECKER JP (2010) An expanded role for the dorsal auditory pathway in sensorimotor control and integration. *Hear Res*. <https://doi.org/10.1016/j.heares.2010.09.001>
- RAUSCHHECKER JP, FRITZ JB, GARRAGHTY PE, FREEDMAN DJ (2014) Is there a tape recorder in your head? How the brain stores and retrieves musical melodies. *Front Syst Neurosci*. <https://doi.org/10.3389/fnsys.2014.00149>
- REFAT F, WERTZ J, HINRICH S, KLOSE U, SAMY H, ABDELKADER RM, SAEMISCH J, HOFMEIER B, SINGER W, RÜTTIGER L, KNIPPER M, WOLPERT S (2021) Co-occurrence of hyperacusis accelerates with tinnitus burden over time and requires medical care. *Front Neurol*. <https://doi.org/10.3389/fneur.2021.627522>
- RIFFLE TL, MARTEL DT, JONES GR, SHORE SE (2020) Bimodal auditory electrical stimulation for the treatment of tinnitus: preclinical and clinical studies. *Curr Top Behav Neurosci*. [https://doi.org/10.1007/7854\\_2020\\_180](https://doi.org/10.1007/7854_2020_180)
- ROSSIGNOL E, KRUGLIKOV I, VAN DEN MAAGDENBERG AMJM, RUDY B, FISHELL G (2013) CaV2.1 ablation in cortical interneurons selectively impairs fast-spiking basket cells and causes generalized seizures. *Ann Neurol* 74(2):209–222. <https://doi.org/10.1002/ana.23913>
- RUAN Q, YU Z, ZHANG W, RUAN J, LIU C, ZHANG R (2018) Cholinergic hypofunction in presbycusis-related tinnitus with cognitive function impairment: emerging hypotheses. *Front Aging Neurosci*. <https://doi.org/10.3389/fnagi.2018.00098>
- RÜTTIGER L, SINGER W, PANFORD-WALSH R, MATSUMOTO M, LEE SC, ZUCCOTTI A, ZIMMERMANN U, JAUMANN M, ROHBOCK K, XIONG H, KNIPPER M (2013) The reduced cochlear output and the failure to adapt the central auditory response causes tinnitus in noise exposed rats. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0057247>
- SCHAETTE R, McALPINE D (2011) Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *J Neurosci* 31(38):13452–13457. <https://doi.org/10.1523/JNEUROSCI.2156-11.2011>
- SHECKELMANN M, LANDGREBE M, KLEINJUNG T, FRANK E, SAND PG, RUPPRECHT R, EICHHAMMER P, HAJAK G, LANGGUTH B (2014) Changes in motor cortex excitability associated with temporal repetitive transcranial magnetic stimulation in tinnitus: hints for cross-modal plasticity? *BMC Neurosci*. <https://doi.org/10.1186/1471-2202-15-71>
- SCHILLING A, TZIRIDIS K, SCHULZE H, KRAUSS P (2021) The stochastic resonance model of auditory perception: a unified explanation of tinnitus development, Zwicker tone illusion, and residual inhibition. *Prog Brain Res*. <https://doi.org/10.1016/bs.pbr.2021.01.025>
- SCHMIDT SA, AKROFI K, CARPENTER-THOMPSON JR, HUSAIN FT (2013) Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity in tinnitus and hearing loss. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0076488>
- SCHMIDT SA, CARPENTER-THOMPSON J, HUSAIN FT (2017) Connectivity of precuneus to the default mode and dorsal attention networks: a possible invariant marker of long-term tinnitus. *NeuroImage Clin* 16:196–204. <https://doi.org/10.1016/j.nicl.2017.07.015>
- SEARCHFIELD GD (2014) Tinnitus what and where: an ecological framework. *Front Neurol*. <https://doi.org/10.3389/fneur.2014.00271>
