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Is temporal processing crucial to improve hearing in tinnitus patients?

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Abstract

Temporal processing of auditory data plays a crucial role in our proposed model of tinnitus development through stochastic resonance (SR). The model assumes a physiological mechanism optimizing auditory information transmission (as quantified by autocorrelation (AC) analysis) into the brain by adding the optimal amount of neuronal noise to otherwise subthreshold signals. We hypothesize that this takes place at the second synapse of the auditory pathway in the dorsal cochlear nucleus (DCN). We propose that after hearing loss, this neuronal noise is tuned up in the affected frequency-band to improve hearing thresholds on the cost of upward propagation of this added noise, which finally may be perceived as tinnitus. We could already show the improvement of hearing thresholds in a large population of patients. Until now, we did not investigate the differences in hearing thresholds based on the biological constrains of early auditory temporal processing (phase locking) that is only possible up to frequencies of 5 kHz. In this report, we grouped our patient database (N=47986) according to tinnitus pitch (TP) of below (TP<5kHz) or above (TP>5kHz) the 5 kHz limit or having no tinnitus (NT) and compared their mean audiograms. We found that TP<5kHz patients showed significantly better hearing thresholds than all other patient groups independent of age. No improvement was seen for TP>5kHz patients who even showed worse thresholds than NT patients for high frequencies. These results are further evidence for our SR model of tinnitus development and the existence of AC analysis at the level of the DCN.

Introduction

About one sixth of the general population suffers from chronic, subjective tinnitus (Shargorodsky *et al.* , 2010). In contrast to the common sense that views tinnitus as a maladaptive process that is triggered by some kind of hearing loss, we have put forward a model of tinnitus development that views the phantom percept as a side effect of a mechanism that permanently optimizes information transmission into the auditory system by means of stochastic resonance (Krauss *et al.* , 2016; Krauss *et al.* , 2017; Schilling *et al.* , 2021). According to this model, neuronal noise from the somatosensory system (Shore & Zhou, 2006) is added to the cochlear input at the level of the dorsal cochlear nucleus (DCN). In case of reduced cochlear input due to inner hair cell damage or denervation ("hidden hearing loss"), the added neuronal noise can lift the otherwise subthreshold cochlear input above the threshold (= stochastic resonance, SR), thereby improving hearing thresholds (Gollnast *et al.* , 2017). For SR to optimize information transmission in the described way, the amplitude of the noise has to be constantly adapted to changing levels of cochlear input. In our model, this is achieved by maximizing the autocorrelation (AC) of the DCN output (Krauss et al., 2017). As a result, hearing would be improved at the cost of added noise into the auditory system that can then be perceived as tinnitus.

This model – although it explains a multitude of tinnitus related phenomena (Schilling *et al.* , 2021) – is challenged by the question of how the AC of the DCN output is computed by the DCN. In general, neuronal networks can compute the AC of a spike train using so-called delay lines and coincidence detectors (Licklider, 1951). It seems plausible that such a network could be implemented within the DCN (Mugnaini & Morgan, 1987), in particular if for each frequency channel only the "expected" time delay between two

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spikes (representing the frequency the channel is tuned to) has to be "hard-wired" rather than a whole array of coincidence detectors. Nevertheless, as a delay line with coincidence detectors analyzes temporal delays between spikes, computing the AC requires precise timing of spikes within a spike train, that is, phase locking of the spikes to the stimulus waveform or envelope. In mammals, even with the aid of Wever's volley theory, such phase locking (in the auditory nerve) is limited to frequencies up to about 5 kHz (Rose *et al.* , 1969; Hind, 1972).

Accordingly, if the described SR mechanism relies on the computation of the AC of the DCN output and AC computation relies on precise spike timing, then the observed improvement of hearing thresholds should only be possible for frequencies up to about 5 kHz. In line with our model, the perceived tinnitus frequency of patients is highly correlated with the frequency of strongest hearing loss (Axelsson & Sandh, 1985; König*et al.* , 2006; Schecklmann *et al.* , 2012), as this is the frequency range where the highest noise levels would have to be added to the DCN to ensure optimal SR and thereby maximal threshold improvement. Consequently, we here put forward the hypothesis that patients with tinnitus frequencies up to 5 kHz should show improved hearing thresholds when compared to patient without tinnitus, while those with tinnitus frequencies above 5 kHz should not show such improvement.

Material and Methods

Data was obtained from the audiological database of the ENT-hospital, head and neck surgery Erlangen, as described before (Krauss *et al.* , 2016; Gollnast *et al.* , 2017). Briefly, anonymized standard clinical pure-tone audiometric data (hearing loss (HL) in dB, tinnitus pitch (TP)) from both ears of 47986 adult patients (0.25 kHz to 8 kHz) collected between 2000 and 2018 were analyzed retrospectively. Therefore, German law required no declaration of consent. Patients who complained about experiencing tonal tinnitus percepts in at least one ear were classified as tinnitus patients (group T) and patients without complaints about any form of tinnitus were classified as non-tinnitus patients' data (group NT). Patients complaining about non-tonal tinnitus were excluded from further analysis.

