Looking for objective correlates between tinnitus and cochlear synaptopathy

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Tinnitus is the perception of a sound in the absence of acoustic stimulation. While usually connected to a hearing loss, there exists a subset of tinnitus sufferers with audiologically normal hearing, whose tinnitus was often initiated by a noise trauma. Noise-induced tinnitus might be connected to the noise exposure that leads to a permanent impairment of the hearing system without affecting sensitivity to sound. This is commonly referred to as hidden hearing loss (HHL) and might be connected to cochlear synaptopathy. The hypothesis that HHL is one of the causes underlying tinnitus is based on suppositions that both phenomena are related to deafferentation of auditory nerve fibres and related central gain adjustments. To investigate this connection, a screening procedure consisting of high frequency audiometry (HFA), tinnitus likeness spectrum and loudness, psychophysical tuning curves (PTC) and tinnitus masking curves (TMC), adaptive categorical loudness scaling, and middle-ear muscle reflex test was developed. Pilot results show that all measurements can be completed within a short time frame, due to a Bayesian procedure being adopted to measure HFA, PTC and TMC. These procedures may contribute to investigating the connection between tinnitus and HHL with a large number of outcome measures. This connection will provide important insights toward the development of better diagnoses and treatment methods.

INTRODUCTION

Tinnitus is a complex phenomenon whose causes and mechanisms are not yet completely understood. Research in this topic is still inconclusive, and treatments are still not effective in many cases. In addition, the results of different studies are inconsistent and often suggest opposing theories to explain the observed phenomena. Because tinnitus has many underlying causes, a categorization of tinnitus is required to obtain an understanding of the underlying mechanisms. Many studies include listeners with tinnitus and a hearing loss (Baracca *et al.*, 2011), which complicates the interpretation of the results. An interesting population to study is therefore tinnitus sufferers with a normal audiogram. It has been suggested that a deafferentation of auditory nerve fibres in the inner ear leads to a reduced excitatory input into the brainstem, which, in turn, leads to a compensatory increase in neural gain and tinnitus.

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This will be in agreement with numerical simulations (Schaette & McAlpine, 2011). This hypothesis is also in line with recent findings in animal models finding that noise overexposure followed by a temporal threshold shift leads to deafferentation in the inner ear (Kujawa & Liberman, 2015). The aim of the present study was to develop a screening procedure composed of psychophysical and acoustic measures suggested to assess tinnitus and the potential presence of synaptopathy, and thereby to categorize a subclass of tinnitus sufferers with normal hearing thresholds. One of the main underlying assumptions is that a noise trauma is the triggering event for the generation of tinnitus by initiating a progressive degeneration of spiral ganglion neurons (SGN) caused by noise-induced synaptopathy (Fig. 1). A shift in hearing thresholds will first be evident after a critical time and after a critical amount of SGN degeneration has been reached (Lobarinas *et al.*, 2016).

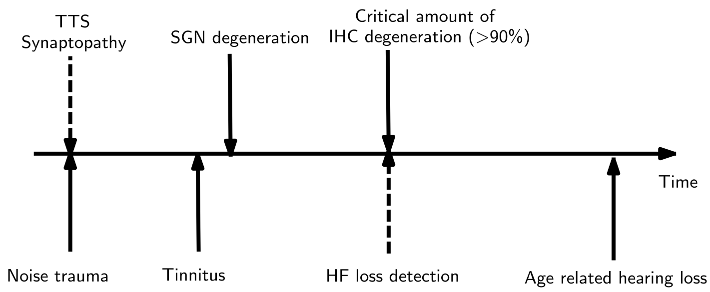

Fig. 1: Assumption behind the connection between tinnitus, cochlear synaptopathy and high-frequency hearing loss. It is assumed that a noise overexposure initiates a temporal threshold shift with subsequent cochlear synaptopathy. Reduced input into the brainstem then leads to a regulation of gain and an overexcitation of specific frequencies, leading to tinnitus. A progressive degeneration of spiral ganglion cells as a consequence of synaptopathy will then, after a critical amount of damage, lead to an increase in audiometric threshold.