- SEARCHFIELD GD, KAUR M, MARTIN WH (2010) Hearing aids as an adjunct to counseling: tinnitus patients who choose amplification do better than those that don't. *Int J Audiol* 49(8):574–579. <https://doi.org/10.3109/14992021003777267>
- SEARCHFIELD GD, FOK C, DONALDSON T, DURAI M, KLEINSTÄUBER M, LINFORD T, MASLIN M (2020) An evaluation of a continuing education workshop for audiologists on the assessment and management of tinnitus. *J Contin Educ Health Prof* 40(2):125–130. <https://doi.org/10.1097/CEH.0000000000000285>
- SEADLEY W, GANDER PE, KUMAR S, KOVACH CK, OYA H, KAWASAKI H, HOWARD MA, GRIFFITHS TD (2016) Neural signatures of perceptual inference. *Elife*. <https://doi.org/10.7554/eLife.11476>
- SHEKHAWAT GS, SEARCHFIELD GD, STINEAR CM (2013) Role of hearing aids in tinnitus intervention: a scoping review. *J Am Acad Audiol* 24(8):747–762. <https://doi.org/10.3766/jaaa.24.8.11>
- SHORE SE, ROBERTS LE, LANGGUTH B (2016) Maladaptive plasticity in tinnitus-triggers, mechanisms and treatment. *Nat Rev Neurol* 12(3):150–160. <https://doi.org/10.1038/nrneuro.2016.12>
- SIMOENS VL, HÉBERT S (2012) Cortisol suppression and hearing thresholds in tinnitus after low-dose dexamethasone challenge. *BMC Ear Nose Throat Disord*. <https://doi.org/10.1186/1472-6815-12-4>
- SINGER W, ZUCCOTTI A, JAUMANN M, LEE SC, PANFORD-WALSH R, XIONG H, ZIMMERMANN U, FRANZ C, GEISLER HS, KÖPSCHELL I, ROHBOCK K, VARAKINA K, VERPOORTEN S, REINBOHE T, SCHIMMANG T, RÜTTIGER L, KNIPPER M (2013) Noise-induced inner hair cell ribbon loss disturbs central arc mobilization: a novel molecular paradigm for understanding tinnitus. *Mol Neurobiol* 47(1):261–279. <https://doi.org/10.1007/s12035-012-8372-8>
- SPANKOVICH C, LE PRELL CG (2019) The role of diet in vulnerability to noise-induced cochlear injury and hearing loss. *J Acoust Soc Am* 146(5):4033–4043. <https://doi.org/10.1121/1.5132707>
- SZCZEPK AJ, FREJO L, VONA B, TRPČEVSKA N, CEDERROTH CR, CARIA H, LOPEZ-ESCAMEZ JA (2019) Recommendations on collecting and storing samples for genetic studies in hearing and tinnitus research. *Ear Hear* 40(2):219–226. <https://doi.org/10.1097/AUD.0000000000000614>
- TRAN AN, KOO JY (2014) Risk of systemic toxicity with topical lidocaine/prilocaine: a review—PubMed. *J Drugs Dermatol* 13(9):1118–1122
- TREVIS KJ, McLACHLAN NM, WILSON SJ (2016) Psychological mediators of chronic tinnitus: the critical role of depression. *J Affect Disord* 204:234–240. <https://doi.org/10.1016/j.jad.2016.06.055>
- TYLER RS, RUBINSTEIN J, PAN T, CHANG SA, GOGEL SA, GEHRINGER A, COELHO C (2008) Electrical stimulation of the cochlea to reduce tinnitus. *Semin Hear* 29(4):326–332. <https://doi.org/10.1055/s-0028-1095892>

- VAN DEN BERGE MJC, VAN DIJK MJMC, METZEMAEKERS JDM, MAAT B, FREE RH, VAN DIJK P (2019) An auditory brainstem implant for treatment of unilateral tinnitus: protocol for an interventional pilot study. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2018-026185>
- VAN GENDT MJ, BOYEN K, DE KLEINE E, LANGERS DRM, VAN DIJK P (2012) The relation between perception and brain activity in gaze-evoked tinnitus. *J Neurosci* 32(49):17528–17539. <https://doi.org/10.1523/JNEUROSCI.2791-12.2012>
