Is phase locking crucial to improve hearing thresholds 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 increased in the affected frequency-band to improve hearing thresholds at the cost of upward propagation of this added noise, which finally may be perceived as tinnitus. We already showed 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 constraints 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 (SR) (Krauss *et al.* , 2016; Krauss *et al.* , 2017; Schilling *et al.* , 2021; Schilling *et al.* , 2022). In other words, the effect of SR is not limited to pure tone thresholds, which are usually investigated in the "normal" audiological studies, but seems to be a fundamental principle of (mammal) hearing and therefore auditory perception. According to this model, neuronal noise, e.g., from the somatosensory system (Shore & Zhou, 2006) or other parts of the auditory pathway is added to the cochlear input at the level of the dorsal cochlear nucleus (DCN). For the function of the model, it is irrelevant, where the neuronal noise has its exact source; it has only to be uncorrelated to the actual auditory input. This makes the somatosensory input, receiving mostly information from the neck and pinna muscles, to one of the most likely candidates and would also explain phenomena like somatic tinnitus (Shore*et al.* , 2007). In case of a reduced cochlear input due to inner hair cell damage (Tziridis *et al.* , 2021) or denervation ("hidden hearing loss", Kujawa & Liberman, 2009), the added neuronal noise can lift the otherwise subthreshold cochlear input above the threshold (= SR), thereby improving hearing thresholds (Gollnast *et al.* , 2017) or even speech perception (Schilling *et al.* , 2022). For SR to optimize information transmission in the described way, the amplitude of the noise (i.e., the spike rate of the incoming uncorrelated neuronal noise) has to be constantly adapted to changing levels of cochlear input, most probably due to modulation of the inhibition

(Chen *et al.* , 2022). In our model, this optimization is achieved by maximizing the autocorrelation (AC) of the DCN output, i.e., the spike rate (Krauss et al., 2017). This effect should be strongest in the frequency range of the most severe hearing impairment and therefore the tinnitus percept should be most prominent in frequency rages around the maximum hearing loss, which could be shown by several studies (Axelsson & Sandh, 1985; König *et al.* , 2006; Schecklmann *et al.* , 2012). As a result of the described mechanism, 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 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 an input 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). Nevertheless, the exact cutoff frequency seems to be somewhat species-dependent (Palmer & Russell, 1986) and its exact upper limit is still under debate for humans (Verschooten *et al.* , 2019). In any case there is a continuous decline of temporal precision of phase locking with increasing frequency.

Independent of the exact upper limit of phase locking in the human auditory system, 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. This does not mean, that SR-induced hearing improvements on the level of thresholds or perception stop right there, but significantly higher tinnitus frequencies might not induce SR-effects anymore as no optimal noise with an optimal AC can be found and therefore the maximum noise might be induced in the system by complete disinhibition of the noise input.

In line with our model and as mentioned above, the perceived tinnitus frequency of patients is highly correlated with the frequency of strongest hearing loss (cf. also Tziridis *et al.* , 2022). 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 hearing threshold improvement. On the other hand, according to our view SR needs a reliable phase locking detector for optimization of that neuronal noise. Consequently, we here put forward the hypothesis that patients with tinnitus frequencies up to 5 kHz – as an approximation of the upper limit of phase locking – should generally show improved hearing thresholds when compared to patient without tinnitus, while those with tinnitus frequencies above 5 kHz should not show such improvement or may be even more impaired due to the maximally increased neuronal noise amplitude.

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, 0.5 kHz, 0.75 kHz, 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, 8 kHz) collected between 2000 and 2018 by identical means were analyzed retrospectively. Therefore, German law required no declaration of consent. Clinical pure-tone audiometry and tinnitus pitch (and loudness) determination were performed using an automated psychophysical approach where patients had to indicate their hearing level / tinnitus pitch by pressing a button as soon as they perceived a pure tone presented with a pitch corresponding to their tinnitus pitch. The anonymized hearing threshold database included the age of the patients but not the gender and an indicator if and what kind of tinnitus the patients perceived. Patients marked as experiencing tonal tinnitus percepts in at least one ear were classified as tinnitus patients (group T) and those without indication of any form of tinnitus were classified as non-tinnitus patients (group NT). Patients indicated of having a non-tonal tinnitus were excluded from further analysis. We cannot rule out completely that some patients may be misclassified using the database.