Because animal models showed a higher prevalence for synaptopathy at tonotopic places connected to high frequencies, HFA was selected as a proxy of the presence of synaptopathy. It has also recently been suggested that the presence of tinnitus might be related to the functioning of the efferent system (Wojtczak *et al.*, 2017) which, in turn, might be connected to cochlear synaptopathy (Furman *et al.*, 2013). Middle ear muscle reflex (MEMR) measurements will be used as an acoustic characterization measure, based on results by Wojtczak *et al.* (2017) where tinnitus sufferers had lower MEMRs compared to a control group. Psychophysical tuning curves (PTC) and tinnitus masking curves (TMC) have been shown to differ within a group of listeners suffering from tinnitus (Fournier *et al.*, In press). This variability provides information about the tuning properties of the system and the potential impact of the mechanism underlying tinnitus on tuning. Combining clinical measures of tinnitus assessment with more experimental procedures in the same listeners will provide a more detailed profile of the tinnitus.

METHODS

The inclusion criteria for the subjects were: a) the tinnitus had to be constant but not intrusive or bothersome, i.e. the ideal participant can ignore the tinnitus the majority of the time. b) tinnitus had to be chronic, not related to acute temporal threshold shift (TTS) or upper respiratory tract infections (URTI). c) audiometric thresholds from 125 Hz to 8 kHz measured with standard audiogram had to be lower than 20 dB HL. The data of the tinnitus group will be compared to the data of a control group, matched in hearing thresholds and age. To have a further characterization of the tinnitus, the Tinnitus Handicap Inventory (THI) questionnaire will be included.

The HFA, PTC (both at 1 kHz and at tinnitus frequency) and the TMC were implemented based on a Bayesian algorithm (Schlittenlacher *et al.*, 2018) for standard audiometry. In short, a continuous function is fitted to estimated values based on a prior grid and a Bayesian statistical approach maximizing the information in each trial to cover the desired spectral range. Initially, specific frequencies with a distance of $\frac{1}{4}$th octave (See Fig. 2) were tested to get at least one positive ("I heard the tone") and one negative answer ("I didn't hear the tone"). The algorithm then iterated through the frequencies and finally applied a continuous fit to the data points. Using an initial grid allowed a reduction in measurement time.

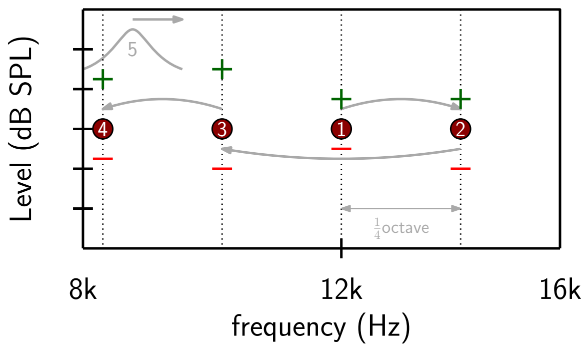

Fig. 2: Bayesian procedure used in the high frequency audiometry. Starting at 12 kHz, an initial estimate of the threshold was made by obtaining a positive and a negative response from the listener. Additional estimates were obtained in the frequency range between 8 kHz and 16 kHz with a spectral distance of 1/4th octaves. After estimation of the lowest frequency threshold, the Bayesian procedure was applied, selecting the frequency and level by maximizing the information. Finally, all estimated points were connected by a continuous differentiable fitting function.

All three experiments consisted of 50 trials. For the HFA and PTC, each interval consisted of 3 pulses of 250 ms duration with a rise/fall time of 20 ms spaced by 100 ms silence intervals. For the TMC, each interval consisted of one pulse of 2s with a rise/fall time of 20 ms. The sampling rate was set to 48 kHz and the step size between the frequencies was set to 0.1 octaves. In the HFA the participant had to indicate if the tone was detected (YES) or not (NO). The tested frequency range was 8 kHz to 16 kHz. To reduce bias effects, 10% of silent trials (in addition to the 50 trials) were randomly presented to test the reliability of the participant. The PTC was measured for a probe tone at 1 kHz and at the listeners' tinnitus frequency in the presence of a narrowband noise masker. The bandwidth of the noise masker was 20% of the probe frequency and at maximum 320 Hz (Kluk & Moore, 2005). The masker centre frequency varied in the range of 0.5 kHz to 2 kHz (for the 1 kHz probe) or within a 1 octave width centred at the tinnitus frequency. For the TMC, the same approach as the PTC was used but in absence of the probe.

To measure the middle-ear muscle reflex (MEMR), wideband tympanometry (WBT) was measured (226 Hz to 8 kHz) to determine the tympanometric peak pressure. Then, the MEMR was measured in correspondence to the maximum of the absorbance found with WBT. The stimulation pattern (Fig. 3) is based on Liberman *et al.* (personal communication). The elicitor was a broad band white noise noise presented ipsilaterally (Interacoustics Titan Suite). The levels were increasing from 60 to 95 dB SPL, or up to 110 dB SPL if the participant did not indicate annoyance.