Group T was further divided based on perceived TP, being below or above 5 kHz (A TP of 5 kHz could not occur because of the frequencies used in the clinical TP test raster which excluded 5 kHz). Data from a total of 44050 NT, 1833 $TP_{<5kHz}TP_{<5kHz}$, and 2103 $TP_{>5kHz}$ patients were analyzed by two-factorial ANOVAs and Tukey post-hoc tests as described before (Krauss *et al.* , 2016; Gollnast *et al.* , 2017). For age group analysis, adults were categorized into three age groups with those below 40 years (a), below 60 a, and 60 a and above.

Results

In a first step, we repeated the analysis performed in the study from Krauss and colleagues (Krauss *et al.* , 2016) including the new patient population examined in our clinic since then. We were able to confirm the result that patients within group T in general show better mean hearing thresholds than patients without the phantom percept (group NT). The two-factorial ANOVA of the HL (dB) with the factors*frequency* and *tinnitus group* indicates a significant ($F(1, 903679) = 467.85$, $p < 0.001$) better hearing for group T patients (mean ± standard error: 27.4 ± 0.1 dB) compared to group NT patients (29.6 ± 0.03 dB; **Figure 1A**). As expected, the overall hearing loss was frequency dependent, with highest losses at high frequencies ($F(9, 903679) = 3382.7$, $p < 0.001$) and both factors showed a significant interaction ($F(9, 903679) = 48.1$, $p < 0.001$, **Figure 1B**). The Tukey post-hoc tests revealed that up to 2 kHz T patients showed significantly better hearing than NT patients, only at 4 kHz this effect flipped in favor of the NT patients.

With the hypothesis described above that temporal processing in the DCN might play a significant role in SR-based threshold benefit, we divided the T group into two subgroups showing individual TP either below or above 5 kHz. The two-factorial ANOVA ($F(2, 903669) = 1376.8$, $p < 0.001$, **Figure 1C**) shows in the Tukey post-hoc tests highly significant ($p < 0.001$) better hearing in $TP_{<5kHz}$ patients (22.4 ± 0.1 dB) compared to the NT group (29.6 ± 0.03 dB) or the $TP_{>5kHz}$ group (31.7 ± 0.1 dB). Note that the $TP_{>5kHz}$ group has significant worse mean hearing levels than the NT group. Again, the overall hearing loss showed a significant frequency dependency as described above ($F(9, 903669) = 2147.7$, $p < 0.001$). The significant

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interaction of both factors (F (18, 903669) = 25.28, p < 0.001;**Figure 1D**) was investigated in detail by Tukey post-hoc tests. These tests revealed that the $TP_{<5kHz}$ group was significantly less affected by hearing loss compared to $TP_{>5kHz}$ and NT groups in all tested frequencies. $TP_{>5kHz}$ and NT groups on the other hand showed similar mean HL for lower frequencies up to 1.5 kHz. From 2 kHz on, the $TP_{>5kHz}$ groups showed significantly worse mean hearing thresholds compared to the NT group (**Figure 1D** , green area).

To rule out a possible age related bias in the different tinnitus groups, we reanalyzed the data independently for different age groups and found the same pattern of hearing loss differences between the tinnitus groups (**Table 1**). With the exception of the two very last values, all Tukey post-hoc tests for the mean HL averaged across all frequencies (factor *TP group* ; **Figure 1E** , right panels) were indicating significant group differences ($p<0.001$) with the $TP_{<5kHz}$ group always showing the smallest HL values (**Figure 1E**). In other words, TP below 5 kHz seemed to be beneficial for hearing thresholds in all age groups.

Discussion

In this short report, we were able to demonstrate that the group of tinnitus patients with tonal TP below 5 kHz showed better mean hearing thresholds than patients with tonal TP above 5 kHz or without tinnitus, independent of age. This result is first evidence in favor of the hypothesis put forward in the Introduction, namely, that SR based optimization of information transmission into the auditory system relies on the computation of the autocorrelation function of the DCN output and consequently on the existence of spike trains that to some degree show a temporal regularity. Such regularity in form of phase locking is limited to 5 kHz in mammals (Rose *et al.* , 1969; Hind, 1972), and TP is related to the frequency range of maximal hearing loss (Axelsson & Sandh, 1985; König *et al.* , 2006; Schecklmann *et al.* , 2012). Note that although the threshold improvement according to this model should be limited to the affected frequency range for an individual patient, i.e. be maximal in the frequency range of the TP, the mean improvement across all patients should result in a more or less parallel shift of the mean threshold function of the group $TP_{<5kHz}$ compared to the mean threshold function of the NT group (cf. **Figure 1D**).