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 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 roughly 5 kHz in mammals (Rose *et al.* , 1969; Hind, 1972; Palmer & Russell, 1986), while the exact upper limit in humans is still under debate (Verschooten*et al.* , 2019). For the interpretation of the data presented here, the exact upper limit of the phase locking in humans is of secondary importance, as we simply need to divide our patients in two subgroups with high or low tinnitus pitch to test our hypothesis. Furthermore, the frequency resolution of the clinical standard audiometry and TP determination used is low and the frequency of the 5 kHz limit we chose was not tested at all. Furthermore, the TP is related to the frequency range of maximal hearing loss (Axelsson & Sandh, 1985; König *et al.* , 2006; Schecklmann *et al.* , 2012). In our view, this means that the neuronal noise is maximally upregulated (i.e., disinhibited, cf. Chen *et al.* , 2022) around the TP, providing maximal hearing threshold improvement around that frequency range but maybe not limited to it (cf. Introduction). Note that although the threshold improvement according to this model should be limited to different frequency ranges for individual patients, 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**).

With the described hypothesis above, we found the expected positive hearing threshold effects for the patients with a TP below 5 kHz. The tinnitus patient group with TP above 5 kHz not profiting from the proposed SR mechanism showed hearing thresholds that on average were even worse than those of the group NT, especially in the frequency range above 2 kHz (cf. **Figure 1D** , green area). This result may possibly reflect a "masking effect" of the tinnitus perceived by the patients in that frequency range (Ivansic *et al.* , 2017) or alternatively it could represent the impairment of hearing thresholds we expect due to the disinhibited neuronal noise level in the DCN.

In our view, tinnitus below and above the upper phase locking limit is based on the same mechanism. That mechanism is the frequency dependent increase in neuronal noise with the aim to utilize this noise for SR-induced enhancement of auditory information transmission. The difference in hearing with lower and higher tinnitus pitches does not rely on the pitch itself but rather is a function of the proposed underlying AC-mechanism that relies on precise temporal processing which is not provided for frequencies above the described limit. In general, temporal processing in the sense of phase locking of neuronal action potentials 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 hearing is affected differently by different TPs while the tinnitus percept itself may result from the same neurophysiological mechanism. The results indicate that for TPs below 5 kHz temporal processing (i.e. phase locking) is crucial for hearing threshold optimization (cf. Schilling *et al.* , 2021) but might not be available above that limit. In other words, tinnitus below 5 kHz does not go in hand with the same effect as tinnitus above 5 kHz and may explain the different findings of several studies on hearing and tinnitus.

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 TPs below 5kHz, but possibly not for patients with a TP above 5 kHz. Those patients may need a modified approach to see any beneficial effects of such therapies.

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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
	Frequency	$F(9, 323635) = 1284.5$	< 0.001
	Interaction	$F(18, 323635) = 16.36$	< 0.001
60 a and above	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

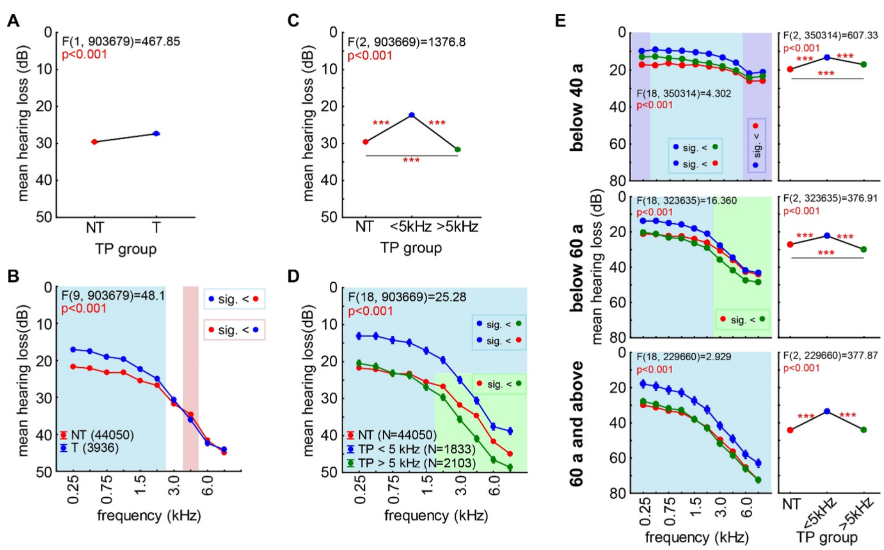

Figure 1: ANOVA results of HL in NT and T patient groups. **A** Mean HL of factor *TP group* with F statistics

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$_{<5\mathrm{kHz}}$ patients show significantly less HL than all other patients, the green area indicates the frequencies, where TP$_{>5\mathrm{kHz}}$ 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.