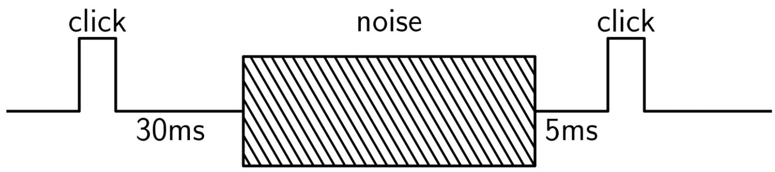

Fig. 3: The stimulus used to measure the middle ear muscle reflex (MEMR). A click preceded a burst of white noise, followed by another click . All stimuli were presented on the ipsilateral side. The paradigm was implemented using the Interacoustics TITAN research platform with custom code.

RESULTS - EFFICACY OF THE PIPELINE

High frequency audiometry

The modified HFA procedure was compared to a 3-alternative forced choice procedure (AFC) (Fig. 4). The figure shows example results for the same subject measured with both the procedures. AFC results are shown by filled symbols, the Bayesian algorithm by circles, crosses and solid line. The AFC procedure took between 8 and 10 minutes to complete, while the Bayesian procedure between 4 and 6 minutes. Moreover, the AFC procedure provided estimates of five discrete frequencies, while the Bayesian procedure provided a continuous estimate of the threshold. For this participant (Fig. 4, control group) the deviations between the AFC results and the estimate based on the Bayesian procedure were below 5 dB. Other participants showed differences between the two methods around 10 dB and even higher, especially at 16 kHz. The similarity of the two methods is promising, but due to the intrinsic high variability found in high-frequency audiometry especially from 14 to 16 kHz (Schmuziger *et al.*, 2004), the comparability of the two measures needs to be further investigated.

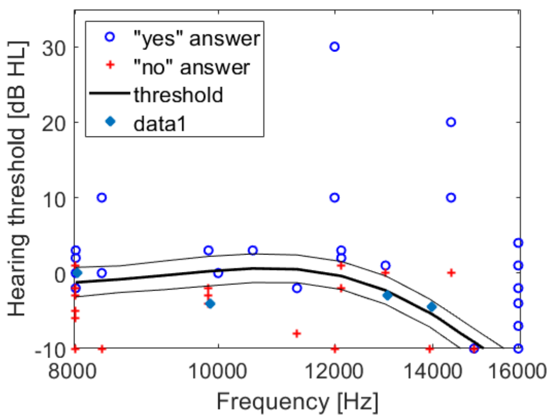

Fig. 4: Comparison of the results obtained using an alternative-forced choice procedure (AFC, filled symbols) and the Bayesian algorithm. Open symbols indicate positive responses of the listeners (tone heard), crosses negative responses (tone not heard). The black line indicates the final estimate with an estimate of the uncertainty.

Psychophysical Tuning curve (PTC) and Middle Ear Muscle Reflex (MEMR)

Figure 5 shows an example of a PTC using a probe tone at 1 kHz for a normal hearing subject (control group). Symbols indicate listeners' responses ("heard", circles; "not heard", red crosses). The solid line indicates the interpolation of the measured points. The PTC showed a clear minimum around the frequency of the probe tone and shallow slopes at the minimum and maximum frequencies. Compared to classical methods where single frequencies are measured, the peak was broader (Q10 = 4). The lack of a sharp peak is a consequence of the fitting procedure which requires the function to be differentiable. Despite the lack of a sharp peak, a clear tuning was found which might be sufficient for a rough classification, but not for indications of, for example, potential outer hair cell loss. The obtained continuous estimate might, however, allow different metrics of PTC tuning using this method. Fig. 6 shows an example result of the measured MEMR (control group). The difference in absorbance was higher for higher levels of the elicitor, in agreement with data from the literature. The difference across elicitor levels was small for the lowest (250 Hz) and the highest (800 Hz) frequencies,