The tinnitus group with TP above 5 kHz that could not profit from the proposed SR mechanism showed hearing thresholds that on average were even worse than those of the group NT in the frequency range above about 2 kHz (cf. **Figure 1D** , green area). This result may reflect a masking effect of the tinnitus perceived by the patients in that frequency range.

In general, temporal processing does seem to be playing a crucial role in tinnitus, especially at the TP itself (Thanikaiarasu *et al.* , 2021) as well as in speech perception (Jain & Dwarkanath, 2016). In most cases, tinnitus patients show deficits in temporal processing but recent findings indicate that the proposed neuronal noise dependent SR mechanism may indeed lead to improvements in temporal processing on the level of the DCN (Shi *et al.* , 2022). A more distinct analysis of patient data taking these finding into account might give new insight into tinnitus pathology.

Conclusion

The presented results indicate that tinnitus perceived with different TP may result from different neurophysiological mechanisms, with temporal processing being crucial for TP below 5 kHz but not above (cf. Schilling*et al.* , 2021). In other words, tinnitus below 5 kHz is not the same as tinnitus above 5 kHz.

Consequently, for therapeutic approaches that are based on the SR model or tinnitus development (Schilling *et al.* , 2020; Tziridis*et al.* , 2022), these results indicate that treatments should be effective for tinnitus patients with TP below 5kHz, but possibly not for patients with TP above 5 kHz.

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Tables

Table 1 : Two factorial ANOVA audiogram results of TP groups categorized by age

Age group	Factors	F statistics	p value
below 40 a	TP group	F(2, 350314) = 607.33	< 0.001
	Frequency	F(9, 350314) = 201.79	< 0.001
	Interaction	F(18, 350314) = 4.30	< 0.001
below 60 a	TP group	F(2, 323635) = 376.91	< 0.001

Age group	Factors	F statistics	p value
60 a and above	Frequency	$F(9, 323635) = 1284.5$	< 0.001
	Interaction	$F(18, 323635) = 16.36$	< 0.001
	TP group	$F(2, 229660) = 377.87$	< 0.001
	Frequency	$F(9, 229660) = 1130.1$	< 0.001
	Interaction	$F(18, 229660) = 2.93$	< 0.001

Note: For visualization of the majority of these results, refer to Fig. 1E.

Figures

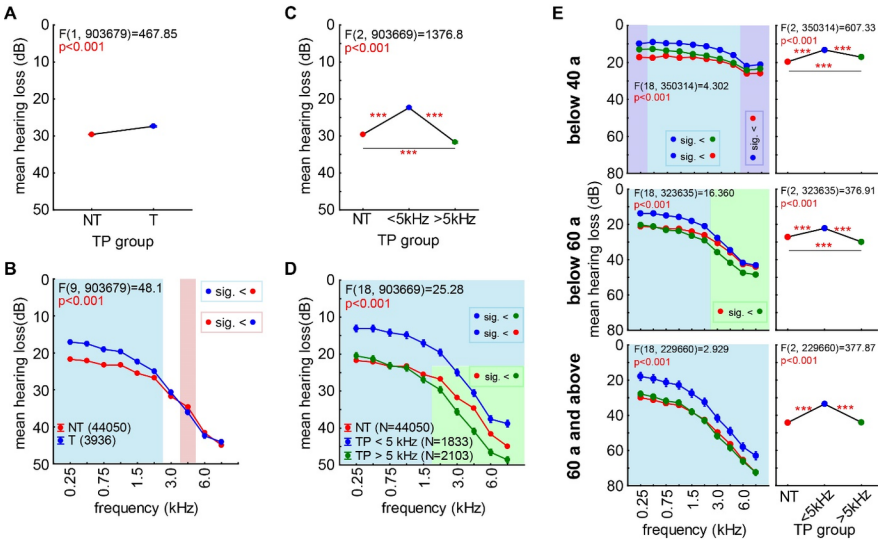

Figure 1: ANOVA results of HL in NT and T patient groups.**A** Mean HL of factor *TP group* with F statistics for all T patients. **B** Mean HL of the interaction of factors*frequency* and *TP group* with F statistics for all T patients. The blue area indicates frequencies where T patients show significantly less HL than NT patients, the red area indicates frequencies where this is reversed. **C** Mean HL of factor*TP group* with F statistics for T patients categorized by TP. Asterisks indicate significance level of Tukey post-hoc tests; *** $p<0.001$. **D** Mean HL of the interaction of factors*frequency* and *TP group* with F statistics for T patients categorized by TP. The blue area indicates frequencies where $TP_{<5kHz}$ patients show significantly less HL than all other patients, the green area indicates the frequencies, where $TP_{>5kHz}$ patients show more severe HL than NT patients. **E** Results of the three independent ANOVAs for the three age groups of the adult patients (below 40 a; below 60 a; 60 a and above). For factor *frequency* please refer to Table 1.

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