- VAN MUNSTER JJCM, VAN DER VALK WH, STEGEMAN I, LIEFTINK AF, SMIT AL (2020) The relationship of tinnitus distress with personality traits: a systematic review. *Front Neurol* 11:1–40. <https://doi.org/10.3389/fneur.2020.00225>
- VANNESTE S, ALSALMAN O, DE RIDDER D (2018a) COMT and the neurogenetic architecture of hearing loss induced tinnitus. *Hear Res* 365:1–15. <https://doi.org/10.1016/j.heares.2018.05.020>
- VANNESTE S, SONG JJ, DE RIDDER D (2018b) Thalamic cortical dysrhythmia detected by machine learning. *Nat Commun*. <https://doi.org/10.1038/s41467-018-02820-0>
- VANNESTE S, ALSALMAN O, DE RIDDER D (2019) Top-down and bottom-up regulated auditory phantom perception. *J Neurosci* 39(2):364–378. <https://doi.org/10.1523/JNEUROSCI.0966-18.2018>
- VANNESTE S, MOHAN A, DE RIDDER D, TO WT (2021) The BDNF Val66Met polymorphism regulates vulnerability to chronic stress and phantom perception. *Prog Brain Res* 260:301–326. <https://doi.org/10.1016/bs.pbr.2020.08.005>
- VIELSMIEIER V, SANTIAGO STIEL R, KWOK P, LANGGUTH B, SCHECKLMANN M (2020) From acute to chronic tinnitus: pilot data on predictors and progression. *Front Neurol*. <https://doi.org/10.3389/fneur.2020.00997>
- VIELSMIEIER V, SCHLEE W, LANGGUTH B, KREUZER PM, HINTSCHICH C, STROHMEYER L, SIMOES J, BIESINGER E (2021) Lidocaine injections to the otic ganglion for the treatment of tinnitus—a pilot study. *Prog Brain Res* 260:355–366. <https://doi.org/10.1016/bs.pbr.2020.08.006>
- WALLHÄUSSER-FRANKE E, DELB W, BALKENHOL T, HILLER W, HÖRMANN K (2014) Tinnitus-related distress and the personality characteristic resilience. *Neural Plast*. <https://doi.org/10.1155/2014/370307>
- WEISZ N, DOHRMANN K, ELBERT T (2007) The relevance of spontaneous activity for the coding of the tinnitus sensation. *Prog Brain Res* 166:61–70. [https://doi.org/10.1016/S0079-6123\(07\)66006-3](https://doi.org/10.1016/S0079-6123(07)66006-3)
- WHITE O, BABIC J, TRENADO C, JOHANNSEN L, GOSWAMI N (2019) The promise of stochastic resonance in falls prevention. *Front Physiol*. <https://doi.org/10.3389/fphys.2018.01865>
- WILTING J, DEHNING J, NETO JP, RUDEL T, WIBRAL M, ZIERENBERG J, PRIESEMAN V (2018) Dynamic adaptive computation: tuning network states to task requirements. *arXiv*. <https://doi.org/10.3389/fnsys.2018.00055>
- WU PZ, LIBERMAN LD, BENNETT K, DE GRUTTOLA V, O'MALLEY JT, LIBERMAN MC (2019) Primary neural degeneration in the human cochlea: evidence for hidden hearing loss in the aging ear. *Neuroscience* 407:8–20. <https://doi.org/10.1016/j.neuroscience.2018.07.053>
- YOO H, BIN, MOHAN A, DE RIDDER D, VANNESTE S (2021) Paradoxical relationship between distress and functional network topology in phantom sound perception. *Prog Brain Res* 260:367–395. <https://doi.org/10.1016/bs.pbr.2020.08.007>
- ZENG FG (2020) Tinnitus and hyperacusis: central noise, gain and variance. *Curr Opin Physiol* 18:123–129. <https://doi.org/10.1016/j.cophys.2020.10.009>

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