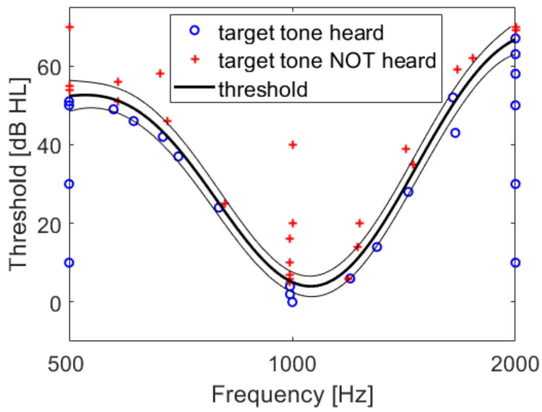

Fig. 5: An example of PTC using the Bayesian algorithm. Compared to literature, the peak is broader using this algorithm. The algorithm used for PTC was modified to use a finer grid and a weighting function in order to collect more data around the frequency of the presented tone (1 kHz) compared to the HFA. The Gaussian process interpolation will provide a differentiable function which makes the result deviate from the classical shape with a sharp tip.

showed a crossing point around 1100 Hz and the highest excursion towards negative absorbance changes between 500 and 700 Hz. The response was clearly visible even after only short measurement time. It is interesting to note that the stimulation with a noise rather than a pure tone as in standard protocols has been reported as less bothering. While of minor importance for normal hearing listeners, this plays an important role when handling participants that suffer from tinnitus. Moreover, the use of the wideband acoustic reflex is particularly recommended for its sensitivity (Hein *et al.*, 2017).

DISCUSSION

The preliminary results for the HFA for a listener in the control group indicate that the Bayesian procedure developed for standard audiometric frequencies (Schlittenlacher *et al.*, 2018) can also be applied to high-frequency audiometry. Despite the challenges connected to high-frequency audiometry in terms of ear-canal acoustics and challenges of the listeners to decide about the presence or absence of the stimulus, HFA obtained with AFC and the Bayesian procedure were very similar in the pilot data. In comparison with the AFC procedure, the Bayesian procedure not only provided an advantage in terms of measurement duration, but also allows an estimation of the threshold directly at any frequency within the measured interval. This is an advantage for measures that rely on the tinnitus frequency identified by the listeners. The comparison between PTC at tinnitus frequency and TMC has been proposed by

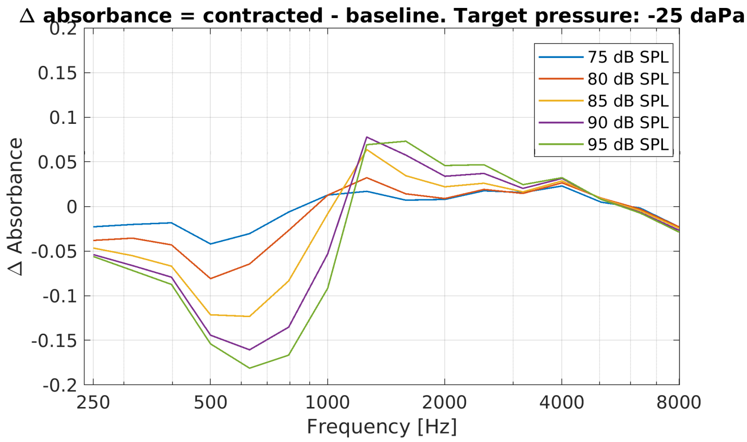

Fig. 6: The MEMR of a healthy subject. The figure shows the changes in the ear-canal sound pressure followed by the presentation of the elicitor for different levels.

(Fournier *et al.*, In press). In that study, the participants were clustered into three groups: 1) V/U shape of the PTC and TMC, 2) V/U shape of the PTC and flat TMC and 3) flat PTC and TMC. The PTC test is a measure of the frequency tuning of the auditory system. In connection to tinnitus and synaptopathy, differences in the PTC for tinnitus sufferers with a normal audiogram can reveal differences about the underlying neural mechanisms. These might differ between listeners suffering from synaptopathy compared to listeners not affected by synaptopathy. The TMC is a way to characterize and quantify the masking effect of an external stimulus on the tinnitus. Depending on the neural origin of the tinnitus, this effect might be different for peripheral mechanisms (including synaptopathy) and central mechanisms. In the study by (Fournier *et al.*, In press) a relationship between the maskability and the type of tinnitus (tonal or noise) was found. Hence, PTC and TMC might provide a more fine grained characterization of the tinnitus sufferers' profile.

The total duration of the suggested screening method is about one hour. This shortened measurement time was mainly achieved by using the Bayesian procedure rather than classical AFC procedures and by using optimized clinical equipment for the measurement of the MEMR. The decreased duration might play an important role when dealing with tinnitus sufferers which often are subjected to stress and report that their tinnitus can be modulated in intensity by external factors.

In conclusion, the combination of the suggested measures and the application of the Bayesian procedure has the potential to provide a detailed, yet fast characterization of the mechanisms underlying tinnitus in listeners with a normal audiogram.

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